



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 809

[Docket No. FDA-2023-N-2177]

RIN 0910-AI85

Medical Devices; Laboratory Developed Tests

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration is issuing a final rule to amend its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act) including when the manufacturer of the IVD is a laboratory. In conjunction with this amendment, the Food and Drug Administration is phasing out its general enforcement discretion approach for laboratory developed tests (LDTs) so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs. This phaseout policy includes enforcement discretion policies for specific categories of IVDs manufactured by a laboratory, including currently marketed IVDs offered as LDTs and LDTs for unmet needs. This phaseout policy is intended to better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance.

DATES: This rule is effective [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: For access to the docket to read background documents or comments received, go to <https://www.regulations.gov> and insert the docket number found in brackets in the heading of this final rule into the “Search” box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

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SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

- A. Purpose of the Final Rule
- B. Summary of Select Provisions of the Final Rule
- C. Legal Authority
- D. Costs and Benefits

II. Table of Abbreviations/Commonly Used Acronyms in This Document

III. Background

- A. FDA's Current Regulatory Framework
- B. Need for the Rule
- C. Summary of Comments on the Notice of Proposed Rulemaking
- D. General Overview of the Final Amendment to the Definition of In Vitro Diagnostic Products
- E. General Overview of the Final Phaseout Policy

IV. Legal Authority

V. Phaseout Policy

- A. Scope
- B. Enforcement Discretion Policies
- C. Stages

VI. Comments on the Notice of Proposed Rulemaking and FDA Responses

- A. General Comments on the Notice of Proposed Rulemaking
- B. Definitions

- C. Need for the Rule
 - D. FDA Authority to Regulate LDTs
 - E. Other Legal Comments
 - F. Phaseout Policy
 - G. Impact on Small Businesses
 - H. Impact on Pricing
 - I. Impact on Access and Innovation
 - J. Level Playing Field
 - K. Impact to Specific Patient Populations
 - L. Specific Types of IVDs
 - M. IVD Modifications
 - N. FDA Resources
 - O. 510(k) Third Party Review Program
 - P. Implementation
 - Q. Interplay with Oncology Drug Products Used with Certain In Vitro Diagnostic Tests
Pilot Program
 - R. Miscellaneous
- VII. Effective Date
- VIII. Economic Analysis of Impacts
- IX. Analysis of Environmental Impact
- X. Paperwork Reduction Act of 1995
- XI. Federalism
- XII. Consultation and Coordination with Indian Tribal Governments
- XIII. References

I. Executive Summary

A. Purpose of the Final Rule

The Food and Drug Administration (FDA, the Agency, or we) is amending its regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory. This amendment reflects that the device definition in the FD&C Act does not differentiate between entities manufacturing the device. In connection with amending the regulation, FDA is phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs (i.e., FDA’s expectations for compliance will generally be the same). This phaseout policy includes enforcement discretion policies for specific categories of IVDs manufactured by a laboratory, including currently marketed IVDs offered as LDTs¹ and LDTs for unmet needs. For purposes of this document, we use “manufacture” and related terms as a shorthand for the various activities that constitute manufacturing as described in FDA regulations (e.g., design, preparation, propagation, assembly, and processing).

In 1976, the Medical Device Amendments of 1976 (the MDA) amended the FD&C Act to create a comprehensive system for the regulation of devices intended for human use. In implementing the MDA, FDA has exercised enforcement discretion such that it generally has not enforced applicable requirements with respect to most LDTs. Enforcement discretion for LDTs developed as a matter of practice. However, the risks associated with LDTs are much greater today than they were at the time of enactment of the MDA. As discussed more fully in the notice of proposed rulemaking (NPRM) (88 FR 68006, October 3, 2023) and this preamble, today’s LDTs are, among other things, used more widely, by a more diverse population, with an increasing reliance on high-tech instrumentation and software, and more frequently for the purpose of guiding critical healthcare decisions. In this regard, today’s LDTs are similar to other IVDs that have not come within FDA’s general enforcement discretion approach.

¹ As discussed in section V.A.1, FDA uses the phrase “IVDs offered as LDTs” throughout this preamble to refer to IVDs that are manufactured and offered as LDTs by laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and that meet the regulatory requirements under CLIA to perform high complexity testing, and used within such laboratories, even if those IVDs do not fall within FDA’s traditional understanding of an LDT because they are not designed, manufactured, and used within a single laboratory.

Given these changes, and for the additional reasons discussed in the NPRM and this preamble, FDA is phasing out the general enforcement discretion approach for LDTs. By phasing out this approach, FDA intends to better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance.

B. Summary of Select Provisions of the Final Rule

FDA is amending the definition of “in vitro diagnostic products” in its regulations to state that IVDs are devices under the FD&C Act “including when the manufacturer of these products is a laboratory.”

In conjunction with this amendment, FDA is phasing out the general enforcement discretion approach for LDTs. As discussed further in this preamble, however, FDA is adopting targeted enforcement discretion policies for several categories of IVDs manufactured by a laboratory in certain circumstances. As with any enforcement discretion policy, FDA may update any of these enforcement discretion policies as circumstances warrant or if the circumstances that inform these policies change, consistent with FDA’s good guidance practices (21 U.S.C. 371(h), § 10.115 (21 CFR 10.115)).

Additional details regarding the phaseout policy are discussed further in section V of this preamble.

C. Legal Authority

FDA is issuing this rule under the Agency’s general rulemaking authorities and statutory authorities relating to devices. These authorities include sections 201(h)(1), 301, 501, 502, 510, 513, 514, 515, 518, 519, 520, 701, 702, 704, and 801 of the FD&C Act (21 U.S.C. 321(h)(1), 331, 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 371, 372, 374, and 381) and section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

D. Costs and Benefits

We quantify benefits to patients from averted health losses due to problematic IVDs offered as LDTs. We focus mainly on certain broad disease categories associated with the majority of misdiagnosis-related harms in the United States. Additional benefits include averted non-health losses from reduced spending on problematic IVDs offered as LDTs and unquantified reduction in costs from lawsuits. We quantify costs to affected laboratories for complying with statutory and regulatory requirements. Additional costs include costs to FDA, which we include in our estimates. We estimate that the annualized benefits over 20 years range from \$0.99 billion to \$11.1 billion at a 7 percent discount rate, with a primary estimate of \$3.51 billion, and from \$1.24 billion to \$13.62 billion at a 3 percent discount rate, with a primary estimate of \$4.34 billion. The annualized costs range from \$566 million to \$3.56 billion at a 7 percent discount rate, with a primary estimate of \$1.29 billion, and from \$603 million to \$3.79 billion at a 3 percent discount rate, with a primary estimate of \$1.37 billion.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
3P510k Review Organization	Third Party Review Organization Accredited Under FDA's Third Party Review Program
510(k)	Premarket Notification
AABB	Association for the Advancement of Blood and Biotherapies
ACGME	Accreditation Council for Graduate Medical Education
ACLA	American Clinical Laboratory Association
ADLT	Advanced Diagnostic Laboratory Test
ACHC	Accreditation Commission for Health Care
AMC	Academic Medical Center
AML	Acute Myeloid Leukemia
AMP	Association for Molecular Pathology
ANI	Average Nucleotide Identity
APA	Administrative Procedure Act
ASHI	American Society for Histocompatibility and Immunogenetics
ASR	Analyte Specific Reagent
AST	Antimicrobial Susceptibility Test
BLA	Biologics License Application
CAP	College of American Pathologists
CAPA	Corrective and Preventive Action
CBRN	Chemical, Biological, Radiological, or Nuclear
CDER	Center for Drug Evaluation and Research

Abbreviation/Acronym	What It Means
CDRH	Center for Devices and Radiological Health
CDC	Centers for Disease Control and Prevention
CDx	Companion Diagnostic
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CGT	Cell and Gene Therapy
CLIA	Clinical Laboratory Improvement Amendments of 1988
CLIAC	Clinical Laboratory Improvement Advisory Committee
CLSI	Clinical and Laboratory Standards Institute
CMS	Centers for Medicare & Medicaid Services
COLA	Commission on Office Laboratory Accreditation
CRO	Clinical Research Organization
Cures Act	21 st Century Cures Act
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
EGFR	Epidermal Growth Factor Receptor
EMR	Electronic Medical Record
EO	Executive Order
EUA	Emergency Use Authorization
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FACT	Foundation for the Accreditation of Cellular Therapy
FCC	Federal Communications Commission
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FDA-ARGOS	FDA dAtabase for Reference Grade MicrObial Sequences
FD&C Act	Federal Food, Drug, and Cosmetic Act
FRIA	Final Regulatory Impact Analysis
GAO	Government Accountability Office
HCFA	Health Care Financing Administration
HCT/Ps	Human Cells, Tissues, and Cellular and Tissue-Based Products
HDE	Humanitarian Device Exemption
HHS	Department of Health & Human Services
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HUD	Humanitarian Use Device
ICCS	International Clinical Cytometry Society
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
ISO	International Organization for Standardization
IVD	In Vitro Diagnostic Product
IVDR	In Vitro Diagnostic Medical Device Regulation
LDT	Laboratory Developed Test

Abbreviation/Acronym	What It Means
LGBTQIA+	Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, and Asexual
LoQ	Limit of Quantitation
MAF	Master File
MDA	Medical Device Amendments of 1976
MDAC	Medical Devices Advisory Committee
MDR	Medical Device Report
MDUFA	Medical Device User Fee Amendments
MolDx	Molecular Diagnostic Services
NCBI	National Center for Biotechnology Information
NDA	New Drug Application
NGS	Next Generation Sequencing
NIFLA	National Institute of Family and Life Advocates
NIH	National Institutes of Health
NIPS	Non-Invasive Prenatal Screening
NLRB	National Labor Relations Board
NMDP	National Marrow Donor Program
NOTA	National Organ Transplant Act
NPRM	Notice of Proposed Rulemaking
NSQAP	Newborn Screening Laboratory Quality Assurance Program
NYS CLEP	New York State Department of Health's Clinical Laboratory Evaluation Program
OED	Oxford English Dictionary
OHT7	Office of Health Technology 7
OIRA	Office of Information and Regulatory Affairs
OMB	Office of Management and Budget
OPTN	Organ Procurement and Transplant Network
OTC	Over-the-Counter
PAMA	Protecting Access to Medicare Act of 2014
PCCP	Predetermined Change Control Plan
PHS Act	Public Health Service Act
PMA	Premarket Approval Application
PrEP	Pre-Exposure Prophylaxis
PRIA	Preliminary Regulatory Impact Analysis
QS	Quality System
QSR	Quality System Regulation
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RUO	Research Use Only
SAMHSA	Substance Abuse and Mental Health Services Administration
SDO	Standards Development Organization
Secretary	Secretary of HHS
STI	Sexually Transmitted Infection
STIC	Susceptibility Test Interpretive Criteria
TMB	Tumor Mutational Burden
UDI	Unique Device Identification
UMRA	Unfunded Mandates Reform Act of 1995

Abbreviation/Acronym	What It Means
USG	United States Government
VALID Act	Verifying Accurate, Leading-Edge IVCT Development Act of 2023
VHA	Veterans Health Administration

III. Background

FDA’s regulations define IVDs as reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae, and intended for use in the collection, preparation, and examination of specimens taken from the human body. IVDs include test systems (also referred to in this preamble as “tests”) that are intended for use in the collection, preparation, and examination of samples taken from the human body, such as blood or tissue, for the purpose of detecting diseases or other conditions, monitoring a person’s overall health, identifying patients who are likely to benefit from specific therapies, or otherwise helping to diagnose, cure, mitigate, treat, or prevent disease or its sequelae. Some IVDs are manufactured by conventional medical device manufacturers for use by other entities such as laboratories, healthcare providers, or, in some cases, patients. Such IVDs may include “test kits,” containing packaged sets of components that are part of or comprise a test system. Other IVDs are manufactured by laboratories for use by the same or other laboratories. Such IVDs include LDTs. FDA has generally considered an LDT to be an IVD that is intended for clinical use and that is designed, manufactured, and used within a single laboratory that is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and meets the regulatory requirements under CLIA to perform high complexity testing.²

However, in implementing the MDA since 1976, FDA has exercised enforcement discretion such that it generally has not enforced applicable legal requirements with respect to most LDTs. This means that, for most LDTs, FDA generally has not enforced requirements

² Such laboratories may include those operating under State licensure programs deemed exempt from CLIA. *See* CMS, “Exempt States Under the Clinical Laboratory Improvement Amendments” (Ref. 1).

related to registration and listing, reporting adverse events to FDA, current good manufacturing practices (CGMPs), or premarket review of an IVD by FDA prior to use of the LDT in patient care, among other requirements. The rationale for this approach was that, at the time of passage of the MDA, LDTs were mostly manufactured in small volumes by laboratories that served their local communities. They were typically intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population, or were generally similar to well-characterized, standard IVDs (Refs. 2 and 3). They also tended to employ manual techniques (and did not use automation) and were performed by laboratory personnel with specialized expertise; to be used and interpreted by physicians or pathologists in a single institution responsible for the patient (and who were actively involved in patient care); and to be manufactured using components legally marketed for clinical use, such as general purpose reagents or immunohistochemical stains marketed in compliance with FDA requirements. Due to these and other factors, FDA exercised enforcement discretion such that it generally has not enforced applicable requirements for most LDTs.³

However, the LDT landscape has evolved significantly since 1976. Today, many LDTs increasingly rely on high-tech or complex instrumentation and software to generate results and clinical interpretations (Refs. 2 and 3). They are often used in laboratories outside of the patient's healthcare setting and are often run in high volume for large and diverse populations. Many LDTs are manufactured by laboratory corporations that market the IVDs nationwide, as they accept specimens from patients across the country and run their LDTs in very large volumes in a single laboratory. Today's LDTs are also more commonly manufactured with instruments or other components not legally marketed for clinical use and are more often used to inform or direct critical treatment decisions, to widely screen for common diseases, to predict personal risk of developing certain diseases, and to diagnose serious medical conditions such as cancer and

³ FDA's general enforcement discretion approach has not applied to LDTs in all contexts; for example, it has not applied to, among other LDTs, those used for declared emergencies/potential emergencies/material threats under section 564 of the FD&C Act (21 U.S.C. 360bbb-3).

heart disease.⁴ The risks associated with most LDTs today are therefore much greater than they were at the time FDA began implementing the MDA, and most LDTs today are similar to other IVDs that have not been under FDA’s general enforcement discretion approach. In addition, FDA is concerned that firms are offering IVDs as “LDTs” even when they are not LDTs as defined on FDA’s website, because they are not actually designed, manufactured, and used within a single laboratory (see, e.g., Refs. 5 and 6).

As LDTs increasingly rely on high-tech instrumentation and software, the potential for cybersecurity vulnerabilities is growing. Many LDTs are connected to Laboratory Information Management Systems and other IT infrastructure, making them a potential conduit for those looking to access information in such systems. This may include patient genetic information, among other things, which could have national security implications. Further, it has been demonstrated that hackers can modify medical test results (Ref. 7). Through premarket review, FDA works with manufacturers to ensure cybersecurity is appropriately considered, mitigating the potential for future problems. Through medical device reporting (MDR) and correction and removal reporting requirements, FDA helps to ensure that any problems are appropriately addressed. In fact, FDA has seen cybersecurity problems with certain instruments and issued two safety communications where laboratories may not have otherwise been aware that the research use only (RUO) versions of the instruments used as part of their LDTs had the same vulnerabilities (Refs. 8 and 9).

As a result of these evolutions in the testing landscape, FDA has long recognized the need for a change in the Agency’s general enforcement discretion approach for LDTs. The history of FDA’s efforts with respect to LDTs is described more fully in the NPRM. Over the past few years, FDA has accumulated even more information supporting the need for a change, as noted in the NPRM and discussed below. In light of these developments, FDA is amending

⁴ See, e.g., Refs. 2-4. These observations are also informed by FDA’s own experience, including the review of submissions and site visits, and staff with prior experience in the laboratory industry manufacturing and performing LDTs.

FDA's regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer is a laboratory.⁵ FDA is also issuing a policy (see section V) under which FDA is: (1) phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs and (2) adopting targeted enforcement discretion policies for specific categories of IVDs manufactured by a laboratory. As reflected in FDA's Final Regulatory Impact Analysis (FRIA), FDA estimates that the benefits of the phaseout policy outweigh the costs (see Ref. 10).

A. FDA's Current Regulatory Framework

A comprehensive system for the regulation of devices is included in the FD&C Act, as amended by the MDA. Section 513 of the FD&C Act (21 U.S.C. 360c) establishes three categories (classes) of devices depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Class I devices are those devices for which the general controls of the FD&C Act (controls authorized by or under section 501, 502, 510, 516, 518, 519, or 520 (21 U.S.C. 351, 352, 360, 360f, 360h, 360i, or 360j) or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness of the device; or those devices for which insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or to establish special controls to provide such assurance, but because the devices are not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and do not present a potential unreasonable risk of illness or injury, are to be regulated by general controls (section 513(a)(1)(A) of the FD&C Act).

⁵ FDA is also amending the statutory citation for the device definition included in § 809.3 (21 CFR 809.3) to reflect that it is now codified at section 201(h)(1) of the FD&C Act.

General controls include, but are not limited to, provisions that relate to establishment registration and device listing; premarket notification; prohibitions against adulteration and misbranding (*e.g.*, labeling that fails to bear adequate directions for use); recordkeeping and reporting, including adverse event reporting and reporting of corrections and removals initiated to reduce a risk to health posed by the device or to remedy a violation of the FD&C Act caused by the device which may present a risk to health; investigational device exemption (IDE) requirements;⁶ and CGMP requirements. These controls apply to all devices unless an exemption applies.

Class II devices are those devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, post-market surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions the Agency deems necessary to provide such assurance (section 513(a)(1)(B) of the FD&C Act).

Class III devices are those devices for which insufficient information exists to determine that general controls and special controls would provide a reasonable assurance of safety and effectiveness, and are purported or represented for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury (section 513(a)(1)(C) of the FD&C Act).

Under section 513(d)(1) of the FD&C Act, devices that were introduced or delivered for introduction into interstate commerce for commercial distribution before the enactment of the MDA on May 28, 1976 (generally referred to as “preamendments devices”) are classified after FDA: (1) receives a recommendation from a device classification panel (an FDA advisory

⁶ Under section 520(g) of the FD&C Act and part 812 of FDA’s regulations (21 CFR part 812), a clinical investigation to determine the safety and effectiveness of certain devices must be the subject of an approved IDE before such investigation may commence. If an IDE has been granted, a failure to comply with a requirement under which the device was exempted for investigational use renders the device adulterated (see section 501(i) of the FD&C Act).

committee); (2) publishes the panel’s recommendation, along with a proposed regulation classifying the device, and provides an opportunity for interested persons to submit comments; and (3) publishes a final regulation classifying the device. A preamendments device for which a classification regulation has not been promulgated is known as an “unclassified device.” Until an unclassified device type has been formally classified by regulation, the marketing of new devices within the device type requires FDA premarket review through a premarket notification (510(k)) under section 510(k) of the FD&C Act.

Devices that were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976 (generally referred to as “postamendments devices”) are classified automatically by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require approval of a premarket approval application (PMA), unless and until: (1) FDA classifies or reclassifies the device into class I or II under section 513(f)(2) or (3) of the FD&C Act, or (2) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act and part 807 of the regulations (21 CFR part 807).

Failure to comply with applicable requirements of the FD&C Act and FDA regulations may render the device adulterated and misbranded under sections 501 and 502 of the FD&C Act and may constitute a prohibited act under section 301 of the FD&C Act (21 U.S.C. 331). For a further discussion of these regulatory measures, and specifically how they help to ensure device safety and effectiveness, see section III.B.1 of this preamble.

IVDs, as defined in § 809.3 (21 CFR 809.3), are devices intended for human use and are subject to the FD&C Act. They include class I, class II, and class III devices, as well as both preamendments and postamendments devices. Like other devices, IVDs are subject to general

controls, and other applicable requirements under the FD&C Act and FDA's regulations. IVDs are also subject to specific labeling requirements in part 809 of the regulations (21 CFR part 809).

For additional discussion of how FDA's legal authorities apply to LDTs, see the "Legal Basis for the Amendment" section (section V.B) of the NPRM (88 FR 68006 at 68017) and sections VI.D and VI.E of this preamble.

B. Need for the Rule

This final rule is the culmination of years of study and deliberation by FDA and represents a significant step forward for public health. By phasing out the general enforcement discretion approach for LDTs, FDA is correcting the imbalance in its oversight between non-laboratory and laboratory IVD manufacturers--an imbalance that harms American patients. As a result of the final phaseout policy, the public will benefit from laboratory manufacturer compliance with basic FDA requirements that protect and promote public health, such as adverse event reporting, establishment registration and device listing, labeling standards, investigational use requirements and, as new IVDs enter the market or are significantly modified, CGMPs and premarket review. Compliance with these time-tested regulatory measures will put patients in a better position to understand and have confidence in IVDs regardless of where they are manufactured. FDA believes that the benefits of this rulemaking will become more and more pronounced over time, as new IVDs come on the market and as the circumstances in which we exercise enforcement discretion narrow correspondingly (as discussed in section V.B of this preamble).

FDA has considered a wide array of input on this topic. In light of that input, we have adapted our thinking and adjusted the phaseout policy in a manner that we believe best serves the public health. The final phaseout policy, as set forth in section V of this preamble, fulfills the core goal of greater oversight of laboratory-manufactured IVDs while also accounting for other key public health interests, such as helping to maintain access to those beneficial IVDs on which

patients currently rely and access to certain IVDs for which there is little financial incentive for development. This final phaseout policy reflects a careful balancing of relevant factors and, overall, will substantially promote and protect public health, both now and in the future.

1. The Device Regulatory Scheme Advances Public Health, Including as Applied to Laboratory Manufacturers

Since Congress first enacted the FD&C Act, over time and across a wide range of product areas, Congress has empowered FDA with a standard set of tools to manage the risks (and, as applicable, help assure the effectiveness) of regulated products. *See* 21 U.S.C. 393(b). These tools--such as adverse-event reporting, establishment registration and product listing, labeling standards, investigational controls, CGMPs, and premarket review--routinely appear in FDA statutory schemes because they effectively serve the public. See section IV for a more complete description of these authorities. As applied to devices, these regulatory measures help ensure product safety and effectiveness and facilitate greater information production and sharing, among other things.⁷ FDA anticipates that compliance with these regulatory measures will have equal benefit in the context of laboratory-manufactured IVDs.⁸

For example, FDA expects that laboratory compliance with MDR requirements will yield significant public health benefits. Today, clinical laboratories comply with CLIA, which means that complaints are investigated and monitored generally only on a laboratory-by-laboratory basis. That approach makes sense in light of CLIA's focus on individual laboratory operations.

⁷ *See, e.g.*, Ref. 11 (finding, for stents, that the testing required under U.S. device premarket review standards improves consumer welfare and reflects "optimal policy in terms of trading off testing versus access to innovation"--while also noting that post-market surveillance or learning could theoretically yield the same benefits as pre-market review at lower cost); Ref. 12 (noting that one benefit of "approval regulation" is the collection of "information useful to 'downstream' product users," such as physicians, who then "exhibit higher consumption and will more readily switch to superior products"); Ref. 13 ("The FDA is a critical component to the industries' success because it (1) provides appropriate reviews for safety and effectiveness, and (2) helps provide consumers with confidence that these technologies are safe and effective.").

⁸ *See, e.g.*, Ref. 14 ("Negative consequences of poorly understood or weakly applied regulatory oversight processes for laboratory developed tests have been vividly demonstrated....Failure to insist on good clinical and laboratory practices, apply rigorous standards for the design, conduct, and analysis of biomedical research, and implement safeguards to address conflicts of interest poses threats to the integrity of biomedical research and exposes patients to potential harms."); Ref. 15 ("Increasing regulatory responsibilities and requirements could encourage laboratories seeking to introduce LDTs...to prioritize tests with the greatest potential to positively affect patient care, which could reduce the clutter of available assays with limited utility.").

However, FDA is focused on identifying problems with an IVD itself--such as design or other manufacturing problems--so FDA looks for different types of errors and applies a different analysis to the MDRs it receives. Among other things, FDA aggregates MDR information across IVD types for tracking and trending, enabling the detection of issues that a single laboratory may never see. FDA has identified and helped resolve a wide range of IVD issues using this type of information (see the response to comment 165 for additional information). For example, using MDRs submitted by multiple manufacturers, FDA discovered that high dose biotin supplements were interfering with certain immunoassays (biotin is commonly used in the design of these assays), which caused inaccurate results among those tests. FDA's investigation of the issue--an issue that could apply equally to laboratory-manufactured tests--led to the redesign of multiple tests on the market (see also comment response 122). In order to maximize the value of medical device reporting, FDA's Office of Health Technology 7 (OHT7): Office of In Vitro Diagnostics, within the Office of Product Evaluation and Quality in FDA's Center for Devices and Radiological Health (CDRH), employs trained staff dedicated to the review of MDRs for each IVD product code. These efforts help ensure that FDA catches and addresses potentially problematic IVDs to better protect the public.

Compliance with registration and listing requirements will also have substantial public health value. The collection of this information provides FDA with the location of device establishments and all devices manufactured at those establishments. Knowledge of the location where devices are manufactured allows for effective planning, coordinating, and scheduling of inspections, ensuring that FDA has visibility into the operations and practices at different manufacturing facilities. Through inspections, FDA has been able to determine when manufacturers have deficient processes, such as failure to investigate complaints and adverse events (which can signal larger problems, as just described). Although CLIA inspections occur for laboratories, such inspections do not have the same focus on design issues, for example, such as design changes that fundamentally alter the IVD's safety or effectiveness and present novel

risks to patients. In addition, compliance with listing requirements will give FDA better information about the universe of IVDs on the market. With respect to the biotin interference issue discussed earlier, for example, FDA's investigation led to the redesign of affected tests in FDA's listing database, but FDA did not have insight into laboratory developed tests on the market that might have the same issue because they were not in the database. It is possible that laboratories today are *still* manufacturing and offering tests with inaccurate results due to biotin interference. With greater listing information, FDA can better protect the public through more comprehensive remediation efforts, among other things. FDA's publicly accessible registration and listing database also gives the public greater knowledge of IVD manufacturers and the range of IVDs on the market, which will benefit patients and providers who seek to better understand the different testing options that are available and the source and location of those testing options. Right now, as noted in the FRIA, there is no reliable inventory of IVDs on the market. More comprehensive information will do a great service to the public and improve patient care.

Laboratory compliance with FDA labeling requirements will also materially advance public health, because it will provide for the availability of a consistent set of information critical to understanding the IVD, whether the IVD is manufactured by a laboratory or another manufacturer. The labeling requirements in § 809.10 (21 CFR 809.10) require IVD manufacturers to disclose basic facts about an IVD that can inform a doctor or patient's selection decisions, such as the intended use, limitations, and performance characteristics of the test. Today, ordering physicians do not necessarily have access to this standardized set of information for IVDs offered as LDTs, and therefore may lack the information needed to understand the use and performance of tests for their intended uses, make decisions in the context of an individual patient's needs, and pass on relevant information to their patients. Laboratory compliance with labeling requirements will mean that laboratories both compile and provide access to this type of information, which will facilitate knowledge transfer and, consequently, more informed healthcare decisions. Labeling also provides a frame of reference for evaluating a manufacturer's

promotional claims, helping FDA determine, for example, whether manufacturers may be misleading the public about the safety or effectiveness of their IVDs. Based on the various lawsuits cited in the NPRM (88 FR 68006 at 68012), FDA is aware that such promotion may be taking place and should be addressed.

FDA is also aware that, today, laboratories are conducting IVD clinical investigations without complying with FDA requirements, including the requirement to submit an IDE application for FDA review before beginning studies involving “significant risk” IVDs. When this occurs, subjects may be enrolled in studies that lack key human subject protections. Among other things, such investigations may lack an appropriate evaluation of whether, for example, the informed consent documents that are provided to potential subjects contain adequate information about the reasonably foreseeable risks or potential benefits of participation in the study. Such investigations of significant risk IVDs may also lack review by FDA to evaluate whether there are sufficient data to justify use of a significant risk IVD in the proposed study population. As explained in an FDA memorandum to file that was part of the record for this rulemaking, FDA is aware of circumstances in which laboratories have failed to conduct appropriate analytical validation studies to support the use of tests in clinical investigations (Ref. 16). In these instances, in the absence of FDA review of these investigations, subjects may have been enrolled in studies that exposed them to safety risks with little potential for benefit or for generating useful information.

Laboratory compliance with CGMP requirements will benefit the public as well. The Quality System Regulation (QSR) requires manufacturers to establish procedures for the consistent, quality manufacturing of devices. FDA recently issued comprehensive amendments to harmonize the QSR with international quality management system requirements (89 FR 7496, February 2, 2024). Under FDA’s quality system (QS) requirements, design controls are a key area of focus, and an area that is distinct from CLIA (see the response to comment 188 for further information). Design controls require manufacturers to have procedures for generating

IVD specifications, making sure their IVDs actually meet those specifications, and confirming that those specifications conform with user needs and intended use(s). By establishing and following a set system of documentation, manufacturers approach device design and modifications systemically, ensuring that the original design and any changes have been properly evaluated and do not have unintended consequences. In 1990, Congress specifically granted FDA authority to issue design control requirements after the Agency found that 44 percent of the quality problems that had led to voluntary recall actions between 1983 and 1989 were due to design errors or deficiencies, and the Agency promulgated corresponding QS regulations in 1996 (61 FR 52602, October 7, 1996). Design controls play such a key role because, as FDA explained when it issued those regulations, “[t]he intrinsic quality of devices, including their safety and effectiveness, is established during the design phase” (61 FR 52602 at 52615). Other QS requirements help ensure effective and appropriate design, such as acceptance activities, corrective and preventive actions, and records requirements. Although FDA recognizes that compliance with the QS requirements is associated with relatively higher costs for laboratories, and has taken that fact into account in crafting the phaseout policy, FDA believes laboratory compliance with the requirements generally will advance public health.

Finally, premarket review is one of FDA’s most important tools for protecting and promoting public health. Through premarket review, the Agency evaluates the scientific information supporting the analytical validity, clinical validity, and safety of high- and moderate-risk IVDs, which helps ensure the IVD’s safety and effectiveness before it reaches a patient. In FDA’s experience, premarket review serves an important gatekeeping function regardless of whether an IVD is manufactured by a laboratory or another manufacturer. For example, FDA has received submissions for IVDs offered as LDTs showing that laboratories do not always properly validate tests or have sound clinical data to support a test’s intended use (Ref. 16). If marketed as originally presented to FDA, many of these tests could have led to missed diagnoses or misdiagnoses, improper patient management decisions, or missed opportunities for beneficial

treatment. Through premarket review, FDA works with applicants to obtain adequate data, determine whether a device works as intended, and refine labeling to reflect the intended use and limitations of an IVD. This process motivates the development of robust scientific data on safety and effectiveness⁹ and gives patients confidence that an independent, expert third party has determined that patients can rely on these IVDs. FDA has recognized circumstances in the final phaseout policy in which the benefits of laboratory compliance with premarket review requirements are outweighed by other public-health considerations. The Agency will exercise enforcement discretion in those circumstances, as described below. Apart from these circumstances, FDA expects that laboratory compliance with premarket review requirements will have a significant positive impact on public health.

2. The Oversight Approach Set Forth in This Preamble Will Advance Public Health

Those who object to this rulemaking appear to argue that the IVDs manufactured by laboratories are so fundamentally different from, or better than, other IVDs that these IVDs should not fall under the oversight scheme outlined above. But these commenters are not able to point to differences that logically sustain that position. Many laboratory-manufactured tests use the same materials and technology, are based on the same scientific principles, are intended for the same or similar purposes, are developed by those with similar expertise, require the same level of training to perform, and are marketed for the same patients as tests from other manufacturers. Although some activities of these laboratories are also subject to CLIA, CLIA is not a substitute for FDA oversight, as detailed throughout this preamble and as the Centers for Medicare & Medicaid Services (CMS) has explained.

Furthermore, a review of the evidence does not bear out the suggestion that laboratory-manufactured IVDs have higher quality or perform better than other IVDs. FDA's memorandum to file describing submissions for IVDs offered as LDTs detailed the many defects FDA has seen with laboratory validation, among other things, and described the submissions as raising

⁹ See Ref. 17.

“significant concerns” in some cases (Ref. 16). During the COVID-19 emergency, FDA’s conversations with laboratory manufacturers revealed that many were unfamiliar with what constitutes appropriate analytical and clinical validation for an IVD generally (see comment response 37 and Ref. 18). FDA’s experience is corroborated by new information in the record from New York State. New York State submitted data indicating that more than half of original applications from laboratories could not be approved by the New York State Department of Health Clinical Laboratory Evaluation Program (NYS CLEP) based on deficiencies such as “design flaws, inadequate validation data, and process problems that call into the question the reliability of the results” (Ref. 19). And in one of the only true head-to-head comparisons between IVDs offered as LDTs and the parallel FDA-authorized IVD¹⁰, the IVDs offered as LDTs were less accurate than the FDA-authorized IVD (Ref. 20). Although some commenters suggested that a reanalysis of that data supports a different conclusion, even under the reanalysis, the laboratory tests had worse performance, with only 8 of 19 laboratories correctly reporting all variants (compared to 7 in the original analysis). For additional information about the analysis and reanalysis, see comment responses 34 and 38.¹¹

In short, based on the information before us, we do not believe that the general enforcement discretion approach for LDTs should continue. Today, IVDs offered as LDTs do not have appropriate assurances of safety and effectiveness. At least one survey suggests that the public agrees.¹² Therefore, FDA is phasing out the general enforcement discretion approach for LDTs, as explained in more detail in section V.

However, FDA also recognizes the effect that its longstanding enforcement discretion approach has had on the market, the role that laboratory-manufactured tests play in modern

¹⁰ For purposes of this preamble, “FDA-authorized” refers to FDA permitting the marketing of a device via the premarket approval, 510(k), De Novo classification, Biologics License Application (BLA), or Humanitarian Device Exemption (HDE) pathway and to devices that are exempt from premarket notification. This term does not include devices authorized for emergency use under section 564 of the FD&C Act.

¹¹ For additional discussion of evidence relevant to IVDs offered as LDTs, see section III.B.2 of the NPRM (88 FR 68006 at 68010-12).

¹² Ref. 21 (“When presented with information on the differences between FDA regulation and CMS oversight, most participants supported FDA having oversight over all diagnostic tests.”).

healthcare, and the presence of other expert regulatory bodies. Many comments emphasized these considerations. FDA agrees with certain comments' concern, for example, that expecting compliance with full QS and premarket review requirements for all currently marketed IVDs offered as LDTs could lead to the loss of access to safe and effective IVDs on which patients currently rely, and we are issuing an enforcement discretion policy to address that issue (see section V.B.3). FDA also agrees with the concern that, for certain LDTs for unmet needs, expecting full compliance with FDA requirements could lead to loss of access to tests for unmet needs for which laboratories cannot recoup the costs of compliance; we are issuing an enforcement discretion policy to address that issue in circumstances in which certain risk mitigations apply (see section V.B.3). FDA has also incorporated enforcement discretion policies recognizing the regulatory role that other Federal and State entities play (see sections V.B.1 and 2). In these and other ways, FDA has crafted a tailored phaseout policy that balances the important public health considerations at issue in this rule.

We anticipate that the final phaseout policy will provide significant benefits to the public. As indicated in the FRIA, the anticipated benefits significantly outweigh the anticipated costs. Through this Agency action, patients will have greater assurance that the IVDs used in their care are safe and effective, a significant step forward for public health. In addition, by applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, FDA will reduce regulatory uncertainty, which will give stakeholders more stability, clarity, and confidence, and facilitate investment in the development of innovative IVDs (Ref. 22). FDA oversight will help to support coverage and reimbursement determinations for IVDs offered as LDTs, which we anticipate will make certain IVDs offered as LDTs for which there is a reasonable assurance of safety and effectiveness more affordable for patients. And with increased oversight, FDA will be able to help promote adequate representation in validation studies, and transparency regarding potential differential performance and unknown performance

in certain patient populations, which will ultimately help advance health equity (see comment response 221 for additional information).

FDA expects the benefits of the phaseout policy to become more and more pronounced over time, as new tests come on the market and as the circumstances in which we exercise enforcement discretion narrow correspondingly. Diagnostic testing is increasingly important; for example, as time goes on, more novel treatments will require use of a specialized test to identify patients likely to benefit from those treatments.¹³ Furthermore, IVDs offered as LDTs are a growing sector of the diagnostic testing market (Ref. 4). FDA anticipates that IVDs will continue to become more complex and play a greater role in modern healthcare (Ref. 3). The U.S. LDT market size is anticipated to grow 6 percent from 2023 to 2030 due to varying factors including increased use in personalized medicine and rising prevalence of chronic diseases. (*Id.*) FDA is therefore taking steps to help ensure that IVDs are safe and effective regardless of where they are manufactured, so that both now and in the future, patients can have confidence about the tests used in their care.

C. Summary of Comments on the Notice of Proposed Rulemaking

In the *Federal Register* of October 3, 2023, FDA published a rule proposing an amendment to its regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer is a laboratory, and proposing a policy under which FDA would phase out its general enforcement discretion approach for LDTs. The comment period for the NPRM closed on December 4, 2023. FDA received more than 6,500 comments on the NPRM from a variety of entities including medical device associations, members of the medical device and pharmaceutical industries, medical and healthcare professional associations, hospitals and academic medical centers (AMCs), accreditation organizations, other advocacy organizations, government agencies, and individuals.

¹³ See, e.g., Ref. 23 (“Demand is increasing in the CDx market, due to the paradigm shift to precision medicine.”).

Comments supporting FDA’s proposal pointed to problems with LDTs, concerns about the significant impact of problematic LDTs on patients and the treatment decisions of healthcare providers, and the need for increased oversight of LDTs by FDA. Some comments also emphasized the importance of creating a “level playing field” between laboratory and non-laboratory manufacturers of IVDs, and described how phasing out the general enforcement discretion approach for LDTs would incentivize innovation by non-laboratory IVD manufacturers.

Some comments raised concerns or requested clarification regarding the following:

- the evidence related to the safety or effectiveness of IVDs offered as LDTs,
- the sufficiency of regulation by CMS and other non-FDA entities,
- FDA’s legal authority to regulate LDTs,
- the impact of the phaseout policy on access to and the pricing of IVDs offered as LDTs,
- the impact of the phaseout policy on test innovation,
- the impact of the phaseout policy on small laboratories,
- the impact of the phaseout policy on specific patient populations, including underrepresented and underserved populations,
- the details of the phaseout policy,
- the types of IVDs offered as LDTs for which FDA intends to continue the general enforcement discretion approach and generally not enforce some or all applicable requirements, and
- FDA’s implementation of the phaseout policy and the resources needed for such implementation.

D. General Overview of the Final Amendment to the Definition of In Vitro Diagnostic Products

FDA is amending its regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory. This amendment reflects that the device definition in the FD&C Act does not differentiate between entities manufacturing the

device, and provides further clarity, including for stakeholders affected by the accompanying changes to FDA's general enforcement discretion approach for LDTs.

FDA is also amending the statutory citation for the device definition included in § 809.3 to reflect amendments to section 201(h) of the FD&C Act as a result of the enactment of the Safeguarding Therapeutics Act (Pub. L. 116-304). For many years, the definition of "device" had been codified at section 201(h) of the FD&C Act. Upon enactment of the Safeguarding Therapeutics Act, the definition of "device" was redesignated as paragraph (h)(1) and a new definition of "counterfeit device" was codified at paragraph (h)(2).

FDA considered comments received on the NPRM, as discussed in more detail throughout this preamble, and has made no changes to the amendment.

E. General Overview of the Final Phaseout Policy

FDA has had a general enforcement discretion approach for most LDTs.¹⁴ FDA is phasing out this general enforcement discretion approach so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs. The phaseout is intended to help assure the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance.

Following a 4-year phaseout period, FDA will no longer have a general enforcement discretion approach for LDTs. The phaseout policy includes the following five stages for IVDs offered as LDTs (a term discussed further in section V.A.1):

- Stage 1: beginning 1 year after the publication date of this final rule, FDA will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (21 CFR 820.198) (complaint files);

¹⁴ As discussed further in section V.A.2, FDA's general enforcement discretion approach has not applied to certain categories of LDTs. For these categories of LDTs, FDA has generally expected applicable requirements to be met, and in the NPRM we proposed that this approach be maintained (88 FR 68006 at 68021). After considering comments received on this topic we are not changing that approach for these categories with the phaseout policy described in this preamble.

- Stage 2: beginning 2 years after the publication date of this final rule, FDA will expect compliance with requirements not covered during other stages of the phaseout policy, including registration and listing requirements, labeling requirements, and investigational use requirements;
- Stage 3: beginning 3 years after the publication date of this final rule, FDA will expect compliance with QS requirements under part 820 (21 CFR part 820) (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1);
- Stage 4: beginning 3½ years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for high-risk IVDs offered as LDTs (IVDs that may be classified into class III or that are subject to licensure under section 351 of the Public Health Service Act), unless a premarket submission has been received by the beginning of this stage in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review; and
- Stage 5: beginning 4 years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs (that require premarket submissions), unless a premarket submission has been received by the beginning of this stage in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review.

The phaseout policy includes targeted enforcement discretion policies for certain categories of IVDs manufactured by a laboratory, as explained in more detail in sections V.B. and V.C. For example, as proposed in the NPRM, FDA generally does not intend to enforce requirements under the FD&C Act and FDA’s regulations for “1976-Type LDTs” (as described in section V.B.1); Human Leukocyte Antigen (HLA) tests that are designed, manufactured, and used within a single laboratory certified under CLIA that meets the requirements to perform high-complexity histocompatibility testing when used in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing, for HLA antibody screening and

monitoring, or for conducting real and “virtual” HLA crossmatch tests; and tests intended solely for forensic (law enforcement) purposes (88 FR 68006 at 68022).

In addition, FDA considered comments received on the proposed phaseout policy and, based in part on those comments, made various changes to the phaseout policy, which include the addition of the following enforcement discretion policies:

- FDA intends to exercise enforcement discretion and generally not enforce requirements for LDTs manufactured and performed within the Veterans Health Administration (VHA) or the Department of Defense (DoD);
- FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP¹⁵;
- FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records))^{16,17} for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system;
- FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to

¹⁵ For purposes of this preamble, FDA uses the phrase “LDTs approved by NYS CLEP” to refer to LDTs that are approved, conditionally approved, or within an approved exemption from full technical documentation, under NYS CLEP. These three categories of LDTs are discussed further below in section V.B.2. Other LDTs, including “LDTs used in Clinical Trials” and “Tests Not Subject to Evaluation” which are described on NYS CLEP’s website (Ref. 24), are not considered “LDTs approved by NYS CLEP” and are not within the enforcement discretion policy with respect to premarket review requirements described in section V.B.2. For additional discussion of the NYS CLEP premarket review program, see section V.B.2.

¹⁶ When the final rule to amend part 820 takes effect in February 2026, the comparable requirements can be found in International Organization for Standardization (ISO) 13485 subclause 4.2 as modified by part 820.

¹⁷ FDA recognizes that part 820, subpart M (Records) includes cross-references to §§ 820.20, 820.22, 820.40, and 820.50 (21 CFR 820.20, 820.22, 820.40, and 820.50). For the categories of IVDs discussed in section V.B.3 of this preamble, FDA generally expects compliance with requirements under subpart M but not §§ 820.20, 820.22, 820.40, and 820.50, or comparable provisions of ISO 13485 in accordance with the amendments to part 820 once that rule takes effect in February 2026.

the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as described in section V.B.3; and

- FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for non-molecular antisera LDTs for rare red blood cell (RBC) antigens where such tests are manufactured and performed in blood establishments, including transfusion services and immunohematology laboratories and where there is no alternative available to meet the patient's need for a compatible blood transfusion.

These enforcement policies do not apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B.

IV. Legal Authority

FDA is issuing this final rule under the Agency's general rulemaking authorities and statutory authorities relating to devices. These authorities include sections 201(h)(1), 301, 501, 502, 510, 513, 514, 515, 518, 519, 520, 701, 702, 704, and 801 of the FD&C Act and section 351 of the PHS Act. In particular:

- Under section 201(h)(1) of the FD&C Act, a device is defined as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (A) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.”

- Section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act.

For additional descriptions of some of the authorities referenced above, see section III.A of this preamble. For additional discussion of how these legal authorities apply to LDTs, see the “Legal Basis for the Amendment” section (section V.B) of the NPRM (88 FR 68006 at 68017) and sections VI.D and VI.E of this preamble.

V. Phaseout Policy

Based on the considerations set forth in the NPRM and this preamble, including the public comments discussed in section VI.F below, FDA is phasing out the general enforcement discretion approach for LDTs in stages, as described in more detail below. FDA’s intent is that following a 4-year phaseout period, IVDs offered as LDTs generally will be expected to meet applicable requirements, with several enforcement discretion policies for certain categories of IVDs manufactured by a laboratory as discussed further below.

We note that these policies may not be the only enforcement discretion policies applicable to these IVDs, and other enforcement discretion policies not addressed in this phaseout policy may apply to certain IVDs. As discussed in the NPRM, FDA has adopted and intends to continue adopting enforcement discretion policies for certain types of IVDs in certain circumstances, as appropriate (88 FR 68006 at 68021). For example, FDA issued final guidance documents with enforcement discretion policies for certain COVID-19 and mpox tests at the beginning of each declared emergency and, concurrent with this final rule, is issuing a draft guidance document with an enforcement policy for certain IVDs for immediate response to a chemical, biological, radiological, or nuclear (CBRN) agent in the absence of a declaration under section 564 of the FD&C Act (21 U.S.C. 360bbb-3).

Although FDA is phasing out its current general enforcement discretion approach over a period of years, the phaseout policy does not in any way alter the fact that it is illegal to offer IVDs without complying with applicable requirements. Regardless of the phaseout timeline

and enforcement discretion policies for certain IVDs discussed below, FDA retains discretion to pursue enforcement action for violations of the FD&C Act at any time, and intends to do so when appropriate.

The details of FDA’s final phaseout policy, including the scope, subsidiary enforcement discretion policies, and stages, are set forth below.

A. Scope

1. IVDs Within the Scope of the Phaseout Policy

While FDA’s general enforcement discretion approach has been focused on LDTs,¹⁸ FDA has determined to apply a broader scope for the phaseout policy, consistent with FDA’s proposal in the NPRM (88 FR 68006 at 68021).¹⁹ Specifically, the phaseout policy applies to IVDs that are *manufactured and offered* as LDTs by laboratories that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing, and used within such laboratories,²⁰ even if those IVDs do not fall within FDA’s traditional understanding of an LDT because they are not designed, manufactured, and used within a single laboratory. Throughout this preamble, these IVDs are referred to as “IVDs offered as LDTs.”²¹ FDA is adopting this scope because it recognizes that not all laboratories have understood the limited nature of FDA’s general enforcement discretion approach and have been offering IVDs based on the approach even when those IVDs do not fit what FDA

¹⁸ As discussed elsewhere in this preamble, FDA has generally considered the term “laboratory developed test (LDT)” to mean an IVD that is intended for clinical use and that is designed, manufactured, and used within a single CLIA-certified laboratory that meets the regulatory requirements under CLIA to perform high complexity testing.

¹⁹ However, certain enforcement discretion policies described in sections V.B and V.C apply only to LDTs.

²⁰ Other laboratories would be out of compliance with CLIA regulations if they were developing and performing tests that are not FDA authorized. Such tests have never fallen within FDA’s general enforcement discretion approach (see, e.g., Refs. 25-27).

²¹ We note that “IVDs offered as LDTs” does not include IVDs manufactured or used *outside* of a laboratory, including collection devices. FDA’s statements and actions have shown that the Agency has expected compliance where, for example, CLIA is inapplicable (e.g., manufacturing outside of a laboratory and collection devices). See, e.g., 61 FR 10484 (“*in-house* developed tests have not been actively regulated by the Agency”) (emphasis added); Ref. 23 (describing an LDT as an IVD that is “designed, manufactured, and *used* within a single laboratory”) (emphasis added); *United States v. Undetermined No. of Unlabeled Cases*, 21 F.3d 1026 (10th Cir. 1994) (FDA enforcement action against a laboratory that “purchased specimen containers, repackaged them into kits which included instruction sheets, and forwarded them along with consent forms to insurers to collect specimens”); Ref. 28 (compliance action regarding a blood lead testing system manufactured outside of a laboratory but for use by a laboratory); Ref. 29 (compliance action involving a laboratory and a sample collection kit).

generally considers to be an LDT. FDA has determined that this approach will help facilitate uniform compliance going forward.

2. IVDs Outside the Scope of the Phaseout Policy

Although FDA is adopting a broader scope for the phaseout policy, it does not intend to sweep in certain IVDs that were excluded from the general enforcement discretion approach, as reflected in compliance patterns, multiple public FDA actions and communications, or both. In particular, the general enforcement discretion approach has never applied to the following tests:

a. Tests that are intended as blood donor screening or human cells, tissues, and cellular and tissue-based products (HCT/P) donor screening tests required for infectious disease testing under § 610.40 (21 CFR 610.40) and § 1271.80(c) (21 CFR 1271.80(c)), respectively, or required for determination of blood group and Rh factors under § 640.5 (21 CFR 640.5).

Under the cited regulations, a blood or HCT/P establishment must not use a test for the purposes listed here unless the test is authorized by FDA for such use. Blood and HCT/P establishments must register with FDA and are subject to FDA inspection (see parts 207, 607, 807, and 1271 (21 CFR parts 207, 607, 807, and 1271)). FDA's general enforcement discretion approach for LDTs has never applied to these tests because these tests are a critical part of the overall process of ensuring the safety of blood and blood components and HCT/Ps by preventing infectious disease transmission and incompatible blood transfusions which can have life-threatening consequences (see, e.g., Refs. 30 and 31). Based on FDA experience, establishments have been generally complying with the requirements to use authorized tests under §§ 1271.80(c), 610.40, and 640.5. FDA addresses comments related, in part, to this category of tests in sections VI.L.14 and VI.L.15.

b. Tests intended for emergencies, potential emergencies, or material threats declared under section 564 of the FD&C Act. After all previous declarations under section 564(b), FDA has generally expected LDTs to comply with applicable requirements in the FD&C Act and

FDA regulations. FDA’s general enforcement discretion approach has not applied to these tests because of the significant risk posed by the disease (as signified by the unusual step of issuing a declaration) and because false results can have serious implications for disease progression and public health decision-making, in addition to the individual patient’s care. As it has done in other areas, FDA has adopted (and may continue to adopt) specific enforcement discretion policies for such tests (see, e.g., Refs. 32 and 33). In addition, consistent with the Government Accountability Office (GAO)’s 2022 recommendation that “FDA should develop a policy for the use of enforcement discretion regarding unauthorized tests in future public health emergencies” (Ref. 34), FDA is issuing a draft guidance document, concurrent with this final rule, on factors to consider in adopting such enforcement discretion policies. FDA has communicated its expectations regarding tests for emergency use in final guidance and elsewhere, including “It has come to our attention” letters posted on FDA’s website and other public communications (see, e.g., Refs. 27, 32 to 37). FDA addresses comments related, in part, to this category of tests in section VI.L.10.

c. Direct-to-consumer tests. FDA’s general enforcement discretion approach has not applied to tests intended for consumer use (without meaningful involvement by a licensed healthcare professional), given the greater risks to patients presented by these tests (see, e.g., Refs. 28 and 39 to 44). FDA’s enforcement discretion approach for LDTs was originally premised, in part, on the participation of medical professionals to help determine whether a particular test was appropriate, counsel patients on the significance and limitations of a test, assist in interpreting results, assess how the results fit in the overall clinical picture, and consider next steps. When patients order tests, receive results, or make decisions (such as a decision to stop medication) without this expert intermediary, there is a heightened need for FDA oversight. FDA addresses comments related, in part, to this category of tests in section VI.L.1.

For these categories of tests, FDA has generally expected applicable requirements to be met, and we are not changing that approach with the phaseout policy. FDA intends to continue to enforce all applicable requirements for these categories of tests. Neither the phaseout policy nor any subsidiary enforcement discretion policies described in sections V.B and V.C apply to these tests.

Finally, as further discussed in the NPRM, tests manufactured and offered for use exclusively for public health surveillance are distinct from other tests where: (1) they are intended solely for use on systematically collected samples for analysis and interpretation of health data in connection with disease prevention and control and (2) test results are not reported to patients or their healthcare providers (88 FR 68006 at 68023). The results of these tests are generally used for trending on a population basis or public health outbreaks, where the test results are not intended for clinical decision making. FDA received several comments on these tests (see section VI.L.6), and for the reasons discussed in the NPRM (88 FR 68006 at 68023) and in our responses to those comments, we continue to believe that these tests should not be affected by the phaseout policy.²²

B. Enforcement Discretion Policies

FDA is phasing out the general enforcement discretion approach for LDTs so that IVDs manufactured by laboratories will generally fall under the same enforcement approach as other IVDs. For certain IVDs, however, FDA intends to exercise enforcement discretion and generally not enforce all or some applicable requirements, for the reasons discussed further below. Specifically, and as described further in section V.B.1, FDA intends to exercise enforcement discretion and generally not enforce all applicable requirements for 1976-Type LDTs, certain HLA tests, tests intended solely for forensic (law enforcement) purposes, and LDTs manufactured and performed within DoD or VHA. As described further in section V.B.2, FDA

²² Surveillance tests are not used for individual decision-making. Screening tests are distinct from public health surveillance tests and do fall within the phaseout policy.

also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs that are approved by NYS CLEP. In addition, and as described further in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system, currently marketed IVDs offered as LDTs, and certain non-molecular antisera LDTs for rare RBC antigens.

As noted above, these policies do not apply to the tests described in section V.A.2. Moreover, in an emergent situation (see additional discussion of this time period below), these policies do not apply to tests that are: (1) intended to detect or diagnose a serious or life-threatening disease or condition that may be attributed to a newly identified, previously unknown, or unusual CBRN agent or agents; or a known agent or agents that results in a newly identified or unusual clinical presentation of such a disease or condition; and (2) needed for immediate response to a potential case or cases of such disease or condition for which there is no adequate, authorized, and available alternative. FDA is proposing a separate enforcement policy for some such tests in a concurrently issued draft guidance entitled “Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564.” As discussed in that draft guidance, that proposed enforcement policy would be for tests that are intended to help ensure the government’s coordinated and effective public health response and so is limited to certain tests and certain laboratories, such as those that are U.S. Government (USG) laboratories, State or local public health laboratories, or other laboratories that have agreements with the USG.²³ FDA believes that the proposed policy

²³ For tests that meet the description included at the beginning of this paragraph but that would not otherwise fall within the proposed policy described in the draft guidance because, for example, they are manufactured by entities that fall outside the scope of the draft guidance, FDA is not proposing an enforcement discretion policy in the draft guidance. For such tests, FDA generally will expect compliance with applicable FDA requirements in line with the phaseout policy during an emergent situation, and outside of an emergent situation, these tests could potentially fall within an enforcement discretion policy described in section V.B. of this preamble.

in that draft guidance (and not the enforcement discretion policies described in section V.B of this preamble) would be appropriate for such tests during the limited time period described in the draft guidance--specifically, during an emergent situation.²⁴ We note that prior to an emergent situation and after an emergent situation has been resolved, when there is not a critical need for a coordinated and immediate public health response and where the implications of false results may not have as serious implications for public health decision-making, such tests may fall within the enforcement discretion policies described in section V.B of this preamble.

As with any enforcement discretion policy, FDA may update any of these policies as circumstances warrant or if the circumstances that inform these policies change, consistent with FDA's good guidance practices (21 U.S.C. 371(h), § 10.115). Notably, these enforcement discretion policies do not confer lawful marketing status on any IVD being marketed as described in the policies. These policies do not in any way alter the fact that it is illegal to market an IVD that lacks required premarket authorization or is otherwise in violation of the FD&C Act, the PHS Act, or FDA regulations. These policies set forth FDA's general priorities and, consistent with FDA's public health mission, FDA intends to take action to enforce applicable requirements for IVDs (including IVDs described in these policies) as appropriate, taking into account any public health concerns as evaluated on a case-by-case basis.²⁵ For example, if FDA receives reports, or otherwise learns of information, that raise safety or effectiveness concerns with an IVD that falls within an enforcement discretion policy, FDA generally intends to take action with respect to requirements applicable to that specific IVD.

1. Enforcement Discretion Policies With Respect to All FDA Requirements

For several categories of tests, FDA intends to continue the general enforcement discretion approach and generally not enforce any applicable requirement because tests in these

²⁴ Prior to finalization of that draft guidance, FDA intends to act consistent with the relevant policies for LDTs included in this final rule and will consider whether to update any policies herein as a result of any changes to the proposed enforcement policy described in the draft guidance, when finalized.

²⁵ See *Heckler v. Chaney*, 470 U.S. 821, 835 (1985) (providing that the FD&C Act's enforcement provisions commit broad discretion to the Secretary to decide how and when they should be exercised).

categories are, in our experience, unlikely to pose significant risks or are conducted in circumstances that themselves will mitigate the risks. One such category of tests is referred to in this preamble as “1976-Type LDTs.” Such tests have the following characteristics common among LDTs offered in 1976: (1) use of manual techniques (without automation) performed by laboratory personnel with specialized expertise; (2) use of components legally marketed for clinical use; and (3) design, manufacture, and use within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing. The characteristics associated with LDTs offered in 1976 resulted in the emergence of FDA’s general enforcement discretion approach for LDTs, and the specific characteristics listed above provide the greatest risk mitigation among the characteristics that were commonly associated with LDTs offered in 1976 (discussed in section III). Based on changes to the LDT landscape since 1976, the risks associated with most modern LDTs are generally much greater today than they were in 1976; however, for tests that share the characteristics listed above, FDA has determined that the risks are sufficiently low such that FDA’s general enforcement discretion approach for LDTs should continue to apply (see section VI.L.3 for a discussion of the comments on this topic and FDA’s responses to those comments). These tests might include, for example, immunohistochemistry tests that involve no automated preparation or interpretation, but would not include, for example, lateral flow tests, as they do not generally rely on laboratory personnel expertise. This enforcement discretion policy does not apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B. FDA intends to consider whether guidance containing additional discussion and examples of tests that may fall within this category would be helpful, and would issue any such guidance in accordance with good guidance practices (see § 10.115).

Another category of such tests is HLA tests that are designed, manufactured, and used within a single laboratory certified under CLIA that meets the requirements to perform high-complexity histocompatibility testing when used in connection with organ, stem cell, and tissue

transplantation to perform HLA allele typing, for HLA antibody screening and monitoring, or for conducting real and “virtual” HLA crossmatch tests (hereinafter “HLA tests for transplantation”). Physicians must often make prompt decisions about transplantation based on medical judgment regarding their patient’s condition and degree of mismatch between the donor and patient should an organ, stem cells, or tissue become available. Because new alleles are continuously identified, and the need for assessing degree of crossmatch is generally urgent, modifications to HLA tests for transplantation are often made rapidly in response to urgent situations. Further, these tests are often individualized within each medical facility; for example, they include reagents that reflect local HLA polymorphisms and patient demographics.

In addition, oversight under certain Federal programs helps to mitigate the risks of harm from inaccurate and unreliable HLA tests for transplantation. For example, the National Organ Transplant Act (NOTA) of 1984 created the Organ Procurement and Transplant Network (OPTN). NOTA, as amended (42 U.S.C. 273 *et seq.*), and the OPTN Final Rule, 42 CFR part 121, establish a comprehensive system for the safe and equitable allocation, distribution, and transplantation of donated organs. The OPTN Final Rule and OPTN bylaws and policies govern operation of all member transplant hospitals, organ procurement organizations, and histocompatibility laboratories in the United States. The Stem Cell Therapeutic and Research Act of 2005 (Pub. L. 109-129), as amended, authorizes a national registry (“Be the Match Registry”) to support patients in need of bone marrow or umbilical cord blood transplants, which is operated under Federal contracts by the National Marrow Donor Program® (NMDP) (Ref. 45). NMDP sets forth minimum requirements for organizations working through the NMDP to facilitate stem cell transplants (Refs. 46 and 47).

OPTN has requirements for performance of HLA typing, antibody screening, and crossmatching tests, and NMDP requires HLA typing for donors and potential recipients for stem cell transplants facilitated by the Be the Match Registry, as well as reporting of test results to

NMDP (Refs. 47 and 48). Both OPTN and NMDP have procedures in place for identifying, investigating, and reporting discrepant tests results (Refs. 48 and 49).

In addition to these safeguards designed to identify and resolve potentially inaccurate results, each OPTN member histocompatibility laboratory must, among other things, meet specified American Society for Histocompatibility and Immunogenetics (ASHI) and/or College of American Pathologists (CAP) standards as a condition of OPTN membership (Ref. 50). NMDP similarly requires histocompatibility laboratories used by U.S. transplant centers and donor centers to be accredited by CAP and/or ASHI (Refs. 46, 51 and 52). Both ASHI and CAP standards have provisions that specifically address OPTN and/or NMDP requirements for histocompatibility laboratories that perform tests for those programs. Importantly, as discussed below, FDA does not believe that a CAP or ASHI accreditation of a laboratory, on its own, is sufficient to mitigate risk and provide assurance of the safety and effectiveness for all IVDs offered as LDTs by the accredited laboratory. However, we consider the fact that OPTN and NMDP require adherence to CAP and/or ASHI standards, including provisions specific to OPTN and NMDP requirements, to be one factor that helps mitigate risk of inaccurate results or unreliable HLA tests for transplantation. After considering this factor in combination with the protections provided through the programs described above and the urgent circumstances in which HLA tests for transplantation may be modified and performed, as well as the comments received on our proposed approach to HLA tests for transplantation, FDA intends to continue the general enforcement discretion approach for these tests. We note that this enforcement discretion policy does not apply to HLA tests used for blood transfusion, which are highly standardized across institutions, nor does it apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B.

An additional category of such tests is tests intended solely for forensic (law enforcement) purposes. FDA has had an enforcement discretion approach for such tests for over 20 years and that approach applies to such tests regardless of whether they are offered as an

LDT. *See, e.g.*, 65 FR 18230, April 7, 2000. Tests used in the law enforcement setting are subject to protections and requirements associated with the judicial process that mitigate risk related to test accuracy and sample collection and that generally are not available in the home, workplace, insurance, and sports settings. These protections include the use of rules of evidence in judicial proceedings and legal representation of the accused (i.e., the person being tested) through the judicial process during which the accuracy of the test may be raised during the adjudication. This enforcement discretion policy does not apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B.

A final category of such tests is LDTs²⁶ manufactured and performed within DoD or VHA. This policy applies only to LDTs used for patients that are being tested and treated within the DoD or VHA. In the NPRM, FDA sought comment on whether it would be appropriate to continue the general enforcement discretion approach, such that FDA generally would not enforce any applicable device requirements, “where outside programs can be leveraged” (88 FR 68006 at 68024). FDA mentioned programs within VHA as an example, and we received several comments stating that FDA should continue the general enforcement discretion approach for LDTs manufactured and performed by VHA, generally on the grounds that it would avoid “duplicating regulatory oversight regimes” and promote the efficient use of resources. Two comments suggested that FDA should not continue the general enforcement discretion approach for LDTs manufactured and performed by VHA because VHA’s program is not in alignment with FDA regulation (though one of these comments supported “leveraging” outside programs “in principle”). FDA received one comment, submitted by DoD, which stated that FDA should maintain an enforcement discretion approach for LDTs “utilized by DoD for our service members.” Among other things, DoD emphasized “the importance of LDTs to DoD’s operational readiness and mission success,” and referenced DoD’s internal programs, including “the

²⁶ Consistent with what FDA has generally considered to be an LDT (as discussed elsewhere in this preamble), this enforcement discretion policy applies only to tests that are designed, manufactured, and used within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing.

authority, oversight, and responsibilities vested in the Assistant Secretary of Defense (Health Affairs).”

FDA recognizes that DoD and VHA have statutory mandates under 10 U.S.C. chapter 55 and 38 U.S.C. chapter 73 to provide for the care of specific populations in their systems and have existing oversight and enforcement groups within their respective systems. Based on consultation with DoD and VHA, FDA understands that both departments use and will continue to use FDA-authorized IVDs wherever available. However, to meet the needs of their patient populations (i.e., military personnel, veterans, and their families) and fulfill their mandates, DoD and VHA often manufacture unique LDTs, such as tests for diseases or chemicals to which their patients may be exposed while serving abroad but which do not exist at home. DoD and VHA have developed expertise for evaluating these unique tests, and are taking steps in consultation with FDA to track all LDTs in their systems and to ensure the analytical and clinical validity of their LDTs, the quality manufacturing of their LDTs, and the central reporting of adverse events.²⁷ Additional oversight by FDA would not be an efficient use of government resources in these circumstances.

This enforcement discretion policy does not apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B.

2. Enforcement Discretion Policies With Respect to Premarket Review Requirements

FDA also generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs²⁸ that are approved by NYS CLEP.²⁹ For these LDTs, FDA

²⁷ To the extent that VHA and DoD anticipate the need for additional resources, FDA understands that such matters will be addressed through the management of those departments.

²⁸ Consistent with what FDA has generally considered to be an LDT (as discussed elsewhere in this preamble), this enforcement discretion policy applies only to tests that are designed, manufactured, and used within a single laboratory that is certified under CLIA and meets the regulatory requirements under CLIA to perform high complexity testing.

²⁹ As noted elsewhere in this preamble, for purposes of this preamble FDA uses the phrase “LDTs approved by NYS CLEP” to refer to LDTs that are approved, conditionally approved, or within an approved exemption from full technical documentation, under NYS CLEP. These three categories of LDTs are discussed further below in this section (section V.B.2). Other LDTs, including “LDTs used in Clinical Trials” and “Tests Not Subject to Evaluation” which are described on NYS CLEP’s website (Ref. 24), are not considered “LDTs approved by NYS CLEP” and are not within the enforcement discretion policy with respect to premarket review requirements described in this section.

intends to exercise enforcement discretion and generally not enforce premarket review requirements given certain risk mitigations under NYS CLEP as discussed further below. This policy applies only to the approved version of the test (FDA is aware that some laboratories may offer different versions of an LDT depending on whether a patient specimen comes from NYS or from elsewhere). This enforcement discretion policy does not apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B.

FDA intends to phase out the general enforcement discretion approach with respect to other applicable requirements for these tests consistent with the stages described in section V.C below. In brief, for these tests, FDA intends at stage 1 to phase out the general enforcement discretion approach with respect to MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files) 1 year after publication of this final rule; at stage 2 to phase out the general enforcement discretion approach with respect to requirements not addressed in the other stages (these requirements include, e.g., registration and listing requirements and labeling requirements) 2 years after publication of this final rule; and at stage 3 to phase out the general enforcement discretion approach with respect to certain QS requirements (see below for further discussion) 3 years after publication of this final rule. See section V.C for further information.

As noted above, in the NPRM, FDA sought comment on whether it would be appropriate to continue the general enforcement discretion approach with respect to LDTs that are under NYS CLEP or certain other programs (88 FR 68006 at 68024), and we received several comments in response (see discussion in section VI.F.5 of this preamble). This policy reflects consideration of those comments. Should experience with this policy indicate that changes are warranted, FDA would consider appropriate policy changes through guidance in accordance with good guidance practices (see § 10.115).

FDA believes that NYS CLEP has a program that provides for certain mitigations that help reduce the risk of harm from inaccurate and unreliable LDTs. Specifically, as discussed further below, NYS CLEP has a program under which high risk and moderate risk LDTs generally are evaluated for analytical and clinical validity. Based on the available information, FDA believes that generally NYS CLEP's review of analytical and clinical validity of LDTs helps to mitigate the risk of harm from inaccurate and unreliable LDTs and that, rather than enforcing premarket review requirements by FDA, it would be more efficient and effective to use our resources for other oversight activities regarding IVDs offered as LDTs.

Under NYS CLEP's program, high risk LDTs require full technical review and approval prior to testing on specimens from NYS (Ref. 53). Moderate risk LDTs require full technical review but may receive conditional approval if the laboratory holds a permit in the appropriate category (Ref. 53). For classification as a moderate risk LDT under NYS CLEP, certain criteria must be met, e.g., the LDT uses well-established methodology (as defined by NYS CLEP, this includes, among other things, the laboratory having demonstrated competence for development of LDTs of the same or similar technology through multiple prior high-quality submissions) (Ref. 53). Upon notification of a moderate risk classification and conditional approval, the laboratory may offer the test (Ref. 53). Once the full technical review has been completed, the moderate risk LDT may receive approval (Ref. 53). For additional information, see NYS CLEP's Tiered Evaluation of Laboratory Developed Tests Policy (Ref. 53).

In its enforcement discretion policy with respect to premarket review requirements, FDA is including not just those moderate risk LDTs that receive full approval by NYS CLEP but also those that receive conditional approval by that agency. For LDTs receiving conditional approval, full technical review is pending and these tests may receive approval by NYS CLEP once their review has been completed. FDA does not intend to use its resources to enforce premarket review requirements for these LDTs that are under review by NYS CLEP and may eventually receive approval. However, if an LDT has its conditional approval withdrawn by NYS (e.g.,

because approval is denied after NYS CLEP completes the full technical review), the LDT would no longer be under this enforcement discretion policy as it would neither have conditional approval nor full approval.³⁰

For purposes of full technical review (as mentioned above, this applies to high risk and moderate risk LDTs), NYS CLEP requires the submission of detailed information as specified in the applicable checklist (either the general checklist or test-specific checklist) (Ref. 24). For example, under the general checklist, laboratories must submit, among other things, a description of the test target, data supporting analytical validity, data supporting clinical validity, sample test reports, standard operating procedures, and other information regarding the subject test (Ref. 54). Additionally, laboratories must submit a “Risk Attestation Form for Laboratory Developed Tests” containing additional information about the test, including a summary of intended use (including target population, methodology and technology, specimen types, and whether the intend use makes claims or direct reference to recognized diseases/conditions), whether the laboratory has full approval of other LDTs using the same test method that is used for the proposed new test, whether the methodology is well-established in the laboratory and generally accepted by the field, evidence of clinical validity, and information regarding the potential impact of an inaccurate test result (Ref. 55).

NYS CLEP also has a process for laboratories to request an exemption from full technical documentation. As described on NYS CLEP’s website, “[o]nce acceptable method validation performance has been demonstrated by the NYS approval of a representative sampling of tests that utilize a methodology that is common across many analytes/targets, the laboratory may request an exemption from the requirement to submit full method validation documentation for future test/assays that utilize the same methodology” (Ref. 24). An application for an exemption from full technical documentation must include: a written request for an exemption that identifies

³⁰ Although not relevant to our decision-making with respect to our policy regarding LDTs approved by NYS CLEP, it is our understanding, based on consultation with NYS CLEP, that withdrawal of conditional approval due to approval being denied after NYS CLEP completes the full technical review is a rare occurrence.

“the previously submitted tests to be used as the predicate submissions for the exemption”; “a standardized protocol for method validation to include a description of the laboratory’s principles and practices for assay development and initial validation”; and “laboratory-specific protocols for on-going validation, including quality control procedures and quality assurance indicators” (Ref. 24). If an exemption is approved, then a streamlined process applies to new LDTs with the same methodology under the exemption. For such new LDTs, certain information must be provided, including data on analytical and clinical validity, but this can be provided in summary form (see the Add Under Exemption Form available on NYS CLEP’s website, Ref. 24). The summary of the validation studies performed must address how analytical and clinical performance characteristics were established (see the Add Under Exemption Form available on NYS CLEP’s website, Ref. 24). Additionally, for such new LDTs, laboratories must submit sample reports for all applicable findings (see the Add Under Exemption Form available on NYS CLEP’s website, Ref. 24), a “Risk Attestation Form for Laboratory Developed Tests” containing additional information about the test, including information regarding the potential impact of an inaccurate test result (Ref. 55), and certain other information if applicable (Ref. 24). Although specific approval of new LDTs added under an approved exemption is not required, it is our understanding that NYS CLEP reviews the information submitted for these LDTs. Further, NYS CLEP reserves the right to rescind an exemption at any time (Ref. 24). Because NYS CLEP reviews the analytical and clinical validity of LDTs that are added under an approved exemption and may rescind an exemption at any time, FDA is including such LDTs within the enforcement discretion policy with respect to LDTs approved by NYS CLEP.

Based on the available information as discussed above, FDA believes that generally NYS CLEP’s review of analytical and clinical validity of LDTs helps to mitigate the risk of harm from inaccurate and unreliable LDTs. First, NYS CLEP reviews much of the same information that FDA reviews in assessing analytical and clinical validity (e.g., data supporting analytical validity, data supporting clinical validity, sample test reports, and standard operating

procedures). For example, in comments submitted to the docket for this rulemaking, NYS CLEP explained, “Applications must include validation data throughout the reportable range, particularly at or near the limit of detection, and for intended specimen types, specimen stability range, clinical indications, and target populations (pediatric vs adult, symptomatic vs asymptomatic, varied ethnicities, etc.)” Second, NYS CLEP is identifying many of the same types of issues that FDA has identified with LDTs. In their comments, NYS CLEP provided a detailed description of the issues they have identified when reviewing LDT applications. For example, NYS CLEP noted that more than half of the LDTs submitted for their review cannot be approved based on the original application. For such applications, NYS CLEP requests additional information, sometimes multiple times, to address a range of issues, including “design flaws, inadequate validation data, and process problems that call into the question the reliability of the results.” These are the same types of issues FDA has observed in the review of emergency use authorization (EUA) requests from laboratories for molecular tests for COVID-19 (see Ref. 18) and in other premarket submissions for LDTs (see Ref. 16). Additionally, FDA collaborated with NYS CLEP in the review of the first authorized tumor profiling test and found substantial alignment in FDA’s and NYS CLEP’s assessments of the analytical and clinical validity of this LDT for tumor profiling. FDA has also accredited NYS CLEP as a Third Party Review Organization accredited under FDA’s Third Party review program (3P510K Review Organization) qualified to conduct reviews of 510(k)s for certain IVDs. Accreditation of 3P510K Review Organizations is based on many factors, including qualification of staff in the scientific disciplines relevant to the review of the specific device types that the 3P510K Review Organization intends to review (Ref. 56). In the case of IVDs, the 3P510K Review Organization must be qualified to assess the analytical and clinical validity of tests which NYS CLEP was able to demonstrate.

Exercising enforcement discretion with respect to the premarket review requirements for LDTs approved by NYS CLEP will facilitate more efficient use of FDA resources. The resources

that FDA would otherwise spend on premarket review of such LDTs can instead be focused on premarket review of other IVDs offered as LDTs and enforcement of other applicable requirements. FDA estimates that 12.1 percent of IVDs offered as LDTs would not experience new costs associated with submission preparation and review as a result of the enforcement discretion policy with respect to LDTs approved by NYS CLEP, as discussed in appendix A of the FRIA (Ref. 10).

As mentioned above, FDA intends to phase out the general enforcement discretion approach with respect to other applicable requirements for LDTs approved by NYS CLEP, consistent with the stages described below in section V.C. Enforcement of other requirements will help to protect and promote the public health, e.g., by providing FDA and the public with important information about these tests. For example, compliance with registration and listing requirements will provide FDA and the public with basic information on these LDTs, and compliance with MDR requirements will provide FDA and the public with adverse event information about these LDTs. Further, under § 807.26(e) (21 CFR 807.26(e)) (additional device listing information), FDA intends to request the labeling for these LDTs, which will provide information on test performance and a summary of the supporting validation, among other things.³¹ Additionally, compliance with labeling requirements, including those in § 809.10(b)(12), will help to ensure that healthcare providers and patients have information on test performance, among other things, and thus enable more informed decision making. The labeling information and adverse event reports will help FDA identify LDTs that raise concerns, e.g., concerns regarding insufficient validation or inaccurate results. Compliance

³¹ Devices licensed under section 351 of the PHS Act register and list pursuant to part 607 (21 CFR 607.1 and 807.20(e)), which does not contain a provision identical to 21 CFR 807.26(e). Most licensed IVDs are tests intended for use as blood donor screening tests or HCT/P donor screening tests subject to § 610.40 and 1271.80(c), respectively, or tests for determination of blood group and Rh factors subject to § 640.5. As explained in the NPRM (88 FR 68006 at 68021), FDA's general enforcement discretion approach for LDTs has never applied to such tests. Therefore, we anticipate that there would be a limited number of IVDs subject to the registration and listing requirements in part 607 that would fall within this policy or other policies for which FDA intends to request laboratories to provide labeling information in connection with listing the device. Should FDA receive listing information under part 607 for an IVD that is not licensed, we will consider if any additional action is appropriate, including with respect to information regarding IVD performance.

with the QS requirements that FDA intends to enforce for these LDTs will help provide for quality manufacturing of these tests. As discussed in section V.C, for LDTs, FDA generally will expect compliance at the 3-year mark with some, but not all, of the QS requirements (specifically, design controls, purchasing controls, acceptance activities, corrective and preventive actions (CAPA), and records requirements). This includes for LDTs approved by NYS CLEP. However, it is our understanding, based on consultation with NYS CLEP, that compliance with NYS CLEP's clinical laboratory standards (which exceed CLIA requirements in certain respects) and its premarket review requirements collectively could generally satisfy these subparts of the QSR except as to certain aspects of design control documentation. Therefore, although not relevant to our decision-making with respect to our policy regarding LDTs approved by NYS CLEP, FDA does not anticipate significant additional burden with respect to compliance with these QS requirements for laboratories offering LDTs approved by NYS CLEP.

Finally, as noted elsewhere in this preamble, regardless of this or any other enforcement discretion policy, FDA retains discretion to pursue enforcement action at any time against violative IVDs when appropriate. We intend to carefully monitor tests falling within this policy and to take action when appropriate to protect the public health.

3. Enforcement Discretion Policies With Respect to Premarket Review and Certain QS Requirements

FDA also intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for three categories of IVDs. These enforcement discretion policies have been added to the final phaseout policy after consideration of comments received on the NPRM.

First, for the reasons discussed further below, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except

for requirements under part 820, subpart M (Records))³² for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. This enforcement discretion policy does not apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B.

In the NPRM, FDA discussed LDTs for unmet needs, stating that a specific enforcement discretion policy for such LDTs was not included in the proposed phaseout policy because we anticipated that programs currently in place (e.g., the Humanitarian Use Devices (HUD)/HDE program and the Breakthrough Devices program) may facilitate the development and premarket authorization of IVDs for unmet needs.³³ *See* 88 FR 68006 at 68026. We received over 100 comments addressing whether FDA should adopt a specific enforcement discretion policy for LDTs for unmet needs (see section VI.L.5). In particular, we received numerous comments that asserted that the perceived burden of premarket review and QS requirements would lead laboratories to stop developing such LDTs, leaving patients without access to the LDTs they need. For this reason, many comments recommended that FDA adopt an enforcement discretion policy for LDTs for unmet needs. Two public interest groups recommended against adopting a separate policy for LDTs for unmet needs for various reasons, including so that LDTs for patients with unmet needs would have the same assurances of safety and effectiveness as LDTs for other patients. Stakeholders further commented that the existing HUD/HDE and Breakthrough Devices programs are insufficient to mitigate the perceived burden that laboratories face with respect to development of LDTs for unmet needs. Specifically, commenters noted the numerical limit of 8,000 tests nationwide per year is too restrictive, the

³² As noted in footnote 17, for the categories of IVDs discussed in section V.B.3, FDA generally expects compliance with requirements under part 820, subpart M (Records) but not §§ 820.20, 820.22, 820.40, and 820.50 (which are cross-referenced in subpart M), or comparable provisions of ISO 13485 in accordance with the amendments to part 820 once that rule takes effect in February 2026.

³³ As described in the NPRM, FDA considered a possible premarket-review approach specific to LDTs for unmet needs in the “Discussion Paper on Laboratory Developed Tests (LDTs)” issued by the Agency on January 13, 2017 (2017 Discussion Paper) (Ref. 57) (88 FR 68006 at 68026).

requirements for use of tests under HDE (e.g., institutional review board approval) dissuade physicians from using them, and the program has only been used for 6 IVDs despite existing for over 30 years. We also received information in comments indicating that laboratories integrated within healthcare systems, including AMCs, often make tests to meet the unique needs of their patients, and that patients may be referred to those systems because of their ability to meet patient needs that cannot be met elsewhere. The comments stated that this is often the case for patients with rare diseases for which the market is so small that there is no financial incentive for non-laboratory manufacturers to meet their needs and for which collecting data to validate a test is particularly challenging due to small patient populations (for example, rare immunohematology problems, Huntington disease, Prader-Willi/Angelman syndrome, and genetic tests for certain cancers).

With respect to AMCs in particular, the Agency sought comment in the NPRM on whether FDA should have a different enforcement policy for tests manufactured by AMC laboratories. *See* 88 FR 68006 at 68023-24. We asked about various aspects of such a policy, including whether any continued enforcement discretion policy should take into account “whether an FDA cleared or approved test is available for the same intended use as the test manufactured by an AMC laboratory,” and the public health rationale for how integration of a laboratory into patient care might support a different approach for tests manufactured by AMC laboratories. *Id.* at 68024. We received over 100 comments addressing whether FDA should adopt a specific enforcement discretion policy for tests offered by AMC laboratories and/or other laboratories integrated within healthcare systems (see section VI.F.4 of this preamble). Many of the comments we received addressing whether FDA should adopt a specific enforcement discretion policy for LDTs for unmet needs addressed LDTs for unmet needs manufactured by AMC laboratories/other laboratories integrated within healthcare systems. These comments were from patients, healthcare providers, AMCs, other healthcare systems, and various entities representing such groups.

The majority of comments recommended that FDA adopt an enforcement discretion policy specific to tests manufactured by AMC laboratories given risk mitigations provided by the integration of the laboratory within the AMC that is providing care to the patient. Many comments stated that because other laboratories are similarly integrated within healthcare systems, any such enforcement discretion policy should not be limited to AMC laboratories. Many of these comments emphasized the built-in communication mechanisms between the laboratory and AMC/other healthcare system within which the laboratory is integrated. For example:

- “[T]he close connection between the clinical pathologists developing the tests and the care providers at AMCs further validates the alignment between diagnostic results and clinical presentation and helps to provide real-time feedback to the LDT developers on test performance and outcomes.”
- “As hospital-based labs, we are integrated into patient care within the healthcare system. Treating clinicians will contact us directly when tests don’t make sense and we adjust our testing strategies if needed. I personally get around 3-10 questions per week from clinicians as a laboratory medical director. At AMCs, while we implement LDTs we seek information and feedback from our clinical colleagues....This direct connection and information flow allows for quality control and real-time communication if a test is not performing as expected.”
- “As a CLIA director of a hospital-based lab, I occasionally see patients with specimens that were sent to our laboratory as well as an off-site, disconnected reference lab for the same test at nearly the same time. The results are often not consistent. I am able to investigate further by getting a new specimen and communicating with the clinician about the patients’ signs, symptoms, and radiology results. I review our other test results, including some of our other LDTs. The reference labs are often not aware of the issues

because they do not have the same line of communication and access to the electronic health record. They continue to offer the same test with no knowledge of the problem.”

- “There is a direct connection or ability to directly connect between the laboratory provider/director and the treating clinician, and laboratory professionals have access to patient electronic medical records, details of which often inform the nuance of laboratory testing that is managed locally. This direct connection and information flow allows for quality control that cannot be engendered by an off-site, disconnected reference lab model for testing and allows for issues associated with any particular testing modality to be identified; thus it provides quality control at both the patient and assay level.”

Several comments recommended against a separate enforcement discretion policy for tests manufactured by AMC laboratories, including because they argued that AMC laboratory tests have the same problems as other IVDs (which FDA acknowledged in the context of the COVID-19 pandemic) and having the same enforcement policies for these tests as for other tests will level the playing field and promote the development of new and improved tests.

As an initial matter, we understand that laboratories that develop LDTs for unmet needs, often laboratories integrated within a healthcare system, may be more likely to stop developing many of these LDTs for unmet needs if the proposed phaseout policy were finalized. The cost of compliance with premarket review and QS requirements may be deemed too high given the limited market for many of these LDTs for unmet needs, and so laboratories may not have financial incentives to develop these types of LDTs in particular (for example, FDA’s primary estimates anticipate the cost per premarket submission to range from approximately \$250,000 to \$4.5 million depending on the type of submission required, in addition to costs associated with QS requirements, annual reporting requirements (for PMAs) and applicable user fees, as described in sections II.F.3, II.F.4 and II.H of the FRIA (Ref. 10)). In their comments, various laboratories noted challenges and limitations associated with the HDE pathway that would dissuade them from seeking HDE approval for their LDTs. Specifically, commenters noted the

numerical limit of 8,000 tests nationwide per year is too restrictive in that it applies to the cumulative testing volume of all patients who would be tested with a diagnostic device annually, and the requirements for use of tests under HDE (e.g., administration of the test in a facility having oversight by an institutional review board, monitoring whether the national testing volume exceeds 8,000 patients per year, and limitations on profit, etc.) dissuade laboratories from developing such tests and submitting them for HDE approval. Although we think that the HDE pathway could help to facilitate the manufacture and premarket authorization of certain LDTs for unmet needs, based on these comments, we are concerned that many laboratories would stop manufacturing LDTs for unmet needs altogether, instead of seeking HDE approval for the LDTs, in light of the perceived financial costs of premarket review and QS requirements. Moreover, although we think that the Breakthrough Devices program would help to facilitate the premarket review process for LDTs for unmet needs, again based on the comments, we are concerned many laboratories would stop manufacturing LDTs for unmet needs altogether if they are expected to comply with premarket review and QS requirements.

As such, and upon further consideration, FDA has determined that a targeted enforcement discretion policy is appropriate to help avoid patients being deprived of critically needed LDTs where certain risk mitigations exist. Specifically, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. FDA intends to phase out the general enforcement discretion approach for these LDTs with respect to all other applicable requirements consistent with the stages described in section V.C. Should experience with this policy indicate that changes are warranted, FDA would consider appropriate policy changes through guidance in accordance with good guidance practices (see § 10.115).

This policy is limited to LDTs for patients who are receiving care within the healthcare system within which the laboratory offering the LDT is integrated. FDA does not consider this to include patients that are being treated at an affiliated hospital with different corporate ownership than the laboratory. Where the laboratory and the treating physicians are in the same corporate entity, there is shared responsibility and potential liability for patient outcomes, which helps mitigate risk. Moreover, the policy is limited to LDTs that are ordered by a healthcare practitioner on the staff or with credentials and privileges at a facility owned and operated by the same healthcare system employing the laboratory director and performing the LDT. In these circumstances, FDA believes that the risk mitigations present help to address some of the concerns raised regarding problematic IVDs offered as LDTs discussed in the NPRM and this preamble.

For LDTs manufactured and performed by laboratories integrated within healthcare systems, FDA generally has greater confidence that ordering physicians will communicate any questions about LDTs or concerns regarding the safety and effectiveness of the LDT (e.g., when the patient's symptoms point to another diagnosis; when subsequent test results contradict the original test result) to a laboratory given the built-in communication mechanisms present. Moreover, FDA generally has greater confidence that laboratories will communicate any limitations of the LDT or other relevant information to the ordering physician given these mechanisms. We think this is particularly likely to happen in the context of LDTs for unmet needs, which are likely to be a focus of attention and communication between laboratorians and providers given the uncommon nature of the issues presented.

Communication from ordering physicians to laboratories may help laboratories to identify any problems with their LDT and make necessary adjustments, improvements, and other changes to the LDT. Although we acknowledge that any identification and subsequent modification of the LDT would happen postmarket, and thus would not prevent potentially problematic LDTs from ever being used, subsequent modification would benefit future patients and providers who are

relying on the LDT. In addition, communication from laboratories to ordering physicians may help to underscore to the ordering physicians any limitations with the LDT and provide other relevant information to ordering physicians, for example that is specific to the unique needs of their patient, which in turn should help inform appropriate use and interpretation of the LDT.³⁴

We believe that generally these features associated with integration of a laboratory within the healthcare system, along with enforcement of other applicable regulatory requirements as described in the phaseout policy (see section V.C), help to mitigate the risk of harm from inaccurate and unreliable LDTs. While we recognize that these features do not mitigate all risk and there may still be some uncertainty about the performance of LDTs that fall within this policy, we believe that these features support an enforcement discretion policy for premarket review and most QS requirements in the specific context of LDTs for unmet needs.

This policy is limited to LDTs for unmet needs. FDA considers an LDT to be for an unmet need where there is no available FDA-authorized IVD that meets the patient's needs. This may be because: (1) there is no FDA-authorized IVD for the disease or condition (for example, because it is for a rare disease or condition); (2) there is an FDA-authorized IVD for the disease or condition but it is not indicated for use on the patient, or a unique attribute needs to be added to the LDT to meet the patient's needs; or (3) there is an FDA-authorized IVD but it is not available to the patient. Examples of LDTs for unmet needs are:

- An LDT that is intended for cytogenetic analysis of certain genes and chromosomes associated with rare diseases or conditions, certain metals testing, viral load monitoring for some transplant-associated viruses, or diagnosis of certain mosquito- and tick-borne-

³⁴ See Ref. 58 (“more aggressive laboratory involvement in [the interpretation and reporting] step may be necessary to ensure a more nearly perfect hit rate on proper interpretation and action after reporting of laboratory results”); *also* Ref. 59. Shaw and Miller compared hospital laboratories and hospital-independent reference laboratories, and highlighted the following advantages, among others, of the former over the latter: (1) tracking problems (hospital laboratories “[c]an easily work with medical and nursing services to coordinate patient care efforts” whereas hospital-independent reference laboratories “[c]an only track internal problems effectively”) and (2) physician consultation (this is “[r]eadily available” for hospital laboratories whereas it is “[n]ot as readily available” for hospital-independent reference laboratories).

diseases, where there is no FDA-authorized IVD for the disease/condition (*rare disease or condition*);

- An LDT to accommodate an alternative specimen type that is infrequently tested when the specimen type required for the FDA-authorized IVD is not and cannot be made available (*variation from the indications for use of an FDA-authorized IVD*);
- An LDT for use on pediatric patients when FDA-authorized IVDs are indicated for use on adults only (*variation from the indications for use of an FDA-authorized IVD*);
- An LDT that generates results in a significantly shorter period (e.g., hours versus days) than an FDA-authorized IVD with the same indication where, due to the circumstances of the patient, the shorter time period to get results is critical for the clinical decision being made (*unique attribute needed to be added to an FDA-authorized IVD*);
- An LDT for the same indication as an FDA-authorized IVD that is offered only in another healthcare system that is not accessible to the patient and the developing laboratory will not make the IVD available outside its system (*FDA-authorized IVD is not available*);
and
- An LDT for an emerging pathogen for which there is no FDA-authorized IVD and for which FDA has not identified an emergent situation (*no FDA-authorized IVD*).

In contrast, FDA does not consider an LDT to be for an unmet need when there is an available FDA-authorized IVD that would sufficiently meet the needs of the patient. For example, potential improvements in performance or lower cost in comparison to an FDA-authorized IVD that meets the patient's needs does not fall within this policy.

FDA intends this policy to be targeted. It is not intended to serve as an alternative “pathway” to market for LDTs for unmet needs. FDA intends to provide additional guidance on this enforcement discretion policy, which would be issued in accordance with good guidance practices (see § 10.115).

We note that if there is no longer an unmet need for an LDT because, for example, FDA authorizes an IVD that meets the needs of the patient, then the LDT would no longer fall within this enforcement discretion policy. This will encourage manufacturers, including the manufacturers of LDTs falling within this policy, to seek premarket authorization, without delaying patient access to the LDT. It also will provide patients and providers with greater confidence that once an IVD has been authorized by FDA, all similar devices, regardless of who makes them, should have appropriate assurance of safety and effectiveness because all such devices should comply with premarket review and QS requirements. Moreover, such a limitation helps to ensure that the enforcement discretion policy will ultimately target only those LDTs where there is insufficient financial incentive to seek authorization for the LDTs (in such cases, there is unlikely to ever be an available FDA-authorized IVD).

Notably, this unmet needs LDT policy applies only to LDTs that are validated. We acknowledge that validation may vary depending on many factors, including the accessibility of specimens and the number of affected patients. FDA intends to consider whether issuing additional guidance regarding validation of tests, including those for rare diseases that takes into consideration the challenges in obtaining a robust number of samples for validation, would be helpful.

In developing this policy, FDA took into consideration various factors that mitigate the risk that LDTs offered as described in this policy may not have appropriate assurance of safety and effectiveness. As an initial matter, the phaseout of the general enforcement discretion approach for all other applicable requirements will provide greater assurances regarding these LDTs than the Agency, healthcare providers, and patients currently have. Compliance with registration and listing requirements, for example, will provide FDA and the public with insight into what LDTs for unmet needs are being offered by laboratories integrated within healthcare systems. Moreover, compliance with labeling requirements, including those in § 809.10(b)(12), will help to ensure that healthcare providers and patients have information on the performance

of the LDT and thus will help to enable more informed decision making. In addition, FDA generally intends to request that laboratories that offer LDTs as described in this policy submit labeling information to FDA in connection with the listing of the device as provided in § 807.26(e) (this regulation is discussed above). This labeling will facilitate FDA surveillance for potentially poor performing LDTs that should otherwise be addressed.

Finally, as noted elsewhere in this preamble, regardless of this or any other enforcement discretion policy, FDA retains discretion to pursue enforcement action at any time against violative IVDs when appropriate. We intend to carefully monitor LDTs falling within this policy and intend to take action regarding such LDTs as appropriate taking into account any public health concerns as evaluated on a case-by-case basis.

We considered various alternative policies proposed in comments regarding LDTs for unmet needs and LDTs manufactured by AMC laboratories or laboratories integrated within other healthcare systems, but we believe this policy best serves FDA's public health mission by helping to assure the safety and effectiveness of LDTs while also accounting for patient access. For example, an enforcement discretion policy whereby FDA generally does not enforce premarket review and most QS requirements for *any* LDT manufactured by AMC laboratories and laboratories integrated within other healthcare systems would appear to be overly broad, including because it would encompass LDTs for which there are FDA-authorized alternatives that we know have appropriate assurances of safety and effectiveness. Similarly, an enforcement discretion policy whereby FDA generally does not enforce premarket review and most QS requirements for *all* LDTs for unmet needs would also appear to be overly broad, as there are not the same risk mitigations present for all such LDTs that would help address and avoid the use of problematic LDTs. We also considered several narrower enforcement discretion policies, such as an enforcement discretion policy where a premarket submission would be expected *after* an LDT is offered for use and where the LDT is offered until FDA makes a final decision on the LDT (see, e.g., the 2017 Discussion Paper (Ref. 57)) or a longer phaseout policy for QS requirements.

We do not think such policies would make sense here because many laboratories would likely be dissuaded from developing LDTs in this space if compliance with premarket review and QS requirements is routinely expected at any point in time due to the lack of financial incentives and perceived costs associated with premarket review and QS requirements.

Second, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records))³⁵ for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule (hereinafter, “currently marketed IVDs offered as LDTs”). FDA intends for this policy to apply to currently marketed IVDs offered as LDTs as long as they are not modified following the issuance of this final rule, or are modified but only in certain limited ways that are described below. This enforcement discretion policy does not apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B.

As part of this policy, FDA intends to request submission of the labeling for currently marketed IVDs offered as LDTs under § 807.26(e) and to use this information, along with information obtained through laboratory compliance with other relevant requirements (such as adverse event reporting), to identify and address those currently marketed IVDs offered as LDTs that specifically raise concerns. We recognize that patients, the healthcare community, and the laboratory industry have likely made decisions in reliance on access to, or the continued manufacturing of, many currently marketed IVDs offered as LDTs, and that loss of beneficial currently marketed IVDs offered as LDTs could cause harm and undermine those reliance interests. We believe this policy appropriately balances the various competing interests at issue to best serve public health because it helps facilitate continued access to those IVDs offered as

³⁵ As noted in footnote 17, for the categories of IVDs discussed in section V.B.3, FDA generally expects compliance with requirements under part 820, subpart M (Records) but not §§ 820.20, 820.22, 820.40, and 820.50 (which are cross-referenced in subpart M), or comparable provisions of ISO 13485 in accordance with the amendments to part 820 once that rule takes effect in February 2026.

LDTs that are beneficial while incorporating targeted use of available tools to identify and act against currently marketed IVDs offered as LDTs that are problematic. As IVDs evolve, compliance with premarket review and QS requirements will be phased in according to the natural lifecycle of test development and use.

FDA is adopting this policy after a review of the comments, which leads us to conclude that an expectation of compliance with premarket review and QS requirements for currently marketed IVDs offered as LDTs may be more harmful than helpful to the public because, for example, it will prompt many laboratories to stop offering tests even if they are safe and effective. One commenter stated that “[i]f the rule is implemented, it is likely that we would consider no longer offer [*sic*] [IVDs offered as LDTs] due to the administrative and financial burdens of the regulations.” Another commenter stated that “the most prominent reason [the proposed rule should not move forward] is that patient care will suffer as most small laboratories will be forced to close because of increased cost and need to reduce their test menu.” These comments corresponded to data in FDA’s Preliminary Regulatory Impact Analysis (PRIA) suggesting a potentially high burden on laboratories associated with compliance for currently marketed IVDs offered as LDTs--a burden that could potentially cause some laboratories (particularly small laboratories) to close (Ref. 60). As reflected in section II.F of the FRIA (Ref. 10), a significant fraction of the estimated overall costs of compliance with applicable requirements under the FD&C Act and FDA’s regulations is attributable to premarket review (where applicable) and QS requirements. Specifically, out of the total estimated discounted costs to industry of \$1.17 billion, the average estimated costs of compliance with stages 1 and 2 of the phaseout policy (as described in section V.C below) are approximately \$9,522 per test (\$74,783 per laboratory) and the average estimated costs of compliance with premarket review and QS requirements are approximately \$3.02 million per test (\$1.26 million per laboratory).

In the NPRM and this preamble, FDA explained that relevant evidence points to a high degree of variability in the performance of IVDs offered as LDTs today, but FDA does not take

the view that all laboratory-manufactured IVDs are problematic (see, e.g., 88 FR 68006 at 68010-68012 and responses to comments 28, 32-33). We believe that an appreciable proportion of IVDs currently offered as LDTs likely help patients and are important to patient care (see section II.E.1 of the FRIA (Ref. 10)), and as noted above, we understand that patients, the healthcare community, and the laboratory industry have likely made decisions in reliance on access to, or the continued manufacturing of, such IVDs. The loss of such IVDs could cause harm and undermine those reliance interests.

FDA is aware, for instance, that certain patients may have embarked on a course of treatment in reliance on regular testing to help monitor their treatment or condition, and the loss of that testing could pose serious risks and complications for that patient. For example, consistent access to tests that are already being used to measure plazomicin to aid in the management of patients with complicated urinary tract infection receiving plazomicin therapy and tests to measure levels of immunosuppressants--such as cyclosporine, tacrolimus, everolimus, and sirolimus--in transplant patients are important for treating physicians to make well-informed treatment decisions for those patients. In the context of patients receiving tests that are not well-standardized to monitor their diseases or conditions, consistent access to the same test at the same laboratory over time is also important for treating physicians to make accurate diagnostic and treatment decisions. Examples of such tests include thyroid hormone tests that are used to monitor thyroid disease, adrenal function tests that are used to monitor adrenal disorders, and flow-cytometry-based minimal residual disease tests that are used to monitor patients with cancer that have undergone treatment to determine if they are at risk for relapse.

FDA also recognizes that healthcare professionals may have made significant financial investments in reliance on access to certain tests (e.g., contracts for certain tests that they need for long-term patient monitoring, where such monitoring must continue with the same test because test results are compared over time and results from a different test are not interchangeable), and that the loss of access could harm their practice and, ultimately, the

patients they serve. In addition, laboratories may have made financial investments and other decisions based on a past assumption about the presence of the general enforcement discretion approach.

In light of these reliance considerations and, in particular, the risk that laboratories may stop offering safe and effective tests on which patients and the healthcare community currently rely, we do not think it is appropriate to expect compliance with premarket review and most QS requirements for all currently marketed IVDs offered as LDTs. Instead, we have determined it is in the best interest of the public health to expect compliance with premarket review and QS requirements in a more targeted fashion--i.e., for those currently marketed IVDs offered as LDTs that specifically raise concerns. As new IVDs come on the market following issuance of this rule, they will be expected to comply with premarket review and QS requirements--in accordance with the phaseout policy--gradually phasing in those requirements for the overall market. In the meantime, compliance with other applicable requirements will help enable FDA to identify and address safety and effectiveness problems that may arise.

In deciding on this policy, FDA considered alternatives to address the concerns identified above, including the risk of market exit, such as: (1) extending the phaseout timeline to give more time for currently marketed IVDs offered as LDTs to come into compliance with premarket review and QS requirements and (2) expecting compliance with premarket review and QS requirements only for high-risk currently marketed IVDs offered as LDTs. However, based on FDA's economic projections, neither of these alternatives resolves the concern about market exit resulting in loss of access to beneficial IVDs on which patients and others currently rely because neither substantially changes the economic burden on laboratories. For example, under Alternative 3 in section II.J of the PRIA, FDA evaluated the reduction in burden of an extended phaseout policy, and based on the calculations there, we doubt that the reduction would be sufficient to prevent the outcomes described above (see Ref. 60). In addition, the PRIA shows that the greatest costs in the phaseout policy are those associated with high-risk IVDs, so a policy

that involves compliance for currently marketed high-risk IVDs offered as LDTs also would not resolve the concern about market exit. Given this information, and given the information we received in comments, FDA has concluded that the best course is to adopt the policy for currently marketed IVDs offered as LDTs outlined above. (This policy is keyed to the date of this final rule, rather than the proposed rule, because patients and the healthcare community may have begun relying on IVDs during the period between publication of the proposed and final rule.)

Based on FDA's understanding of the current IVD industry, we expect IVDs offered as LDTs to continue to advance to meet new patient needs, accommodate new technologies, and incorporate the latest scientific findings. Under this policy for currently marketed IVDs offered as LDTs, when such IVDs are modified in certain significant ways that would, under FDA requirements, generally prompt the need for premarket review relative to the original currently marketed IVD, FDA expects laboratories to comply with premarket review and QS requirements for that modified IVD. This policy is intended to preserve access to beneficial IVDs on which patients and the healthcare community currently rely, including versions of that IVD with minor changes. However, we expect compliance with premarket review and QS requirements once the IVD is changed in certain, more significant ways that could affect its basic safety and effectiveness profile. In particular, under this policy, FDA generally expects compliance with premarket review and QS requirements for currently marketed IVDs offered as LDTs when a laboratory's modifications (individually or in aggregate):

- change the indications for use of the IVD;
- alter the operating principle of the IVD (e.g., changes in critical reaction components);
- include significantly different technology in the IVD (e.g., addition of artificial intelligence or machine learning to the test algorithm, a change from targeted sequencing to whole genome sequencing, a change from immunoassay to mass spectrometry, or a change from manual to automated procedures); or

- adversely change the performance or safety specifications of the IVD.³⁶

FDA believes this approach appropriately limits the scope of this policy and reduces the risk for patients.

As noted above, FDA also intends to take targeted steps to address currently marketed IVDs offered as LDTs that are problematic. In particular, we intend to use available tools to identify and act against currently marketed IVDs offered as LDTs that specifically raise concerns, such as IVDs that are potentially inaccurate or poorly validated. In this way, FDA can work to assure the safety and effectiveness of currently marketed IVDs offered as LDTs without creating the risk of widespread market exit. FDA has a range of tools to assist in this effort.

First, FDA intends to request that laboratories offering currently marketed IVDs offered as LDTs submit labeling to FDA as provided in § 807.26(e). Labeling includes IVD performance information and a summary of supporting validation, as applicable. This information will help FDA more closely monitor currently marketed IVDs offered as LDTs and identify those that may lack analytical validity, clinical validity, or safety. As part of its review of labeling, FDA also intends to look closely at claims of superior performance and whether those claims are adequately substantiated.³⁷ Such claims are of particular public health concern because, in FDA’s experience, they have led to escalating claims from competitors that can ultimately mislead the public. FDA generally intends to take action where the labeling of a currently marketed IVD offered as an LDT is false or misleading, and/or the IVD offered as an LDT lacks the appropriate assurance of safety and effectiveness for its intended uses as a result of any such claims that are not adequately substantiated.

³⁶ Under FDA regulations, the listed modifications to an IVD would generally require a new submission, such as a new 510(k), PMA, BLA, or De Novo, or certain types of PMA or BLA supplements. *See, e.g.*, 21 CFR 601.2, 601.12, 807.81(a)(3), 814.39, and 860.200; see also “Deciding When to Submit a 510(k) for a Change to an Existing Device” (Ref. 61).

³⁷ *See, e.g.*, FDA, Final Guidance for Industry: Medical Product Communications That Are Consistent With the FDA-Required Labeling--Questions and Answers at 18 (June 2018) (“[P]romotional material is misleading” when “it makes a claim of superior effectiveness for Drug A versus Drug B based on a study that was not designed to establish superiority of Drug A to Drug B.”). *See* Ref. 62.

Second, FDA intends to enforce records requirements in part 820, subpart M, for manufacturing activities related to a currently marketed IVD offered as an LDT that occur after the date of issuance of this final rule. Compliance with these requirements will facilitate FDA's review of these IVDs during inspections, enabling FDA to understand the validation bases and processes underlying these IVDs, and will support appropriate adverse event reporting (MDRs).

Third, under the policy, FDA expects laboratories to comply with applicable requirements other than premarket review and most QS requirements, including MDR requirements, corrections and removals reporting requirements, registration and listing requirements, and labeling requirements. Compliance with these requirements will provide FDA with additional important information regarding currently marketed IVDs offered as LDTs, such as information enabling FDA to track adverse-event trends.

Finally, based on our experience with other devices, we anticipate that laboratory manufacturers will alert us to potential problems with their competitors' IVDs once IVD performance information is transparent, which will help direct FDA's attention to problematic tests.

FDA emphasizes that these tools are not a substitute for premarket review or full QS compliance. FDA continues to believe that premarket review and full QS compliance are important tools to help assure the safety and effectiveness of IVDs going forward. However, there are sufficient countervailing reasons to take a more targeted approach for currently marketed IVDs offered as LDTs, including the risk of market exit and the potentially significant reliance on currently marketed IVDs offered as LDTs. Thus, FDA has determined that the enforcement discretion policy outlined above best serves public health.

The third category of tests for which FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements

under part 820, subpart M (Records))³⁸ is non-molecular antisera LDTs³⁹ for rare RBC antigens when such tests are manufactured and performed by blood establishments, including transfusion services and immunohematology laboratories⁴⁰ and when there is no alternative IVD available to meet the patient's need for a compatible blood transfusion. This policy does not apply to molecular tests used for genotyping RBC antigens. This policy also does not apply to any IVDs identified in section V.A.2 as falling outside the scope of the phaseout policy or as discussed in section V.B.

Some individuals develop antibodies to certain antigens that they lack on their own RBCs following exposure to foreign RBC antigens through blood transfusion or pregnancy. These may be clinically significant, causing a hemolytic transfusion reaction if the patient receives a transfusion of RBCs that have the corresponding antigen(s). As of July 2023, there are currently 45 recognized blood group systems containing 360 RBC antigens (Ref. 63). FDA understands that there are occasions where licensed antisera IVDs are not available for rare RBC antigens but testing for such rare antigens is necessary to help ensure that patients receive a compatible blood transfusion⁴¹ and avoid potentially life-threatening reactions. Although FDA has also approved molecular tests for use in genotyping RBC antigens, there may not be an available, approved molecular test to use as an alternative for all rare antigens.

FDA is adopting this policy after consideration of comments that requested that FDA continue to exercise enforcement discretion with respect to antisera LDTs for rare RBC

³⁸ As noted in footnote 17, for the categories of IVDs discussed in section V.B.3, FDA generally expects compliance with requirements under part 820, subpart M (Records) but not §§ 820.20, 820.22, 820.40, and 820.50 (which are cross-referenced in subpart M), or comparable provisions of ISO 13485 in accordance with the amendments to part 820 once that rule takes effect in February 2026.

³⁹ Consistent with what FDA has generally considered to be an LDT (as discussed elsewhere in this preamble), this enforcement discretion policy applies only to tests that are designed, manufactured, and used within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing.

⁴⁰ In our experience, establishments that perform compatibility tests for blood transfusion include establishments, such as reference laboratories, that are not integrated within a healthcare system. Therefore, the non-molecular antisera LDTs at issue may not fall within the policy described above for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

⁴¹ Such tests are not subject to the requirements in § 640.5. As noted elsewhere in this document, FDA's general enforcement discretion approach for LDTs has not applied to tests for determination of blood group and Rh factors that are subject to § 640.5.

antigens and/or molecular tests for genotyping rare RBC antigens. This included comments pointing to FDA's existing 2018 final guidance (Ref. 64), which, among other things, recognized that blood establishments sometimes use unlicensed antisera tests or unapproved molecular tests for RBC antigen typing in circumstances where a licensed reagent for a rare antigen is not available.

The non-molecular antisera LDTs within the scope of this policy share certain characteristics with "1976-Type LDTs," as they use manual techniques performed by laboratory personnel with specialized expertise. For such LDTs, in instances where there is no available alternative to ensure that a patient receives a compatible transfusion, FDA has determined it is in the best interest of public health to adopt this enforcement discretion policy. However, this policy does not apply to molecular tests for genotyping RBC antigens. Compared to serologic tests, molecular RBC typing is a relatively new and complex technique for detection of RBC antigens. Some limitations of molecular RBC typing tests include that the genotype does not always correlate with the phenotype due to samples with rare null phenotypes, and the assay may not be designed to detect all rare or new variants of an antigen. As such, FDA has greater concern regarding risk of error with molecular tests for genotyping RBC antigens that do not comply with applicable FDA requirements.

For LDTs offered as described in this policy, FDA expects the LDT to be validated. As discussed previously, we acknowledge that such expectations may vary depending on many factors, including the accessibility of specimens and the number of affected patients.

In addition, this enforcement policy applies only to premarket review and QS requirements (except for requirements under part 820, subpart M (Records)). FDA expects compliance with records requirements in part 820, subpart M, for non-molecular antisera LDTs that fall within this policy. Compliance with these requirements will facilitate FDA's review of these LDTs during inspections and will support appropriate adverse event reporting. The phaseout of the general enforcement discretion approach for other applicable requirements will

provide greater assurances regarding tests that fall within this policy than the Agency, healthcare providers, and patients currently have.

Finally, as noted elsewhere in this preamble, regardless of this or any other enforcement discretion policy, FDA retains discretion to pursue enforcement action at any time against violative IVDs. We intend to carefully monitor LDTs falling within this policy and intend to take action regarding such LDTs as appropriate, taking into account any public health concerns as evaluated on a case-by-case basis.

C. Stages

As previously discussed, FDA has determined to gradually phase out its current general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs. In particular, FDA has structured the phaseout policy to contain five key stages:

- Stage 1: beginning 1 year after the publication date of this final rule, FDA will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files).
- Stage 2: beginning 2 years after the publication date of this final rule, FDA will expect compliance with requirements not covered during other stages of the phaseout policy, including registration and listing requirements, labeling requirements, and investigational use requirements.
- Stage 3: beginning 3 years after the publication date of this final rule, FDA will expect compliance with QS requirements under part 820 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1).
- Stage 4: beginning 3½ years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for high-risk IVDs offered as LDTs, unless a premarket submission has been received by the beginning of this stage in which

case FDA intends to continue to exercise enforcement discretion for the pendency of its review.

- Stage 5: beginning 4 years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs (that require premarket submissions), unless a premarket submission has been received by the beginning of this stage in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review.

These stages, along with certain narrower enforcement discretion policies specific to certain stages, are discussed in further detail below.

We note that FDA generally does not intend to enforce requirements to include certain information (e.g., registration numbers, premarket submission numbers) in reports or other submissions to the Agency until the information is addressed in a later stage of the phaseout policy.

We received several comments on the structure, sequencing, and timing of the proposed phaseout policy described in the NPRM (see section VI.F.6 of this preamble). Some indicated that the proposed timing for all phases was appropriate while others recommended it be shortened or lengthened. Some also proposed different approaches for organizing or implementing the phaseout.

FDA carefully considered these comments, and also considered the impact of other policies included in the final phaseout policy on the considerations noted in these comments. For the reasons discussed below and in section VI.F.6, FDA has determined that it should retain the general structure, sequencing, and timelines proposed in the NPRM (88 FR 68006 at 68021) for the phaseout policy in this final rule.

FDA encourages laboratory manufacturers to begin early and work toward compliance with requirements sooner than the end of the timeframes specified for each stage of the phaseout policy, as described below. FDA also intends to consider providing more targeted

guidance and/or making additional resources available on specific topics, such as compliance with applicable labeling requirements, over the course of the phaseout period, as discussed in section VI.P.

1. Stage 1: Beginning 1 Year After the Publication Date of This Final Rule, FDA Will Expect Compliance With MDR Requirements, Correction and Removal Reporting Requirements, and QS Requirements Under § 820.198 (Complaint Files)

As detailed elsewhere in this preamble, FDA is concerned that some IVDs offered as LDTs may be posing risks to patients; therefore, FDA seeks to obtain information about potentially harmful IVDs offered as LDTs as soon as feasible. In light of that objective, and after reviewing the comments, FDA continues to believe that 1 year is an appropriate time for laboratory manufacturers to come into compliance with MDR and correction and removal reporting requirements. Among other things, this timeline is reasonable in light of the estimates in the FRIA, and under CLIA, laboratories should already have some processes in place for detecting problems with their IVDs. In addition, the new enforcement discretion policies set forth in section V.B (particularly the policy for currently marketed IVDs offered as LDTs) may help laboratories with limited resources focus on compliance with requirements at stage 1. Therefore, FDA is retaining the 1-year period for the phaseout of the general enforcement discretion approach with respect to MDR and correction and removal reporting requirements, in order to prioritize the phaseout of the general enforcement discretion approach for requirements that would help FDA identify and monitor significant issues with IVDs offered as LDTs.

Enforcement of the MDR requirements under 21 U.S.C. 360i(a) through (c) and part 803 (21 CFR part 803), in particular, will enable FDA to systematically monitor significant adverse events to identify problematic IVDs offered as LDTs, such as those with poor performance or other safety issues. FDA has made a determination that gathering this information early in the phaseout period is important for IVDs that do not have the safeguards associated with compliance with other FDA requirements, such as manufacturing under QS

requirements or confirmation of appropriate safety and effectiveness through premarket review.

For similar reasons, FDA is prioritizing the collection of information about when a manufacturer has initiated a correction or removal of its IVD to reduce a risk to health or to remedy a violation of the FD&C Act that may present a risk to health. Under 21 U.S.C. 360i(g) and part 806 (21 CFR part 806), manufacturers are required to report such corrections or removals to FDA, and FDA intends to phase out the general enforcement discretion approach for these requirements at the same time it does so for MDR requirements.

In addition, FDA has determined that it should include compliance with one additional regulatory provision at stage 1 of the phaseout policy. In particular, while FDA generally expects compliance with most QS requirements beginning in stage 3 of the phaseout policy (as described below), FDA intends to phase out the general enforcement discretion approach with respect to the QS requirements under § 820.198 (complaint files)⁴² in stage 1 of the phaseout policy, given the connection between the complaint investigation and complaint file requirements under § 820.198 and the MDR reporting regulations. Under § 820.198, manufacturers are required to document complaints, investigate them, and determine if they require reporting under MDR requirements. Absent compliance with these requirements under § 820.198, manufacturers would not be able to comply with applicable MDR requirements (see § 803.18(e)), and FDA believes that developing procedures for compliance with § 820.198 can be accomplished on the same timeline as compliance with MDR requirements.

⁴² 21 CFR 820.198 generally requires that a manufacturer maintain complaint files and establish and maintain procedures for receiving, reviewing, and evaluating complaints, including requiring that certain complaints which are required to be reported to FDA under part 803 be promptly reviewed, evaluated, and investigated. When the final rule to amend part 820 takes effect in February 2026, the comparable requirements can be found in International Organization for Standardization (ISO) 13485 subclause 8.2.2 as modified by part 820. Under these provisions, manufacturers will generally be required to document procedures for timely complaint handling, including minimum requirements and responsibilities for receiving and recording information, evaluating whether the information constitutes a complaint, investigating complaints, determining the need to report information to appropriate regulatory authorities, handling of complaint-related product, and determining the need to initiate corrective action. Additionally, new § 820.35 will require, among other things, that manufacturers maintain records of such review and report to FDA complaints that are required under part 803.

2. Stage 2: Beginning 2 Years After the Publication Date of This Final Rule, FDA Will Expect Compliance With Requirements Not Covered During Other Stages of the Phaseout Policy, Including Registration and Listing Requirements, Labeling Requirements, and Investigational Use Requirements

After considering the comments, FDA has determined to phase out the general enforcement discretion approach for requirements not covered during other stages of the phaseout policy (i.e., requirements other than MDR, correction and removal reporting, QS, and premarket review requirements) 2 years after publication of this final rule. These other requirements include registration and listing requirements under 21 U.S.C. 360 and parts 607 and 807 (excluding subpart E); labeling requirements under 21 U.S.C. 352 and parts 801 and 809, subpart B (21 CFR parts 801 and 809, subpart B); and investigational use requirements under 21 U.S.C. 360j(g) and part 812 (21 CFR part 812).⁴³ We have included compliance with investigational use requirements at this stage, in recognition that there has been some confusion about our enforcement approach in this area. Our understanding is that laboratories often are not complying with investigational use requirements currently, even though FDA has generally expected compliance with these requirements.⁴⁴ We are therefore including these requirements in the phaseout policy.

As described in the NPRM (88 FR 68006 at 68025), FDA anticipates that it will best serve the public health to phase out the general enforcement discretion approach for these

⁴³ An IVD that is also a biological product and subject to licensure under section 351 of the PHS Act may be studied under an IND and subject to the investigational use requirements in section 351(a)(3) of the PHS Act and 21 CFR part 312, instead of the IDE requirements in part 812 (see, e.g., 21 CFR 312.2(a) and Ref. 65). IVDs studied under an IND are generally those intended for use as blood donor screening or HCT/P donor screening tests to which FDA's general enforcement discretion approach for LDTs has not applied (see section V.A.2). Therefore, we anticipate that there would be a limited number of IVDs offered as LDTs, if any, subject to investigational use requirements under 21 CFR part 312 for which the phase out of enforcement discretion would be relevant. However, to the extent such IVDs offered as LDTs exist, we intend to phase out enforcement discretion with respect to those investigational use requirements at stage 2, consistent with our policy regarding other investigational use requirements.

⁴⁴ For example, FDA stated in the "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" draft guidance that "FDA intends to *continue to enforce* investigational device requirements under 21 CFR Part 812 for all clinical investigations of LDTs that are conducted under clinical protocols that require institutional review board approval" (Ref. 38).

requirements at the 2-year mark, and FDA did not receive information changing its view with respect to that timeline. Under this timeline, FDA will obtain registration and listing information before the enforcement discretion phaseout for premarket review requirements, which may give the Agency a better understanding of the universe of IVDs offered as LDTs to facilitate premarket review of those IVDs. Relatively few commenters raised concerns about this timeline, and FDA's estimates of the resources required for compliance with the requirements covered by stage 2 suggest 2 years is adequate time (see FRIA section II.F.2). Furthermore, the new enforcement discretion policies set forth in section V.B may free up time and resources for laboratories to focus on compliance with requirements at stage 2. FDA has determined that this timeline appropriately balances the importance of compliance with registration and listing, labeling, and investigational use requirements, among others, relatively quickly--in order to address IVDs offered as LDTs that are problematic, among other things--with the recognition that laboratories generally have not complied with FDA requirements and may need time to order their affairs and build out FDA-compliant systems.

FDA notes that the labeling requirements under part 801 include unique device identification (UDI) requirements, as applicable (see part 801, subpart B).

3. Stage 3: Beginning 3 Years After the Publication Date of This Final Rule, FDA Will Expect Compliance With QS Requirements

At the 3-year mark, FDA generally will expect compliance with the CGMP requirements of the QS requirements under 21 U.S.C. 360j(f) and part 820. (FDA notes that we expect compliance with requirements under § 820.198 (complaint files) during stage 1 of the phaseout policy.) We recognize that the costs of compliance with QS requirements are comparatively high among the range of costs quantified in the FRIA (and as suggested in certain comments), but FDA continues to believe that the 3-year timeline is appropriate given, in particular, the new enforcement discretion policies in section V.B.3, which we anticipate will significantly reduce laboratories' work at this stage (see section II.F.3 of the FRIA). FDA

has determined that this timeline is consistent with our goal of improving the quality of IVDs manufactured by laboratories as soon as feasible while also taking into account the resources and time required to set up quality systems.

FDA also notes that we expect laboratories to retain manufacturing records they may already have or may create for certain IVDs prior to stage 3 of the phaseout policy. In particular, for any IVDs for which FDA generally intends to exercise enforcement discretion for all QS requirements other than requirements under part 820, subpart M (Records), FDA expects laboratories to retain existing records and records created prior to the start of stage 3 that are relevant to validation and the other topics covered under part 820, subpart M (Records)). This documentation will help FDA understand the manufacturing for IVDs offered as LDTs that are marketed prior to stage 3, including helping FDA identify IVDs that are potentially problematic.

FDA issued its final rule amending the QSR on February 2, 2024, which will take effect on February 2, 2026, meaning that the amended QS requirements will be in effect before the beginning of stage 3. When a laboratory undertakes to comply with QS requirements, FDA will expect compliance with the QS requirements that are in effect at that time whether that be at the start of stage 3 or earlier (if the laboratory complies with QS requirements prior to the start of stage 3).⁴⁵ For further information on the QS requirements established pursuant to the amendments to the QSR, please refer to 89 FR 7496.

In addition, specifically for LDTs⁴⁶, FDA is adopting the enforcement discretion policy proposed in the NPRM under which FDA generally will expect compliance at the 3-year mark

⁴⁵ As noted elsewhere in this phaseout policy, FDA intends to phase out the general enforcement discretion approach with respect to requirements under § 820.198 (complaint files) during stage 1 of the phaseout policy. However, upon the start of stage 1, and prior to the effective date of the amended QSR, FDA intends to exercise enforcement discretion and generally not enforce requirements under § 820.198 for laboratories that are in compliance with Subclause 8.2.2 of ISO 13485. Following the effective date of the amended QSR (February 2, 2026), laboratories must comply with the QS requirements that are in effect at that time.

⁴⁶ As explained elsewhere in this preamble, FDA has generally considered the term “laboratory developed test (LDT)” to mean an IVD that is intended for clinical use and that is designed, manufactured, and used within a single CLIA-certified laboratory that meets the regulatory requirements under CLIA to perform high complexity testing.

with some, but not all, of the QS requirements (88 FR 68006 at 68025). FDA continues to believe this policy is helpful and appropriate. Although FDA and CMS regulation are different and complementary, compliance with CLIA requirements provides some quality assurances that may be relevant to laboratories' manufacturing practices. In particular, laboratories may in practice be able to apply concepts set forth under CLIA requirements for laboratory operations to certain manufacturing activities regulated by FDA. For FDA to effectively take into account the CLIA requirements, this policy will apply only for LDTs (i.e., when all manufacturing activities occur within a single laboratory and the IVD is not transferred outside that laboratory). However, this policy is limited in scope because CLIA regulations do not provide relevant assurances for certain QS requirements. These requirements include design controls under § 820.30; purchasing controls (including supplier controls) under § 820.50; acceptance activities (receiving, in-process, and finished device acceptance) under §§ 820.80 and 820.86; CAPA under § 820.100; and records requirements under part 820, subpart M.^{47,48} Because CLIA does not provide assurances relevant to these requirements, FDA has determined to phase out the general enforcement discretion approach for these specific requirements 3 years after publication of this final rule (except for requirements under § 820.198 (complaint files), for which FDA intends to phase out the general enforcement discretion approach during stage 1 of the phaseout policy).

Finally, FDA notes that under section 515(d)(2) of the FD&C Act, the Agency may not approve a PMA if the applicant fails to demonstrate conformity with the QS requirements.

Therefore, compliance with the QS requirements is needed to support approval of a PMA. As

⁴⁷ For LDTs, FDA generally expects compliance with requirements under part 820, subpart M (Records) but not §§ 820.20, 820.22, and 820.40 (which are cross-referenced in subpart M), or comparable provisions of ISO 13485 in accordance with the amendments to part 820 once that rule takes effect in February 2026.

⁴⁸ Upon the effective date of the amendments to the QSR, the requirements relating to design controls, purchasing controls, acceptance activities, CAPA, and records requirements will be set forth in the following ISO 13485 clauses as modified by the codified for part 820: Clause 4. Quality Management System, Subclause 4.2.5; Clause 6. Resource Management; Clause 7. Product Realization, Subclause 7.1, Subclause 7.3, Subclause 7.4, and Subclause 7.4.3; and Clause 8. Measurement, Analysis, & Improvement, Subclause 8.2.2., Subclause 8.2.5, Subclause 8.2.6, and Subclause 8.3.

provided in section 520(f)(2) of the FD&C Act, any person subject to the QS requirements may petition for an exemption or variance from any QS requirement (see also § 820.1).

4. Stage 4: Beginning 3½ Years After the Publication Date of This Final Rule, FDA Will Expect Compliance With Premarket Review Requirements for High-Risk IVDs Offered as LDTs, Unless a Premarket Submission Has Been Received by the Beginning of This Stage in Which Case FDA Intends to Continue to Exercise Enforcement Discretion for the Pendency of its Review

FDA has determined that the phaseout for the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs offered as LDTs should occur 3½ years from publication of this final rule, consistent with the timeline proposed in the NPRM (88 FR 68006 at 68026). The premarket review requirements for PMAs are set forth in 21 U.S.C. 360e and part 814 (21 CFR part 814). The information in the record has not changed our view that 3½ years will provide sufficient notice and opportunity for laboratories manufacturing IVDs to plan for and prepare PMAs.⁴⁹ Although we received comments indicating that it would be difficult for laboratories to comply within this 3.5-year timeline, the new enforcement discretion policies included in this final phaseout policy should help address those concerns. For example, the policy for currently marketed IVDs offered as LDTs and the policy for certain unmet needs LDTs mean FDA generally does not expect compliance with premarket review requirements for a substantial subset of IVDs. Overall, in light of these policies, FDA has determined that a 3.5-year period is a reasonable amount of time to expect laboratories to come up to speed on PMA requirements, gather the information required for PMAs, and complete their PMA submissions (see section II.F.4 of the FRIA).

This timeline is also intended to align the phaseout for the general enforcement discretion approach for premarket review requirements for high-risk IVDs offered as LDTs with the start of

⁴⁹ Under the phaseout policy, laboratories that intend to submit an HDE application or a BLA should do so within the same 3½-year timeframe for submission of PMAs. As in the case of PMAs, under the phaseout policy, FDA generally does not intend to enforce against IVDs after a complete HDE application or BLA has been submitted (within the 3½-year timeframe) until FDA completes its review of the application. Premarket review requirements specific to HDE applications are set forth in 21 U.S.C. 360j(m) and part 814, subpart H. Licensure requirements are set forth in 42 U.S.C. 262 and 21 CFR part 601.

fiscal year 2028, which coincides with the beginning of a new user fee cycle. This alignment will provide an opportunity for industry participation in negotiations regarding the next user fee cycle with the knowledge that laboratory manufacturers will be expected to comply with premarket review requirements. (Although a trade association representing laboratories previously has participated in Medical Device User Fee Amendments (MDUFA) negotiations, the prior negotiations have not incorporated similar expectations regarding laboratory compliance with premarket requirements.) Thus, we have determined that this amount of time is appropriate to foster stability and consistency in the marketplace for the current MDUFA cycle, and FDA will take into account the need for adequate FDA resources to implement the phaseout policy in a manner that does not compromise the capacity to achieve MDUFA V performance expectations. FDA anticipates that during this 3½-year period, laboratories will work with FDA to determine whether PMAs should be submitted for their IVDs.

Under this phaseout policy, FDA generally does not intend to enforce against IVDs offered as LDTs for lacking premarket approval after a complete PMA has been submitted until FDA completes its review of the application, provided that the PMA has been submitted within the 3½-year timeframe. Given that such IVDs may already be on the market and available to patients, FDA generally does not intend to interrupt access at the point when a submission is made. IVDs for which a PMA is submitted after the 3½-year timeframe would not fall within this enforcement discretion policy; FDA approval is expected prior to such IVDs being offered.

Based on a review of the comments, FDA is also adopting a policy under which it generally does not intend to enforce premarket review requirements for certain laboratory changes to another manufacturer's lawfully marketed test. In particular, this policy applies when a laboratory certified under CLIA and meeting the regulatory requirements under CLIA to perform high complexity testing modifies another manufacturer's 510(k) cleared or De Novo authorized test, following design controls and other quality system requirements for which FDA

expects compliance as described in section V.C.3, in a manner that could not significantly affect the safety or effectiveness of the test and does not constitute a major change or modification in intended use, and where the modified test is performed only in the laboratory making the modification. FDA is adopting this policy to promote more efficient and effective use of Agency resources and because it understands laboratories may make such changes to, for example, integrate a test into its operations, accommodate local conditions (e.g., storage conditions), or address supply shortages. Under the policy, FDA would expect premarket submissions from laboratories modifying a third party's 510(k) cleared or De Novo authorized test for the same types of changes for which FDA would expect a premarket submission from the *original* manufacturer making changes to its own IVD. Taking into account the risks associated with relatively minor changes to 510(k) cleared or De Novo authorized tests when they occur in a single laboratory (i.e., without broad distribution), at this time, we believe the resources needed to review these types of changes generally can be better spent on other Agency priorities and activities. For a description of changes that could significantly affect the safety or effectiveness of the test or constitute a major change or modification in intended use under this policy, see FDA's regulations at § 807.81(a)(3) and further discussion in the final guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device" (Ref. 61). If the modification (individually or in the aggregate) could significantly affect the safety or effectiveness of the test or does constitute a major change or modification in intended use and the modified test does not fall within an enforcement discretion policy discussed in section V.B above, FDA expects laboratories to submit the applicable premarket submission. If the laboratory modification is so significant that the IVD is no longer substantially equivalent to the original IVD and requires a PMA, FDA expects the PMA to be submitted either by stage 4 or before the modified test is marketed, whichever comes later.

We are not applying this enforcement discretion policy to modifications to another manufacturer's PMA-approved or BLA-licensed test because such tests are high-risk, and

changes to such tests pose corresponding increased risks. We note that relatively few IVDs are considered high risk today, and, further, FDA has announced its intent to initiate the reclassification process for most IVDs that are currently class III into class II (Ref. 66). FDA aims to complete this reclassification process before stage 4 of the phaseout policy. We therefore anticipate that there will be even fewer class III (high-risk) IVDs going forward. As such, these tests present resource considerations that are different from those discussed above.

5. Stage 5: Beginning 4 Years After the Publication Date of This Final Rule, FDA Will Expect Compliance With Premarket Review Requirements for Moderate-Risk and Low-Risk IVDs Offered as LDTs (that Require Premarket Submissions), Unless a Premarket Submission Has Been Received by the Beginning of This Stage in Which Case FDA Intends to Continue to Exercise Enforcement Discretion for the Pendency of its Review

FDA has determined to phase out the general enforcement discretion approach with respect to premarket review requirements for moderate-risk IVDs offered as LDTs (IVDs that may be eligible for classification into class II) and low-risk IVDs offered as LDTs (IVDs that may be eligible for classification into class I) that require a premarket submission 4 years from publication of this final rule. These premarket submissions include 510(k) submissions, the requirements for which are set forth at 21 U.S.C. 360(k), 360c(i), and part 807, subpart E. These submissions also include De Novo requests, which laboratories may submit for IVDs offered as LDTs for which there is no legally marketed device upon which to base a determination of substantial equivalence, and for which the laboratory seeks classification into class I or class II. These requirements are set forth at 21 U.S.C. 360c(f)(2) and 21 CFR part 860, subpart D.

FDA is retaining the same 4-year timeline that was proposed in the NPRM for stage 5 for reasons similar to those for stage 4 (see 88 FR 68006 at 68027). Specifically, when taking into account the enforcement discretion policies in section V.B, we believe the original timeline for compliance with 510(k) and De Novo requirements is feasible, particularly given

that these submissions are generally less resource-intensive than PMAs (for additional information see section II.F.4 of the FRIA (Ref. 10)). As noted in the NPRM, the 6-month interval between stages 4 and 5 will enable FDA to prioritize the review of applications for high-risk IVDs offered as LDTs (subject to premarket approval requirements), so that we can focus first on IVDs for which the consequences of a false result are generally most significant (88 FR 68006 at 68027). In addition, this timeline aligns with the user fee cycle, as previously discussed.

FDA generally does not intend to enforce against IVDs offered as LDTs for lacking premarket authorization after a complete 510(k) or De Novo request has been submitted until FDA completes its review of the submission, provided that the 510(k) or De Novo request has been submitted within the 4-year timeframe. Given that such IVDs may already be on the market and available to patients, FDA generally does not intend to interrupt access at the point when a submission is made. IVDs for which a 510(k) or De Novo request is submitted after the 4-year timeframe would not fall within this enforcement discretion policy; FDA clearance or authorization is expected prior to such IVDs being offered.

FDA is also adopting the policy regarding laboratory modifications to another manufacturer's lawfully marketed test that is discussed under stage 4. As explained in that discussion, under this policy, FDA generally does not intend to enforce premarket review requirements when a laboratory certified under CLIA and meeting the regulatory requirements under CLIA to perform high complexity testing modifies another manufacturer's 510(k) cleared or De Novo authorized test, following design controls and other quality system requirements for which FDA expects compliance as described in section V.C.3, in a manner that could not significantly affect the safety or effectiveness of the test and does not constitute a major change or modification in intended use, and where the modified test is performed only in the laboratory making the modification. If the modification (individually or in the aggregate) could significantly affect the safety or effectiveness of the test or does constitute a major change or modification in

intended use and the modified test does not fall within an enforcement discretion policy discussed in section V.B above, FDA expects laboratories to submit the applicable premarket submission. If the applicable premarket submission is a 510(k) or De Novo request, FDA expects the 510(k) or De Novo request to be submitted either by stage 5 or before the modified test is marketed, whichever comes later.

FDA also anticipates that laboratories may seek to utilize FDA's Third Party review program. FDA currently operates a Third Party review program for medical devices, and multiple organizations are accredited to conduct reviews of 510(k) submissions for certain IVDs (see Ref. 67). We anticipate interest in the Third Party review program among IVD manufacturers, as well as potential new 3P510k Review Organizations. In particular, FDA is aware of certain CLIA accreditation organizations that have expressed interest in potentially becoming Third Party reviewers under FDA's program, and to the extent laboratories are already familiar with these organizations, laboratories may be more inclined to use the Third Party review program. In addition, under the MDUFA V agreement, FDA is currently working to enhance the Third Party review program, which may make it more attractive to manufacturers including laboratories.

VI. Comments on the Notice of Proposed Rulemaking and FDA Responses

We received more than 6,500 comment letters on the NPRM by the close of the comment period, each containing one or more comments on one or more issues. We received comments from medical device associations, members of the medical device and pharmaceutical industries, medical and healthcare professional associations, hospitals and AMCs, accreditation organizations, other advocacy organizations, government agencies, and individuals. We describe and respond to the comments in this section of the document. We have numbered each comment to help distinguish between different comments. We have grouped similar comments together under the same number so that FDA's responses can be addressed by topic, and, in some cases, we have separated different issues discussed in the same comment and designated them as

distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received or considered.

A. General Comments on the Notice of Proposed Rulemaking

(Comment 1) FDA received comments in support of and in opposition to the NPRM. Comments supporting the proposal generally discussed the importance of FDA oversight of IVDs offered as LDTs to protect the public health and ensure that patients and healthcare providers are able to trust and rely on test results which impact important healthcare decisions. Some comments expressed concern regarding the use of IVDs offered as LDTs that are not clinically validated, and regarding scientifically dubious claims made about such IVDs, especially in areas like cancer prognosis and genetic screening. Several comments noted that without independent oversight the work to ensure LDT effectiveness and consistency is left to those with a financial interest in the continued use of those LDTs. Comments expressing general opposition cited various reasons for their opposition, including that the proposal is too broad in scope, is too difficult for laboratories to follow, would require laboratories to “follow processes that are unfit for the purpose of assessing the quality of laboratory tests,” is not necessary, and reflects regulatory overreach.

(Response 1) FDA agrees that phasing out the general enforcement discretion approach for LDTs is important to protect the public health, as discussed further in section III.B. Current evidence points to problems associated with IVDs offered as LDTs such that there is a fundamental uncertainty about whether IVDs offered as LDTs provide accurate and reliable results. These issues highlight the need for increased oversight to help ensure the safety and effectiveness of IVDs offered as LDTs.

FDA disagrees with the comments stating that FDA's proposal is overly broad. As described throughout this preamble and in the NPRM, the evidence supports increased oversight of IVDs offered as LDTs. The final phaseout policy fulfills the goal of greater oversight of such

IVDs while also accounting for other key public health interests. For example, upon further consideration, including of the comments received regarding particular aspects of the phaseout policy, FDA is adopting several new targeted enforcement discretion policies, as detailed in section V.B.

FDA also disagrees with comments stating that FDA's proposal is difficult to follow. We believe the scope and five stages of the proposed and final phaseout policy, discussed further in section V, are clear and, as noted throughout this preamble, we intend to issue additional guidance as appropriate and offer other resources to the public, which will assist stakeholders during implementation of the phaseout.

In addition, we disagree with the statement that the proposal would require laboratories to follow processes that are "unfit for the purpose of assessing the quality" of IVDs offered as LDTs. As further discussed in sections VI.C.2 and VI.C.3 of this preamble, FDA has the experience and the scientific and regulatory expertise to oversee IVDs, including LDTs. Moreover, the requirements and processes for devices in the FD&C Act and FDA regulations apply to all IVDs, including LDTs, and the requirements/processes set forth in part 809 are specifically tailored to IVDs, including LDTs. We also disagree that the proposal (or final rule) reflects "regulatory overreach" for the reasons discussed in section VI.D.

B. Definitions

(Comment 2) Several comments stated that the rule should explicitly define in § 809.3 terms such as "LDTs," "IVDs," and "enforcement discretion" for clarity. Other comments suggested that FDA identify the differences between IVDs and LDTs, with one comment suggesting that FDA refer to LDTs as CLIA-LDTs because laboratories must be CLIA-certified. Another comment requested that FDA define the terms "diagnostic" and "impact clinical outcomes" as used in the proposed rule. One comment requested clarity on whether digital scanning of pathology slides is within the scope of the LDT definition included in the NPRM.

(Response 2) The term “in vitro diagnostic products” (IVDs) is defined in § 809.3(a). Through this rulemaking, FDA is amending the definition of “in vitro diagnostic products” in its regulations to state that IVDs are devices under the FD&C Act “including when the manufacturer of these products is a laboratory.” Therefore, as amended by this rule, IVDs are defined in § 809.3(a) as those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)(1) of the FD&C Act, and may also be biological products subject to section 351 of the PHS Act, including when the manufacturer of these products is a laboratory.

FDA disagrees that the terms “LDTs” and “enforcement discretion” should be defined in § 809.3. Neither term is used in part 809, so adding definitions to part 809 would have no effect, and would likely be confusing. To the extent the commenter believed the use of those terms in the NPRM was not sufficiently clear, FDA also disagrees, as it has clearly explained those terms in both the proposed and final rules (see, e.g., 88 FR 68006 at 68008 (stating that “FDA has generally exercised enforcement discretion such that it generally has not enforced applicable requirements with respect to most LDTs”); 88 FR 68006 at 68009 (stating that “FDA has generally considered an LDT to be an IVD that is intended for clinical use and that is designed, manufactured, and used within a single laboratory that is certified under [CLIA] and meets the regulatory requirements under CLIA to perform high complexity testing”))).

With regards to the definition of “diagnostic,” FDA interprets this comment as a request to further define the term in the definition of an IVD. We see no reason, and the comment does not include any rationale, why this term should be defined. Moreover, we note that the term applies across many devices and so defining it in part 809, which is limited in scope to IVDs, would likely cause confusion. With regard to the comment requesting clarification of the phrase

“impact clinical outcomes,” FDA did not use the phrase “impact clinical outcomes” in the NPRM and, as a result, does not understand this request.

Finally, regarding the comment requesting clarity on whether digital scanning of pathology slides is within the scope of the LDT definition, FDA would need to know more about the product to assess whether it falls within what FDA has generally considered to be an LDT-- i.e., an IVD that is intended for clinical use and that is designed, manufactured, and used within a single laboratory that is certified under CLIA and meets the regulatory requirements under CLIA to perform high complexity testing. FDA notes that whole slide imaging systems are class II devices with special controls and are subject to 510(k) notification requirements (21 CFR 864.3700). For additional information about specific classifications for devices, we recommend consulting 21 CFR parts 862 through 892.

(Comment 3) A comment requested FDA clarify how it regulates common laboratory equipment (such as general-purpose computer monitors or printers, microscopes, centrifuges, and incubators), and expressed concern that increased FDA oversight of LDTs would impact FDA’s regulation of such equipment.

(Response 3) FDA regulates common laboratory equipment that meets the FD&C Act’s definition of a device. Section 201(h)(1) of the FD&C Act defines a device, in relevant part, as “An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:....(B) intended for use⁵⁰ in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals,The term ‘device’ does not include software functions excluded pursuant to section 520(o) [of the FD&C Act].” Whether a product falls within the device definition involves a fact-specific inquiry, including an inquiry into the

⁵⁰ “Intended use” as used in this provision is determined by the objective intent of the persons legally responsible for the labeling of an article (or their representatives) (see § 801.4). The intent may be shown by such persons’ expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article (*Id.*).

product's intended use. In general, general-purpose computer monitors or printers that are not intended for a medical use would not fall within the device definition, whereas general purpose laboratory equipment labeled or promoted for specific medical uses intended to prepare or examine specimens from the human body would fall within the device definition.

FDA has classified such general purpose laboratory equipment into class I and has exempted these devices from premarket notification under section 510(k) of the FD&C Act (21 CFR 862.2050). FDA has also classified certain microscopes and accessories and microbiological incubators into class I and has exempted them from premarket notification under section 510(k) of the FD&C Act (21 CFR 864.3600 and 866.2540). For additional information about specific classifications for devices, we recommend consulting 21 CFR parts 862 through 892. This rule does not change FDA's authority to regulate such equipment and FDA does not anticipate a significant impact from the phaseout policy on such equipment, which is generally not designed, manufactured, and used within a single CLIA-certified laboratory.

C. Need for the Rule

1. FDA's Description of the Current State of the LDT Market

(Comment 4) FDA received several comments on the current state of the LDT market. Some asserted that the potential risk to patients of false results from LDTs remains unchanged from 1976.

(Response 4) FDA disagrees with comments which claim that the risk to patients is unchanged from 1976. As discussed in the NPRM and this preamble, today LDTs are commonly used to diagnose infectious diseases, screen for various diseases and conditions, and identify the best treatment for patients with cancer, among other uses. The consequences of false results in these contexts can include spread of disease, missed diagnoses, misdiagnoses, use of ineffective treatments with toxic side effects, and lack of use of life-saving treatments. LDTs are relied upon for high stakes medical decisions. Further, genetic sequencing technology has advanced such that a person's deoxyribonucleic acid (DNA) can be quickly sequenced and different variations

identified in a single analysis; the clinical significance of many of these variations is unknown. FDA is aware of IVDs offered as LDTs, particularly genetic IVDs offered as LDTs, that are offered for uses that lack sufficient scientific support. The availability of new technologies and increasing reliance on them for clinical decision-making has increased the risk of IVDs offered as LDTs.

(Comment 5) Some comments claimed FDA overestimated the number of IVDs offered as LDTs on the market while others claimed FDA underestimated the number of IVDs offered as LDTs on the market. Some comments said the breadth of reach of LDTs is small whereas another comment pointed out that LDTs are used for routine clinical tests in addition to “advanced diagnostics.” One comment claimed that FDA’s estimate of the number of IVDs offered as LDTs was more than “10 times what researchers found in a peer-reviewed study published in the American Journal of Clinical Pathology of actual clinical test orders at University of Utah Health: 3.9%” (see Ref. 68).

(Response 5) FDA acknowledges that it does not know exactly how many IVDs are currently offered as LDTs, precisely what those IVDs are used for, or the exact breadth of the reach of those IVDs. FDA will receive information regarding IVDs offered as LDTs and their intended uses through registration and listing in stage 2 of the phaseout policy. FDA disagrees with the assertion that the cited publication suggests that FDA’s estimates may be 10 times higher than what has been reported in scientific literature. According to the publication cited in the comment, the percentage of test orders fulfilled with IVDs offered as LDTs at a single health system was 3.9 percent (which seems to have been the basis of the commenter’s “10 times higher” claim) but the percentage of distinct tests that were IVDs offered as LDTs within this health system was 45 percent (880/1,954). While it is helpful to understand that 3.9 percent of test orders were fulfilled with IVDs offered as LDTs, this does not support the assertion that FDA’s estimate of the percentage of *distinct* IVDs offered as LDTs is “10 times higher” than that reported by the publication. In section II.D of the PRIA, FDA estimated that LDTs account for

about 50 percent of total IVDs that are used in some laboratories (see Ref. 60), which is very similar to the 45 percent reported in the publication. Additional information regarding these estimates is provided in response to comment 3 in the FRIA (see Ref. 10).

(Comment 6) One comment questioned FDA’s statement that test results are often used by treating clinicians to inform their professional judgments and that the incidence of false positive and false negative test results inherent in any form of testing can present treatment challenges. This comment asserted that treating clinicians are well aware of the inherent limitations of testing, regardless of whether the test is an LDT or not, and that such clinicians base their treatment on holistic considerations of treatment factors. Thus, an erroneous test result from an LDT does not necessarily mean an erroneous treatment decision. A similar comment from a physician stated that FDA oversight will not increase the safety of LDTs and any risks associated with inaccurate test results are better left to physicians to assess.

(Response 6) FDA disagrees with these comments. Despite the suggestion to the contrary, not all clinicians are “well aware” of limitations of tests, including tests that are not FDA-authorized. Rather, FDA routinely consults with experts and has encountered many who do not understand the limitations of tests and do not consider that a test result provided by a test may be incorrect. For example, a cardiologist at an FDA public workshop on troponin testing stated, “[d]octors trust numbers and if they are wrong we don’t care we trust them anyway” (Ref. 69). Similarly, an article authored by a physician and published in the Washington Post explained that his “research has found that many physicians misunderstand test results” and noted that “your doctor may have a blind spot, an unconscious tendency to have too much trust in a test” (Ref. 70). While we agree that erroneous test results do not *always* lead to direct harm/erroneous treatment decisions, they often do, and FDA is addressing these risks in the phaseout policy.

2. CLIA Oversight

(Comment 7) FDA received comments stating that CLIA and CLIA regulations do not provide sufficient regulation of manufacturer laboratories and their tests. One comment noted that this is because laboratories are not equipped with appropriate “QMS systems,” development teams, manufacturing, and production processes. Some comments stated that CLIA lacks requirements related to design controls and other important QS requirements. Comments also asserted that CMS does not review a laboratory’s methodology for assessing analytical validity, does not assess clinical validity, and inspects only every 2 years under CLIA. A comment stated that CLIA and the related laboratory accreditation by CMS do not necessarily preclude additional oversight by FDA, especially for direct-to-consumer and “commercialized” products.

(Response 7) FDA agrees that CLIA and CLIA regulations are not a substitute for FDA’s oversight of IVDs offered as LDTs under the FD&C Act. As discussed in the NPRM, laboratories that offer IVDs as LDTs are subject to both the FD&C Act and CLIA (88 FR 68006 at 68013-14). CMS determines whether a laboratory meets CLIA requirements, which is a specific role distinct from FDA’s statutory responsibilities. FDA’s device authorities under the FD&C Act are intended to help ensure that devices, including IVDs offered as LDTs, have appropriate assurance of safety and effectiveness.

FDA acknowledges that CLIA establishes requirements for laboratory operations and personnel and the issuance of clinical laboratory certifications. However, those requirements do not provide sufficient assurance of safety and effectiveness for the tests themselves. For example, in administering CLIA, CMS does not regulate critical aspects of laboratory test development; does not evaluate the performance of a test before it is offered to patients and healthcare providers; does not assess clinical validity (i.e., the accuracy with which a test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient); does not regulate certain manufacturing activities, such as design controls and acceptance activities; does not provide human subject protections for individuals who participate in clinical trials; and does not require adverse event reporting. FDA also agrees that inspections

under CLIA do not provide sufficient assurances of safety and effectiveness for IVDs offered as LDTs, as discussed further in response to comment 8.

CMS has consistently agreed that its role in administering the CLIA Program, which regulates the operations of clinical laboratories performing testing, is distinct from FDA's role in enforcing the FD&C Act to ensure that tests have appropriate assurance of safety and effectiveness. In order to ensure the accuracy and reliability of patient test results, the CLIA regulations provide oversight covering the operation and administration of the laboratory, to include the appropriate qualification of its personnel. For example, the CLIA regulations include requirements pertaining to proficiency testing, laboratory personnel qualifications, test ordering and reporting, quality control, and the development and use of laboratory processes and procedures. FDA and CMS have long stood together in mutual support of FDA oversight of the analytical and clinical validity of LDTs, and CMS agrees with FDA that the CLIA program is separate in scope and purpose from FDA oversight (Ref. 71). Each regulatory scheme serves a different function, and as CMS notes, "CMS and FDA's regulatory schemes are different in focus, scope, and purpose, but they are intended to be complementary" (Ref. 26). In 2015, Dr. Patrick Conway, then the Deputy Administrator for Innovation and Quality & Chief Medical Officer of CMS, stated that "CMS does not have scientific staff capable of reviewing complex medical and scientific literature in determining clinical validity. This expertise resides within the FDA, which assess the clinical validity in the context of premarket reviews and other activities aligned with their regulatory efforts under the Food, Drug and Cosmetic Act." Statement of Dr. Patrick Conway, Deputy Administrator for Innovation and Quality & Chief Medical Officer, CMS, Committee Hearing (October 29, 2015), at 25. This was not a new position for CMS; nearly 30 years earlier, the then-Administrator of the Health Care Financing Administration (HCFA, CMS's predecessor agency) stated that FDA, under the FD&C Act, had a role to play in the regulation of laboratory testing: "On the quality issue, first, the Health Care Financing Administration has oversight authority and will use that to do a better job under our new

regulations. The role of the Centers for Disease Control is to provide expert advice to us on how we regulate laboratories. The role of the FDA is in oversight of the devices and other technical aspects of lab testing.” Statement of Dr. William L. Roper, Administrator, HCFA, Committee Hearing on H.R. 4325 (July 6, 1988), at 77.

(Comment 8) FDA received several comments stating that CLIA provides sufficient regulation of IVDs offered as LDTs. Some comments stated that regulation under CLIA is sufficient because obtaining a CLIA certificate requires a laboratory to demonstrate that the personnel in the laboratory have the training, experience, and level of proficiency required to perform the types of tests offered by the laboratory. Other comments stated that regulation under CLIA is sufficient because CLIA-certified laboratories are subject to inspections to confirm that the testing complies with CLIA regulations, including ensuring that there is adequate validation of the tests, supervision by the laboratory director, and quality procedures. Many comments contended that laboratories certified by CLIA follow a robust and rigorous set of requirements regarding validation, verification, and monitoring of IVDs offered as LDTs. In particular, some comments asserted that CLIA provides a regulatory mechanism designed to ensure accurate test results. Other comments stated that FDA has not demonstrated that FDA’s premarket review process is more effective than CLIA in ensuring the accuracy of tests.

(Response 8) FDA acknowledges that CLIA and CLIA regulations establish requirements for laboratory operations and laboratory personnel, and specific requirements that must be met to obtain a clinical laboratory certification (see, e.g., 42 CFR part 493 subparts C, K, and M). CLIA-certified laboratories also are subject to inspection under 42 CFR part 493 subpart Q to verify that laboratories are conducting testing in compliance with the CLIA regulation. Inspections do not, however, verify that the tests themselves comply with the requirements of the FD&C Act that are designed to ensure that tests have appropriate assurance of safety and effectiveness for their intended purpose. Likewise, while FDA agrees that CLIA-certified laboratories are required to meet certain verification, validation, and monitoring requirements,

FDA disagrees that those requirements provide sufficient assurance of safety and effectiveness for the tests themselves. As more fully set forth in response to comment 7, CMS does not regulate critical aspects of laboratory test development; does not evaluate the performance of a test before it is offered to patients and healthcare providers; does not assess clinical validity; does not regulate certain manufacturing activities; does not provide human subject protections for individuals who participate in test clinical trials; and does not require adverse event reporting.

FDA disagrees with comments indicating that FDA's premarket review process "is not more effective" than CLIA regulation. FDA's premarket review process serves a role that CLIA regulation does not. During review of a marketing submission for an IVD, FDA reviewers closely examine data relevant to safety and effectiveness and draw on their expertise and experience to understand both the product and the science supporting the product. FDA reviewers evaluate whether a test accurately and reliably detects or quantifies its intended target and whether results from the test accurately and reliably identify, measure, or predict the presence or absence of the intended clinical condition or predisposition. For example, for a test that is intended to detect genetic variants to predict the risk of a person developing a particular disease, FDA reviewers would evaluate whether the test can accurately and reliably detect the intended genetic variants in the intended use specimen type (e.g., blood, saliva), and they would also evaluate evidence demonstrating whether the genetic variant is associated with the risk of developing that particular disease. As another example, for a test intended to quantify the levels of a protein to aid in the diagnosis of a particular disease, FDA would evaluate whether the device can accurately and reliably quantify the levels of the protein in the intended specimen type and also whether the levels of protein quantified by the test can be used to diagnose the disease. FDA also reviews IVD labeling to ensure there are adequate instructions for use, which includes directions for performing the test and interpreting the results, warnings, limitations, a summary of test performance (for example, accuracy), and how the results are reported. See our response to comment 10 for additional discussion of FDA's expertise.

(Comment 9) FDA received comments stating that regulation under CLIA is sufficient because CLIA-certified laboratories perform proficiency testing to ensure that assays are performing properly. One comment suggested that FDA authorization is a one-time event with no ongoing monitoring of product performance, whereas proficiency testing is an ongoing requirement through which laboratories periodically confirm their capabilities to perform tests. In contrast, FDA received a comment which suggested that proficiency testing is not sufficient, as a laboratory may fail proficiency testing several times before receiving a notice to cease testing.

(Response 9) FDA disagrees that proficiency testing provides sufficient regulation of IVDs offered as LDTs. Under CLIA, enrollment in a Department of Health & Human Services (HHS)-approved proficiency testing program is a requirement for only a portion of tests that a laboratory offers, and proficiency testing programs do not address all IVDs offered as LDTs (see 87 FR 41194). Under the CLIA regulations, proficiency testing is required for only the limited number of analytes found in 42 CFR part 493 subpart I (Proficiency Testing Programs for Nonwaived Testing), which are referred to as “regulated” analytes by CMS. From the list of LDTs approved by NYS CLEP, FDA has seen that many IVDs offered as LDTs are tests for analytes other than the regulated analytes listed in 42 CFR part 493 subpart I. Additionally, the list of regulated analytes does not include any genetic markers, and FDA is aware from the NYS CLEP approval database as well as discussions with stakeholder that many IVDs offered as LDTs are genetic tests. There are also many other analytes for which there are no programs that offer proficiency testing. When a laboratory performs tests, including IVDs offered as LDTs, for analytes that are not regulated under CLIA or where there is no proficiency testing program available, the laboratory is required only to verify the accuracy of the test at least twice annually, which may be done by splitting a patient sample with a laboratory that offers the same test and comparing results. The number of samples tested and the acceptability of the results is determined by the laboratory director. Comparing results from a small number of samples,

possibly even a single sample, without prospective metrics for success is not equivalent to a prospective determination of safety and effectiveness prior to initiating testing on patient samples. FDA also appreciates the concern raised in the comment which stated that laboratories may potentially continue testing after failing proficiency testing. For these reasons, proficiency testing alone does not provide sufficient assurance of safety and effectiveness for an IVD offered as an LDT for its intended use.

FDA also disagrees with the suggestion that FDA regulation involves no ongoing monitoring of product performance. Under FDA regulations, test manufacturers are generally subject to a variety of ongoing requirements, including labeling requirements, registration and listing, quality system requirements, adverse event reporting, and periodic inspections that confirm compliance with design controls and other QS requirements.

(Comment 10) A number of comments suggested that FDA is not the appropriate entity to oversee LDTs, and that any changes to the manner in which tests are regulated should be implemented through amendments to CLIA, or through modifications to the CLIA regulation, which many comments described as “modernizing” that regulation. Comments asserted that FDA does not have the required expertise, and one comment stated that CMS/CLIA and certain CLIA accreditation organizations are best able to verify the accuracy of laboratory testing. This comment stated that requiring all “laboratory testing” to be certified under CLIA would be better than enforcing laboratory compliance with medical device regulations. Other comments stated that complaints about test quality should be evaluated by CMS rather than FDA, to avoid creating what the comments described as duplicative regulation. Some comments noted that laboratories are unfamiliar with the premarket requirements and other requirements of the FD&C Act. Some comments argued that FDA is slow to clear or approve tests, and asserted that for that reason, FDA should not oversee IVDs offered as LDTs. On the other hand, some comments asserted that FDA has a role to play in assuring that tests produce reliable results for patients and

providers, and some comments pointed to FDA's demonstrated expertise in review of analytical and clinical validity of IVDs.

(Response 10) FDA does not agree that concerns regarding the safety and effectiveness of LDTs should be addressed by amending CLIA or modifying the CLIA regulation. CMS determines whether a laboratory and its personnel meet CLIA requirements, whereas FDA, among other things, reviews and evaluates the tests themselves, including IVDs offered as LDTs, to ensure that they have appropriate assurance of safety and effectiveness under the FD&C Act. CMS and FDA agree: CMS does not have the resources and expertise to assure that tests work for their intended clinical purpose; FDA does (Ref. 71). Congress specifically charged FDA with such oversight, as discussed further in response to comments in section VI.D.2. In particular, FDA has the scientific and regulatory expertise to review data and information on individual IVDs offered as LDTs and determine their safety and effectiveness. FDA employs hundreds of scientists with expertise in review of safety and effectiveness, including those who have worked in clinical laboratories and developed LDTs. FDA is comprised of physicians, statisticians, engineers, biologists, chemists, geneticists, and others, who evaluate the science behind medical products before they are marketed and utilized. Understanding the complex technical information in applications, such as clinical trial data, bench testing results, and product design characteristics--and putting that information in context to assess whether a product has appropriate assurance of safety and effectiveness for its intended use--is within FDA's unique expertise. This type of expertise is no less important for IVDs offered as LDTs, the safety and effectiveness of which may significantly impact not only individual health but also the public health, as described elsewhere in this preamble.

Moreover, establishing a duplicative system for the oversight of IVDs would create bureaucracy and inconsistencies (Ref. 71). As described in the NPRM, such an approach would cause a problematic split in oversight, with the same types of IVDs being reviewed by different Agencies depending on where the IVD was made (88 FR 68006 at 68014). For example, a cancer

diagnostic test developed by a conventional manufacturer would be reviewed by FDA while a similar cancer diagnostic test (using the same sample type and testing for the same analytes) developed by a laboratory would be reviewed by another Agency. Further, with that divided oversight, an IVD developed by a conventional manufacturer could even be reviewed and cleared by FDA and subsequently reviewed by another Agency if a laboratory made certain modifications to it. However, if those same modifications were made by the original manufacturer, they would be reviewed by FDA. This could lead to confusion and inconsistency.

In response to the comment that stated that CLIA should require certification of all “laboratory testing,” FDA acknowledges that CLIA establishes requirements for laboratory operations and their personnel and issues clinical laboratory certifications. However, FDA disagrees that those requirements provide sufficient assurance of safety and effectiveness for the tests themselves. CLIA does not assess clinical validity or certain manufacturing activities.

We further note that to the extent laboratories may be unfamiliar with the premarket requirements of the FD&C Act, current familiarity with applicable requirements is not determinative of the need for such requirements to be enforced. FDA has made several resources available to stakeholders to increase familiarity with applicable requirements, including final guidance documents and information on FDA’s website (see, e.g., Ref. 72), and will provide additional materials and outreach to laboratories during the phaseout period. In addition, with respect to the speed of FDA’s premarket review, FDA notes that its premarket review timelines are negotiated with industry in connection with MDUFA reauthorization. For information regarding FDA’s recent performance with respect to MDUFA decision goals, see Ref. 73. FDA generally meets the timeframes for MDUFA decisions negotiated with industry, including for IVD submissions. However, FDA’s response to the unprecedented COVID-19 public health emergency significantly impacted the Agency’s ability to meet its MDUFA IV performance goals, resulting in some missed decision goals.

(Comment 11) Comments stated that CLIA has its own mechanism for making improvements to its regulations, through the Clinical Laboratory Improvement Advisory Committee (CLIAC), which includes members from the Centers for Disease Control and Prevention (CDC) and FDA. Comments noted that CLIAC has provided advice and guidance to HHS on revisions and improvements to the CLIA standards. Comments suggested that modernizing CLIA is a pathway which is supported by a significant number of “major organizations.” A comment stated that effectuating changes through CLIA would be a streamlined and cost-effective approach, for both the government and laboratories, and the least disruptive and burdensome approach to addressing clinical and analytical validity, transparency, and other concerns.

(Response 11) FDA disagrees with these comments. CLIAC’s advice is one of many sources available to the Secretary of HHS (Secretary) and is only a recommendation (Ref. 74). As set forth in response to comments 7 and 10, neither CMS nor FDA consider changing CLIA or the CLIA regulations to be appropriate to address the issues discussed in this preamble; to the contrary, it would lead to costly and inefficient bifurcation of the regulation of IVDs offered as LDTs. FDA appreciates that stakeholders seek a streamlined, cost-effective approach that is the least disruptive to their laboratories. FDA shares those goals, which are addressed throughout this preamble, and particularly in the phaseout policy described in section V.

(Comment 12) FDA has received comments stating that FDA oversight of IVDs offered as LDTs would be duplicative of, or conflict with, CLIA. In particular, comments stated that QS requirements and validation requirements would be duplicative or conflict. A comment stated that FDA oversight of LDTs is not in line with Executive Order (EO) 13563, which asks executive branch agencies to harmonize regulatory requirements. In addition, some comments stated that increased oversight would be cumbersome, and therefore would not follow FDA’s least burdensome principles.

(Response 12) FDA disagrees with these comments. As set forth elsewhere in this preamble, CMS and FDA enforce two different regulatory schemes, separate in scope and purpose from each other. CMS agrees the two are complementary, not duplicative, as discussed in response to comment 7. The portion of CLIA that addresses quality systems relates to laboratory operations, laboratory personnel, and requirements for laboratory procedures relevant to testing. FDA's QS requirements are focused on design control and validation and other requirements intended to ensure that the IVD has appropriate assurance of safety and effectiveness for its intended use. FDA also notes that this rule comports with EO 13563 because this rule promotes coordination and harmonization by taking into account the assurances that CLIA provides (see section V.C).

As described in section V.C regarding FDA's intention to phase out the general enforcement discretion approach with respect to QS requirements during stage 3 of the phaseout policy (other than requirements under § 820.198 (complaint files), which are addressed in stage 1), FDA intends to take into account CLIA requirements as appropriate. As to validation, CLIA regulations do not address clinical validation of tests, and analytical validation under CLIA is different from that under the FD&C Act. FDA's review of analytical validity (i.e., the ability of the test to accurately and reliably measure or detect the analyte(s) it is intended to measure or detect) is done prior to marketing, and FDA assesses the analytical validity of the IVD offered as an LDT in greater depth and scope. FDA also assesses clinical validity, which is the accuracy and reliability with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient, in reviewing the safety and effectiveness of the test. As noted, unlike the FDA regulatory scheme, CMS' CLIA program does not address the clinical validity of any test.

We also note that FDA collaborates closely with CMS. The two Agencies have entered into a memorandum of understanding that facilitates information sharing, and FDA, CMS, and CDC participate in monthly "Tri-Agency" meetings to discuss topics related to CLIA oversight.

Tri-Agency meetings often include sharing of non-CLIA information that is pertinent to the CLIA program, such as issues related to specific tests, safety communications, recalls, or warning letters. FDA and CMS also share information between meetings as needed, particularly when there are signals that may warrant investigation by either Agency.

FDA also disagrees that increased FDA oversight of IVDs offered as LDTs would not follow FDA's least burdensome principles. As explained in a final guidance document issued by FDA on February 5, 2019, entitled "The Least Burdensome Provisions: Concept and Principles," FDA "defines least burdensome to be the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time (e.g., need to know versus nice to know). Our least burdensome definition and principles do not change the applicable statutory and regulatory standards, such as the device authorization standards, nor the applicable requirements, including premarket submission content requirements and the requirement for valid scientific evidence" (Ref. 75). In developing the phaseout policy, FDA has considered least burdensome principles consistent with this definition. As described extensively in the NPRM and this preamble, oversight of LDTs is necessary to adequately address safety and effectiveness concerns regarding LDTs. The phaseout policy is designed to achieve this objective in the most efficient manner and at the right time, by phasing out the general enforcement discretion approach with respect to applicable statutory and regulatory requirements in a gradual manner and including various targeted enforcement discretion policies, as further described in section V. With respect to the comment that invoked EO 13563, we note that section 7(d) of the EO states that it "is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity...."

(Comment 13) FDA received comments which stated that FDA oversight is not necessary, as CLIA has its own enforcement mechanism. Some comments stated that CMS can, and has, used its enforcement capability from CLIA to sanction both laboratories and individual laboratory directors. Some comments stated that FDA oversight is unnecessary, because

laboratory medical directors have medical, legal, and ethical responsibility for their laboratories, which includes personally approving all new technical procedures and approving all test validations. One comment stated, however, that when an LDT does not meet specifications or “quality standards,” a laboratory director can continue to release results after making “a deviation/exception report.”

(Response 13) FDA agrees that CLIA has certain enforcement capabilities, and that CMS has exercised those enforcement tools to take certain actions against laboratories that do not comply with CLIA regulations. FDA also agrees that medical and laboratory directors have responsibilities for their laboratories, and that some of those responsibilities include approving certain procedures and activities. However, FDA disagrees that relying on CMS enforcement tools, personal responsibilities, or the activities of the laboratory director alone are sufficient to protect the public health if a test does not have appropriate assurance of safety and effectiveness. As one comment noted, under CLIA, laboratory directors may continue to release test results that do not meet their own specifications. The CLIA regulations focus on laboratory operations whereas the FD&C Act focuses on the design and manufacturing of the test. While this rule does not change the responsibilities of a laboratory director, FDA oversight ensures compliance with quality requirements set forth in the FD&C Act.

In contrast to CMS, FDA generally is authorized to review the safety and effectiveness of individual IVDs, including an IVD offered as an LDT, prior to marketing, to impose special controls or post-approval conditions for certain tests as risk mitigations, to receive reports of device malfunctions and adverse events, and to require reports of corrections and removals of a device, as well as to take specific steps when a device presents a risk to the public health such as advisory, administrative, or enforcement actions, including issuance of warning letters, injunction, seizure, mandatory recall, and assessment of civil monetary penalties.

(Comment 14) A comment suggested that instead of implementing FDA’s proposal, FDA should work with CMS to establish a national registry of LDTs to register all existing and new

LDTs. The comment suggested that FDA include in that registry test type classification, clinical utility claims, and validated performance with confidence intervals or other relevant statistics. The comment further suggested that FDA coordinate with CMS, CAP, clinical laboratory professional organizations, AMCs, and “commercial” laboratories to establish a system for LDT review and regulation.

(Response 14) FDA enforcement of existing registration and listing requirements is appropriate for IVDs offered as LDTs. FDA already has a process and database for establishment registration and device listing, and there is no need to establish a new “registry” for LDTs. FDA also has labeling requirements for IVDs in part 809 that include, among other things, required information on performance characteristics. Given the existing statutory and regulatory framework, there is no need to establish a new system for LDT review and regulation as suggested by the comment. As set forth in section V.C, FDA is phasing out the general enforcement discretion approach with respect to registration and listing requirements (21 U.S.C. 360, part 607 (for IVDs subject to licensure), and part 807 (excluding subpart E)) 2 years after the phaseout policy is published. Under this timeline, FDA will be able to utilize registration and listing information to obtain an initial understanding of the universe of IVDs offered as LDTs to facilitate premarket review of those IVDs. As set forth in section V.C, FDA also is phasing out the general enforcement discretion approach with respect to labeling requirements 2 years after the phaseout policy is published.

(Comment 15) Some comments claimed that the fact that FDA has identified some problematic tests demonstrates that CLIA is providing sufficient oversight. Comments requested that FDA explain why CLIA regulation is insufficient for the majority of laboratories that follow CLIA guidelines. See also comment 16.

(Response 15) FDA agrees that CLIA serves an important role: CMS regulates laboratories that perform testing on individuals in the United States by regulating laboratory testing and personnel under CLIA. As discussed elsewhere in this preamble, CLIA is separate in

scope and purpose from the FD&C Act and FDA regulations. CLIA regulations help to determine whether laboratories are conducting testing in a manner consistent with CLIA, but CLIA does not ensure that the test itself has appropriate assurance of safety and effectiveness for its intended use.

As more fully set forth in section III.B and in response to comments in section VI.C.4, FDA is aware of numerous examples of potentially inaccurate, unsafe, ineffective, or poor quality IVDs offered as LDTs that caused or may have caused patient harm. FDA would not expect the types of problems observed among these IVDs offered as LDTs to be identified under CLIA, and as described elsewhere in this preamble, the evidence of these problems cuts across test types and laboratories and is from a variety of sources, including published studies in the scientific literature, allegations of problematic tests reported to FDA, FDA's own experience in reviewing IVDs offered as LDTs, news articles, and class-action lawsuits.

(Comment 16) Several comments asserted that FDA's experience with Theranos is evidence that FDA oversight will not address problematic tests, particularly those that are fraudulent. They pointed out that FDA cleared a 510(k) from Theranos and that the company's fraudulent behaviors were addressed by CMS through the CLIA program.

(Response 16) This comment does not reflect a complete accounting of events. First, FDA cleared one test from Theranos early in our experience with the company. Per standard practice, FDA reviewed the data provided and based our decision on it. We subsequently identified significant device performance concerns based on the data submitted in submissions for other tests of Theranos, including questions about inaccurate results that may put patients at risk. We did not clear those devices. Less than 2 months after the clearance of the one test, we sent investigators to all Theranos sites, where we identified concerns with IVDs offered as LDTs and an unapproved collection device (Ref. 76). Recognizing the immediate risk to patients, we took a strategic compliance approach. Specifically, FDA took quick action that directly led to the firm ceasing distribution of its unapproved collection device. We also alerted CMS to potential

CLIA concerns, and CMS promptly confirmed CLIA violations in a follow-up inspection. Thus, FDA was integral to the government's handling of Theranos, and FDA disagrees with the comment's assertions that FDA did not address problematic IVDs offered as LDTs by Theranos.

(Comment 17) Some comments suggested that CLIA could be "modernized" to incorporate oversight of clinical validity and address concerns raised by FDA.

(Response 17) These comments are outside the scope of this rulemaking. This rulemaking is focused on FDA's oversight of devices under the current statutory authorities set forth in the FD&C Act, and in consideration of CMS's current authorities under CLIA.

In any event, FDA disagrees that concerns with IVDs offered as LDTs should be addressed through expansion of CLIA. First, the authority and expertise to oversee the safety and effectiveness of tests already lies with FDA, and not with CMS; expanding CMS oversight would require legislation and would establish a duplicative regulatory program. Second, neither FDA nor CMS supports such an approach. It would establish a dual system for the oversight of tests and create more government bureaucracy, duplication of effort, and potential inconsistencies. For example, a test made by a non-laboratory manufacturer (and any modifications to that test made by the laboratory manufacturer) would be regulated by FDA, but if the test is modified by a laboratory, CMS would regulate it. The same/similar tests made by a laboratory and non-laboratory manufacturer would be reviewed by two different agencies under different frameworks. This approach does not make sense.

3. Other Controls

(Comment 18) FDA received comments claiming that FDA should not enforce the requirements of the FD&C Act for IVDs offered as LDTs, as it is more appropriate for accrediting entities, including the Commission on Office Laboratory Accreditation (COLA), CAP, the Accreditation Commission for Health Care (ACHC), the Association for the Advancement of Blood and Biotherapies (AABB), the Joint Commission, and ASHI to oversee IVDs offered as LDTs. Some comments suggested that FDA should exercise enforcement

discretion with respect to IVDs offered as LDTs at certain facilities with relevant accreditations, such as accreditation by ASHI or the Foundation for the Accreditation of Cellular Therapy (FACT), because such accreditations provide the necessary assurances relevant to the type and volume of work performed by these accredited facilities.

(Response 18) FDA disagrees that CLIA accreditation organizations such as COLA, CAP, or ACHC provide sufficient oversight of IVDs offered as LDTs. As discussed in response to comment 7, CLIA accreditation entities, including COLA, CAP, and ACHC, determine whether a laboratory meets CLIA requirements. Moreover, various accreditation entities, including AABB, the Joint Commission, ASHI, and FACT, may also determine whether a laboratory meets these organizations' voluntary accreditation standards. Unlike these organizations, which assess laboratories/laboratory operations under CLIA and their own accreditation standards, FDA (and FDA's device authorities under the FD&C Act) focus on whether devices, including IVDs offered as LDTs, have appropriate assurances of safety and effectiveness.

In particular, COLA evaluates and, if appropriate, certifies that certain laboratories that conduct tests in certain specialties (chemistry, hematology, microbiology, immunology, and immunohematology/transfusion services) meet CLIA requirements and any applicable COLA accreditation standards (Ref. 77). CAP conducts inspections to determine compliance with CLIA and applicable CAP accreditation standards (Ref. 78). Although CAP and COLA have their own accreditation standards, these additional standards address the manner in which the laboratory performs tests, and do not assess the clinical validity of the test itself. COLA and CAP do not perform premarket review of individual IVDs offered as LDTs for overall safety and effectiveness for the devices' intended uses. More generally, third-party accreditation entities have their own standards for accreditation of facilities that may not assess the clinical validity of the tests that the facility performs. Thus, an accreditation of a facility by one of these third

parties does not, on its own, provide sufficient assurance of safety and effectiveness for the IVDs offered as LDTs by the accredited facility for their intended uses.

We note that pursuing CAP, COLA, ACHC, AABB, Joint Commission, ASHI, or FACT (or other) accreditation is a voluntary process. CAP, COLA, and other accreditation organizations' standards are not regulatory or statutory requirements.

Finally, we note that for reasons more fully set forth in response to comment 7, FDA is the appropriate entity to provide the necessary oversight of IVDs offered as LDTs to better assure their safety and effectiveness.

(Comment 19) FDA received comments stating that many laboratories follow guidelines provided by the Association for Molecular Pathology (AMP), the International Clinical Cytometry Society (ICCS), and the Clinical and Laboratory Standards Institute (CLSI), and voluntary standards issued by ISO. Some comments suggested that laboratories that follow such standards are already highly regulated. Other comments stated that following such guidelines and/or standards provides a level of assurance that the laboratories' assays are "safe and reliable." Comments recommended that FDA permit AMP, ICCS, CLSI, and other entities to continue to offer such guidelines. Another comment stated that the "solution for...incompetent tests should be...standardization and not regulation."

(Response 19) FDA acknowledges that many entities, including the entities that the comments listed, offer guidelines, standards, and other resources to laboratories. However, the guidelines and standards that the comments describe are, in most instances, voluntary and non-binding.⁵¹ FDA disagrees that a laboratory that chooses to follow such guidelines or standards is "highly regulated" as a result of these voluntary actions. FDA further disagrees that following such voluntary guidelines or standards provides assurances of safety or reliability (or effectiveness), as the guidelines and standards do not address IVD safety and effectiveness (see,

⁵¹ FDA may incorporate a voluntary consensus standard by reference. *See* 5 U.S.C. 552(a) and 1 CFR part 51. Where FDA has incorporated a voluntary consensus standard by reference, that standard is treated as if it were published in the *Federal Register* and CFR, and this material has the full force and effect of law.

e.g., Refs. 79 to 81). Notably, nothing in this rule will prevent AMP, ICCS, CLSI, or other entities from continuing to provide voluntary guidelines or standards to laboratories.

(Comment 20) Comments asserted that the Federal program entitled Molecular Diagnostic Services (MolDx) already provides significant regulatory oversight and overlaps with FDA's proposal. Comments also stated that MolDx addresses technical requirements for assays by assessing a test's analytical and clinical validity, and for this reason, the comments suggested that increased FDA oversight is not needed.

(Response 20) FDA regulation and the MolDx program differ in several key respects. MolDx is a limited program, which evaluates whether tests are reasonable and necessary with a focus on the Medicare population (Ref. 82). In contrast, FDA's authority extends to IVDs for all people and includes various compliance and enforcement authorities (that MolDx lacks), which enable FDA to take action when an IVD presents a risk to health (e.g., through recalls). The MolDx program does not mitigate the need for increased FDA oversight of IVDs offered as LDTs.

(Comment 21) FDA received a comment stating that CDC's Newborn Screening Laboratory Quality Assurance Program (NSQAP) administers proficiency testing and validates new screening tests, ensuring the accuracy of results generated by laboratories. The comment suggested that because of this program, increased FDA oversight is not needed.

(Response 21) FDA disagrees that NSQAP is a substitute for FDA oversight of IVDs offered as LDTs. The NSQAP program provides quality assurance services to newborn screening laboratories by providing reference materials, providing proficiency testing regarding laboratory operations, providing quality control reports, and offering training and consults (Ref. 83). NSQAP evaluates the proficiency of laboratory personnel and procedures, not the safety and effectiveness of IVDs offered as LDTs. See our response to comment 9 for additional discussion regarding proficiency testing.

(Comment 22) Comments stated that New Jersey and Washington certification programs ensure that laboratories conduct LDT validations and proficiencies at high quality standards. The comments stated that laboratories that adhere to New Jersey's certification requirements and other certification programs provide patients with a high level of care. The comments suggested that such certification programs obviate the need for increased FDA oversight.

(Response 22) FDA acknowledges that several States have certification programs. New Jersey and Washington State certification programs certify laboratories within those states if they meet the State certification requirements. FDA disagrees, however, that compliance with these State certification requirements provides sufficient risk mitigations for IVDs offered as LDTs. For example, there is no indication that these State programs evaluate both the analytical and clinical validity of LDTs (see Refs. 84 and 85). According to the website of the cited program in Washington State, the program covers licensure, biennial surveys, and proficiency testing (Ref. 84). In the comment submitted to the docket regarding New Jersey's program, no specific information or citation was provided regarding the program. Nor did FDA receive a comment to the docket from the New Jersey program. Based on information available to FDA regarding New Jersey's program, we believe this program is focused on laboratory operations, and not the evaluation of the IVDs themselves (see Ref. 85).

(Comment 23) Some comments stated that when electronic medical records (EMRs), inter-specialty cooperation, and educational and safety-reporting systems are integrated within a healthcare system, the risk to patients from IVDs manufactured by the laboratory within that system is minimized and there is no need for additional FDA oversight.

(Response 23) FDA disagrees that these elements alone are a substitute for FDA oversight of IVDs offered as LDTs. FDA acknowledges that these elements may play a role in patient care, but FDA oversight of IVDs offered as LDTs serves a vital role in assuring the appropriate safety and effectiveness of the IVDs. Critical aspects of FDA's oversight, including

premarket review, QS, registration and listing, centralized adverse event reporting, labeling, and other requirements, are not addressed by the elements described in these comments.

We note that FDA does believe that integration of a laboratory within a healthcare system provides some risk mitigations, as discussed further in section V.B.3. FDA has taken those risk mitigations into consideration in adopting an enforcement discretion policy for premarket review and most QS requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

(Comment 24) One comment stated that concerns about manufacturing controls and other device-specific concerns regarding IVDs offered as LDTs are managed by “lot-to-lot” validation and a laboratory’s quality control.

(Response 24) FDA disagrees with this comment. While premarket and post-market validation activities are an essential element of quality management, there are other critical aspects of a quality management system, and a laboratory’s quality control does not address other critical aspects of FDA oversight.

(Comment 25) FDA received comments which noted that laboratories consult with clinicians, diagnosticians, tumor boards, and case conferences, and which suggested that this consultation provides clinical validation and ensures that tests are interpreted appropriately.

(Response 25) FDA disagrees that consultation provides clinical validation, or that consultation alone is a substitute for FDA oversight of IVDs offered as LDTs. Although FDA agrees that consultation between laboratories and clinicians, diagnosticians, and others as described in this comment may help to mitigate risks from IVDs offered as LDTs in certain circumstances and particularly in the context of LDTs for unmet needs (see further discussion in section V.B.3), such consultation does not obviate the need for FDA oversight such as would justify continuing the general enforcement discretion approach for all FDA requirements for all LDTs, as suggested by the comments.

(Comment 26) FDA received a comment stating that “financial restrictions to laboratory testing” represent another layer of oversight beyond CMS and FDA regulation, and serve to maintain the quality of laboratory testing. The comment did not define “financial restrictions,” but referenced payment codes and payor coverage decisions. The comment suggested that because of this additional layer of oversight, increased FDA oversight is not needed.

(Response 26) FDA disagrees that “financial restrictions” related to coverage and reimbursement considerations provide sufficient assurances of safety and effectiveness for IVDs offered as LDTs. In the analysis that CMS conducts to determine Medicare coverage, it may consider various factors, including coverage indications, coverage limitations, and the clinical circumstances that demonstrate medical necessity, but those factors are not equivalent to, or a substitute for, the assurances of safety and effectiveness provided by FDA oversight. In general, CMS considers claims after marketing evaluations regarding whether expenses incurred are reasonable and necessary for the diagnosis and treatment of illness or injury or improve the functioning of a malformed body member, and whether the claim for payment contains the necessary information for CMS to process the claim (see section 1862(a)(1)(A) and section 1833(e) of Title XVIII of the Social Security Act).

(Comment 27) One comment indicated that “review by peer organizations” would be superior to FDA review due to subspecialty expertise and cost “to the taxpayer.”

(Response 27) FDA disagrees that review by peer organizations would be superior to FDA review of IVDs offered as LDTs due to subspecialty expertise. First, FDA has the appropriate expertise to review the safety and effectiveness of IVDs, as discussed in response to comments 7 and 10. Where additional expertise may be beneficial, FDA can seek input from advisory committees in accordance with the Federal Advisory Committee Act. Second, peer review may introduce bias and variability of oversight, particularly if unblinded. For example, where two peers review each others’ work, they may potentially be inclined to overlook issues and expect the same in return.

Use of peer reviewers is also not necessary to address costs to taxpayers or FDA. FDA receives funding from Congressional non-user fee appropriations (“budget authority”) and user fees to support operation of the medical device program, including premarket review. FDA also intends to enhance the Third Party review program, which will reduce costs to the Agency while providing for assistance with 510(k) reviews by entities that are independent of the manufacturer.

4. Evidence of the Need for Greater FDA Oversight

(Comment 28) FDA received comments stating that there is no problem with LDTs. One comment from a laboratory director voiced confidence in LDT results and stated that any areas for improvement seldom have to do with “faulty results or improper care related to testing.” Other comments stated that the errors in laboratory testing often stem from operational issues and human error rather than the design or nature of LDTs, and opined that FDA oversight would not address these issues. Several asserted that laboratories are diligent in their validation of LDTs, that there is no evidence of problems with LDTs, and that LDTs are as safe as FDA-authorized tests. One comment cited a 2014 publication concluding that the quality of clinical DNA testing for rare diseases in the United States was excellent (Ref. 86). Another comment pointed to a 2022 opinion article in the Wall Street Journal claiming “a review of all reported cases in state and federal courts reveals no reported suits filed against a laboratory for an LDT result” (Ref. 87).

FDA also received comments indicating problems with LDTs. One comment described the commenter’s experience witnessing “unsafe practices similar to those described in FDA’s proposed rule” while working in a profitable laboratory. This commenter left that laboratory to work at “labs that care for the health of individuals.” Another comment described the commenter’s experience with marketing of RUO products for clinical diagnostic testing. One company reported that laboratories offer inferior LDTs that compete with the company’s FDA-approved test, and that proficiency testing programs allow inferior tests to pass. In these cases,

patients receiving an inferior test may not get the most up to date treatment they should have. An AMC laboratory director indicated the laboratory often sees inconsistent results for the same patient tested in the AMC laboratory and at reference laboratories. Several other comments, including comments submitted by healthcare providers, laboratorians, patients, and public interest organizations, provided specific examples of problematic IVDs offered as LDTs, including IVDs offered as LDTs that, according to the comments, lacked clinical validity, provided false results, provided inconsistent results, or were promoted with false or misleading claims. A comment submitted by NYS CLEP described several examples of LDTs that NYS CLEP did not approve based on the original application due to issues such as design flaws and inadequate validation data, including an LDT with an “error [that] would have endangered patient safety.” Another comment submitted in support of FDA’s proposal stated that “[t]he current state of laboratory developed testing in the US is quite honestly, astonishingly bad....as a CAP inspector, I have seen firsthand the absolutely shoddy laboratory developed tests in place at many laboratories.”

(Response 28) The information discussed in the NPRM, and additional information provided in various comments submitted to the Agency, demonstrates that performance problems exist with certain IVDs offered as LDTs (see 88 FR 68006 at 68010-12). FDA disagrees with comments claiming that there is no problem with LDTs or that deficiencies in laboratory testing are mostly caused by operational or human error. As described in the NPRM (88 FR 68006 at 68010-12), in memoranda included in the docket for this rulemaking (Refs. 16 and 18), and in other comments submitted to the docket such as those described above, we are aware of problems with IVDs offered as LDTs, many of which stem from issues with the IVD itself, such as design issues. We have become aware of these problems even though the general enforcement discretion approach has applied to requirements for postmarket reporting, such as MDR requirements.

We acknowledge that the 2014 publication cited in the comment refers to a “high level of confidence that most U.S. laboratories offering rare disease testing are providing consistent and reliable clinical interpretations”; however, this is based on a survey conducted from 2010 through 2012 for a proficiency testing program to assess the performance of laboratories running Sanger sequencing IVDs for rare and ultra-rare disorders. Laboratory proficiency testing results for Sanger sequencing IVDs for rare and ultra-rare diseases from over a decade ago do not support the assertion that the quality of clinical DNA testing in the United States is excellent today, let alone that there are no concerns with IVDs offered as LDTs generally. First, proficiency testing data are not appropriate as standalone or comparative results to support test validation and performance. Please see our response to comment 34 for a more detailed assessment of the limitations of proficiency testing data. Second, laboratory performance for Sanger sequencing IVDs for rare and ultra-rare disorders, which are a limited subset of genetic IVDs, do not represent the landscape of clinical genetic tests used today where most tests use next generation sequencing (NGS) and other technologies. As noted in the NPRM, FDA’s concerns with IVDs offered as LDTs have grown in recent years (88 FR 68006 at 68010). Moreover, we disagree with the statement that no suits have been filed against a laboratory for a false result associated with an IVD offered as an LDT; the NPRM cited evidence to the contrary (see 88 FR 68006 at 68012 (stating that “consumers, shareholders, and investors are filing lawsuits against laboratory manufacturers for false and misleading statements about test efficacy,” and citing to Complaint, *Davis v. Natera, Inc.*, No. 3:22–cv–00985 (N.D. Cal. 2022); *Biesterfeld v. Ariosa Diagnostics, Inc.*, No. 1:21–CV–03085, 2022 WL 972281 (N.D. Ill. 2022); and other lawsuits)). FDA shares the concern of comments that described problems observed with IVDs offered as LDTs.

(Comment 29) FDA received comments stating that the proposed rule is not necessary for FDA “to take action against bad actors” or “ill-intended individuals and laboratories” that abuse

the system, because FDA could choose to enforce in “egregious cases of patient harm or attempts to exploit regulatory loopholes.”

(Response 29) FDA agrees that the Agency may choose to enforce against violations of the FD&C Act or PHS Act at any time, including (but not limited to) in response to egregious cases of patient harm, attempts to exploit loopholes, or other conduct involving “bad actors” or “ill-intended individuals and laboratories.” The general enforcement discretion approach does not bind the Agency or prevent FDA from taking enforcement action. However, as described in section III.B of this preamble, FDA is choosing to adjust its approach to enforcement discretion moving forward to address the fundamental uncertainty about whether IVDs offered as LDTs provide accurate and reliable results. The phaseout policy clarifies FDA’s expectations regarding laboratories’ compliance with applicable requirements and will bring more stability to the overall testing market. By phasing out the general enforcement discretion approach for LDTs, FDA may gain a more comprehensive understanding of the universe of IVDs offered as LDTs (through enforcement of registration and listing requirements), monitor safety signals and more readily identify problematic IVDs (through enforcement of MDR requirements and corrections and removals reporting requirements), better assure that patients and providers have access to the information they need and that IVDs are not promoted with false or misleading claims (through enforcement of labeling requirements), and better assure analytical validity, clinical validity, and safety (through enforcement of QS, premarket review, and other applicable requirements). Ultimately, as noted elsewhere in this preamble, by applying the same general oversight approach to both laboratory and non-laboratory manufacturers of IVDs, FDA may better assure the safety and effectiveness of IVDs offered as LDTs, incentivize innovation by nonlaboratory manufacturers, and help ensure that innovation from laboratory manufacturers yields IVDs for which there is a reasonable assurance of safety and effectiveness (Refs. 15, 22, 88 to 90).

(Comment 30) FDA received comments suggesting certain steps FDA should take prior to phasing out the overall general enforcement discretion approach. Different comments provided different suggestions, but several suggested that FDA first gather more information about IVDs offered as LDTs through, for example, a survey, use of CMS's "data from every licensed laboratory on the test type and annual volume," use of data available from CAP, or a U.S. GAO study. One comment suggested FDA enforce registration and listing and adverse event reporting requirements in order to gather information prior to determining whether to phase out the general enforcement discretion approach for premarket review requirements. Another comment stated that FDA needed to develop a better understanding of how "in-office" tests in particular are operationalized in clinical practice and undertake a more "inclusive and deliberative process" that accounts for "diverse stakeholders," but did not specify how.

(Response 30) FDA acknowledges that we do not know exactly how many laboratories manufacture IVDs offered as LDTs nor precisely how many such IVDs they make. Based on direct interactions with CMS and CAP, FDA understands that neither organization collects this information for all IVDs offered as LDTs. However, FDA's FRIA provides estimates of how many laboratories currently offer IVDs as LDTs and how many IVDs offered as LDTs are on the market (Ref. 10). The basis for these estimates is described in section II.D.1 and appendix A of the FRIA. FDA does not agree that it should wait until it has more precise information about how many laboratories offer IVDs as LDTs and how many IVDs offered as LDTs are on the market before finalizing this rule, because more precise numbers would not affect the fundamental public health concerns that have motivated this rulemaking. FDA also notes that the longer it waits, the higher the numbers will become and the greater the risk posed to patients. Nor does FDA believe it should gather more information about potential problems with IVDs offered as LDTs prior to phasing out the overall general enforcement discretion approach; as discussed further in response to comments 32 and 160, while FDA is uncertain of the impact to the existing market, FDA already possesses enough information to conclude that there is no longer a sound

basis to generally treat LDTs differently from other IVDs, and that the general enforcement discretion approach for LDTs does not best serve the public health.

With respect to the suggestion that FDA initially focus solely on registration and listing and adverse event reporting requirements, please see the response to comment 160 in section VI.F.6 of this preamble.

With respect to the comment about a more inclusive and deliberative process, FDA notes that, through this rulemaking, it has solicited and received many comments from diverse stakeholders that provided information on how in-office and other tests are operationalized in clinical practice, and we have carefully considered those comments. Furthermore, FDA has engaged with the public on this topic on multiple occasions over the last 30 years, including through draft guidances and public meetings. This rulemaking reflects FDA's best judgment based on a significant amount of input over many years, and we intend to continue to engage with the public on this topic. See our response to comment 296 for additional discussion regarding stakeholder engagement.

We also note that FDA does not control the U.S. GAO, and cannot compel a U.S. GAO study.

(Comment 31) Comments called on CMS, the National Institutes of Health (NIH), and HHS to review FDA's proposal.

(Response 31) Per standard practice, all relevant components of HHS, including CMS, NIH, and HHS leadership, reviewed and cleared FDA's proposed rule and this final rule.

(Comment 32) FDA received comments calling on FDA to produce more evidence of a problem. Some noted that FDA's existing evidence is largely anecdotal and called for "evidence of multiple, conclusive, high-quality studies that show...that errors in laboratory testing are a pervasive and particularly dangerous problem." Other comments asked FDA to provide evidence of a problem with LDTs in specific areas, such as clinical toxicology. Some stated that the examples provided are not reflective of the landscape of LDTs, particularly at AMCs.

(Response 32) FDA does not agree with these comments. FDA has considered a wide range of evidence, including evidence described in the NPRM (88 FR 68006 at 68010-12) and information submitted in comments, and has determined that this evidence is adequate to conclude that there is a concerning level of variability in the performance of IVDs offered as LDTs.

As discussed in the NPRM, information about IVDs offered as LDTs in the scientific literature, as well as news articles and anecdotal reports submitted to the Agency, among other sources, has exposed evidence of problems associated with some of these tests (88 FR 68006 at 68010-12; Refs. 20 and 91 to 97). Regarding the scientific literature, the NPRM described multiple publications that document high variability in performance among IVDs offered as LDTs, including the potential for inaccurate or incomplete results (see comment responses 38, 39, and 41 for additional information) (88 FR 68006 at 68010-12). In addition, in support of this rulemaking, FDA prepared and submitted a memorandum to the docket regarding “Examples of In Vitro Diagnostic Products (IVDs) Offered as Laboratory Developed Tests (LDTs) that Raise Public Health Concerns,” which contained additional details from non-public sources (and some public MDRs) regarding examples of IVDs offered as LDTs with reported or known issues that were referenced in the NPRM (Ref. 16). FDA also submitted a second memorandum to the docket entitled “Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2” (Ref. 18). Comments submitted to the docket provided additional evidence that further exposed problems associated with IVDs offered as LDTs (see discussion in response to comment 28). FDA also notes that the evidence of problematic IVDs offered as LDTs has been growing, a trend that increases FDA’s concerns⁵².

⁵² For example, consider the years in which concerns with the IVDs offered as LDTs that raise public health concerns described in FDA’s memorandum in the docket (Ref. 16) were first identified. Four concerns were identified between 2008 and 2011, 10 concerns between 2012 and 2015, 15 concerns between 2016 and 2019, and 23 concerns between 2020 and 2023.

To the extent that comments raised questions about the quality of the evidence cited in the NPRM, FDA has addressed those questions in our responses to other comments in this section, including comments 36, 37, 38, and 43.

FDA does not take the position that all IVDs offered as LDTs are problematic, but the collective evidence, including anecdotal evidence, regarding certain IVDs offered as LDTs is of significant concern, especially given there is no consistent reporting of adverse events. Because this evidence covers a wide variety of tests across a range of laboratories, including AMCs, FDA considers it fairly representative of the landscape of IVDs offered as LDTs, contrary to one comment's claim. FDA also disagrees that it must have evidence specific to every type of test, such as clinical toxicology tests, in order to justify this rulemaking, and we disagree that "multiple, conclusive, high-quality studies" are needed here. *See FCC [Federal Communications Commission] v. Prometheus Radio Project*, — U.S. —, 141 S. Ct. 1150, 1160, 209 L.Ed.2d 287 (2021) ("[T]he [Administrative Procedure Act (APA)] imposes no general obligation on agencies to conduct or commission their own empirical or statistical studies."). Instead, FDA has "made a reasonable predictive judgment based on the evidence it ha[s]." *Id.* Specifically, based on careful consideration of the information in the record, FDA has determined that the final phaseout policy appropriately balances the relevant considerations and will advance public health.

(Comment 33) FDA received comments regarding the risks and benefits of FDA's proposal, with some comments indicating that FDA has not adequately considered the benefits of IVDs offered LDTs. One comment stated that the data provided by FDA "appears to overstate the risks associated with LDTs, while understating the benefits."

(Response 33) FDA disagrees that the data provided in the NPRM overstates the risks associated with IVDs offered as LDTs. FDA has considered evidence from a variety of sources that, taken together, demonstrates fundamental uncertainty about whether such IVDs provide accurate and reliable results. FDA acknowledges the benefits that IVDs offered as LDTs offer

when those IVDs do provide accurate and reliable results, and has taken these and other public health considerations into account in developing the phaseout policy. The fact that accurate and reliable IVDs offered as LDTs have benefits does not mean that the current status quo--in which problematic IVDs offered as LDTs are marketed with limited FDA oversight--should continue indefinitely.

(Comment 34) FDA received comments indicating FDA failed to include all available data relevant to the need for rulemaking. For example, one comment stated FDA is “ignoring broad evidence of the high quality of genetic LDTs.” Comments asserted that there was omission of multiple publications claiming comparable or better performance of IVDs offered as LDTs compared to “FDA IVDs.” Comments pointed to the following publications:

- Benayed, R., Offin, M., Mullaney, K., Sukhadia, P., et al. (2019). “High Yield of RNA [Ribonucleic acid] Sequencing for Targetable Kinase Fusions in Lung Adenocarcinomas with no Mitogenic Driver Alteration Detected by DNA Sequencing and Low Tumor Mutation Burden.” *Clinical Cancer Research*, 25(15), 4712-4722. (Ref. 98).
- Keegan, A., Bridge, J. A., Lindeman, N. I., Long, T. A., et al. (2020). “Proficiency Testing of Standardized Samples Shows High Interlaboratory Agreement for Clinical Next-Generation Sequencing-Based Hematologic Malignancy Assays with Survey Material-Specific Differences in Variant Frequencies.” *Archives of Pathology & Laboratory Medicine*, 144(8), 959-966. (Ref. 99).
- Kim, A. S., Bartley, A. N., Bridge, J. A., Kamel-Reid, S., et al. (2018). “Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing.” *JAMA Oncology*, 4(6), 838-841. (Ref. 100).
- Merker, J. D., Devereaux, K., Iafrate, A. J., Kamel-Reid, S., et al. (2019). “Proficiency Testing of Standardized Samples Shows Very High Interlaboratory Agreement for Clinical Next-Generation Sequencing–Based Oncology Assays.” *Archives of Pathology & Laboratory Medicine*, 143(4), 463-471. (Ref. 101).

- Moncur, J. T., Bartley, A. N., Bridge, J. A., Kamel-Reid, S., et al. (2019). “Performance Comparison of Different Analytic Methods in Proficiency Testing for Mutations in the BRAF, EGFR, and KRAS Genes: A Study of the College of American Pathologists Molecular Oncology Committee.” *Archives of Pathology & Laboratory Medicine*, 143(10), 1203-1211. (Ref. 102).
- Zehir, A., Nardi, V., Konnick, E. Q., Lockwood, C. M., et al. “SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance.” *Archives of Pathology & Laboratory Medicine*. (Ref. 103).
- Zhang, B. M., Keegan, A., Li, P., Lindeman, N. I., et al. (2021). “An Overview of Characteristics of Clinical Next-Generation Sequencing-Based Testing for Hematologic Malignancies.” *Archives of Pathology & Laboratory Medicine*, 145(9), 1110-1116. (Ref. 104).

One comment further asserted that “publications have demonstrated major deficiencies in FDA-approved tests that would result in patient mismanagement had LDTs not been available to address those deficiencies,” citing to the above-listed publication from Benayed et al. There were two other publications referenced by a comment that were mis-cited or not identifiable from the information provided.

(Response 34) FDA does not agree that the publications cited by these comments vitiate the need for greater oversight of IVDs offered as LDTs. FDA does not take the position that all IVDs offered as LDTs are problematic. Instead, as described in section V.B.3, FDA believes that beneficial IVDs offered as LDTs are likely on the market. But the fact that some IVDs offered as LDTs that are on the market may be beneficial does not mean that the current status quo--in which problematic IVDs offered as LDTs are marketed with limited FDA oversight--should continue indefinitely. Thus, even if the seven articles cited above showed that certain IVDs offered as LDTs have performance comparable to or better than that of certain FDA-authorized

tests--which FDA does not believe to be the case, as discussed below--that would only support the accuracy and reliability of the cited tests. It would not negate evidence of problematic IVDs offered as LDTs or uncertainty as to whether IVDs offered as LDTs provide accurate and reliable results, as discussed in the NPRM and elsewhere in this preamble.

Moreover, we disagree that the referenced publications demonstrate comparable or better performance of IVDs offered as LDTs compared to FDA-authorized IVDs, for the reasons described below.

a. Six of the 7 publications report results from proficiency testing, which are not appropriate as standalone or comparative results to support test validation and performance. Performing well during proficiency testing does not mean that a test is analytically and clinically valid. Kim et al., Moncur et al., Keegan et al., Merker et al., and Zehir et al. (Refs. 99 to 103) use data from the CAP proficiency testing programs for NGS, which are only a subset of IVDs overall, to contend that IVDs offered as LDTs are accurate and have comparable performance to FDA-authorized tests. However, proficiency testing data, as standalone or comparative results, do not support test validation and performance expectations. Proficiency testing programs evaluate the performance of laboratories running tests that should have already been validated. Proficiency testing is performed to ensure that certain characteristics, e.g., detection of a specific analyte, can be achieved at a similar level in relation to results obtained by a group of referee laboratories or “peers.” Proficiency testing samples ensure results are detected within an acceptable range within a pre-determined limit, independent of an individual test’s performance specifications. Proficiency testing program data is an aggregate assessment of laboratory performance rather than an evaluation of results on a test-by-test basis, the latter of which is more aligned with the clinical reality that patient care is generally determined by a single test performed in a single laboratory. One cannot assess the performance of an individual test from aggregate data across multiple tests. Looking at data in aggregate can mask poor performance of an individual test. Proficiency testing programs are not adequately representative of the routine

conditions of clinical use, do not consider a test's intended use, and do not represent the challenges encountered in routine testing. For example, proficiency testing does not cover the entire test procedure. Specimens in proficiency testing are generally highly contrived and do not closely mimic patient specimens. Proficiency testing is generally insufficiently challenging (e.g., less complex variant types and variant allele fractions for genetic tests). Although laboratories are expected to adhere to their typical testing protocols, proficiency testing exercises are highly controlled and come with specific instructions, so laboratories are aware that they are participating in a proficiency testing exercise, which may influence how the test is performed and results obtained. Proficiency testing does not ensure that a test has been analytically and clinically validated based on its intended use.

b. Even if the results of proficiency testing were appropriate to evaluate the performance of IVDs offered as LDTs compared to FDA-authorized tests, these studies only evaluated NGS-based IVDs, which are only a subset of IVDs. In addition, 2 publications purported to compare the performance of IVDs offered as LDTs to FDA-authorized tests but because of flawed methodology did not do so; 1 publication reported results that suggest performance issues with IVDs offered as LDTs; and 1 publication did not evaluate the performance of IVDs offered as LDTs compared to FDA-authorized tests. Two publications (Kim et al. and Moncur et al.) (Refs. 100 and 102) purporting to compare IVDs offered as LDTs with FDA-authorized tests were actually mainly comparing IVDs offered as LDTs with other IVDs offered as LDTs and not comparing IVDs offered as LDTs with FDA-authorized tests. These publications provided limited information about the relative performance of FDA-authorized tests and IVDs offered as LDTs because the majority of tests referred to as "FDA-approved companion diagnostics" had been modified in ways outside of their FDA authorizations, rendering them IVDs offered as LDTs. In addition, the authors considered any test from a manufacturer with any FDA-approved companion diagnostic (CDx) to be "FDA-approved," even though some of these tests may not in fact have been FDA-authorized.

Zehir et al. (Ref. 103) used CAP proficiency testing methods and data to reanalyze a comparison of the performance of an FDA-approved CDx with IVDs offered as LDTs intended for the same use using the same set of samples that was reported in another publication (Pfeifer et al) (Ref. 20). Despite the authors' claims that the study demonstrated excellent laboratory performance, individual laboratories had a significant number of errors. Only eight laboratories correctly reported all variants in Zehir et al.'s reanalysis, and four laboratories had greater than five errors. The laboratory performing the FDA-approved CDx correctly reported all variants in both dry and wet samples. Therefore, while FDA does not consider it appropriate to use proficiency testing data to demonstrate or compare test performance (as earlier explained), this study does not in any way undermine FDA's position regarding the need for increased oversight. Please see our response to comment 38 for a more detailed assessment of this study.

Zhang et al. provided an overview of certain NGS-based test characteristics for hematologic malignancies with no discussion of test validation or performance and, therefore, does not conclude or even assert equivalence between IVDs offered as LDTs and FDA-authorized IVDs (Ref. 104). This may be an erroneous citation given the lack of relevant content to support the comment's assertion.

c. Of the 7 publications cited above, only one (Benayed et al.) did not report on proficiency testing results. This publication did not demonstrate comparable or better performance of IVDs offered as LDTs compared to FDA-authorized tests, nor did it identify "major deficiencies" in FDA-authorized tests as the comments assert. FDA disagrees that the publication from Benayed et al. supports the assertion that "publications have demonstrated major deficiencies in FDA-approved tests that would result in patient mismanagement had LDTs not been available to address those deficiencies." (Ref. 98). After careful review, FDA has determined that the study did not identify a "major deficiency" with an FDA-approved test and does not demonstrate that the unauthorized IVD offered as an LDT in question was necessary in order to avoid patient mismanagement. Moreover, even if the study had demonstrated that the

unauthorized IVD offered as an LDT was necessary to avoid patient mismanagement in certain instances, that fact would not mean that FDA oversight is unnecessary for IVDs offered as LDTs in general.

The Benayed study evaluated the use of the FDA-authorized MSK-IMPACT DNA sequencing test and use of the unauthorized MSK-FUSION RNA sequencing IVD offered as an LDT in patients with lung cancer. The MSK-FUSION was designed to detect fusions and rearrangements (complex variants) while the MSK-IMPACT is authorized for detection of single nucleotide variants, insertions and deletions (indels), MET exon 14 skipping, and microsatellite instability but not complex variants. The authors concluded that the IVD offered as an LDT identified complex variants that were not detected by the FDA-authorized test (and which the FDA-authorized test was not intended to detect). However, a test's inability to identify variants that it is not intended to detect is not inherently a "major deficiency" for that test. We note that FDA oversight of IVD labeling helps ensure that the instructions for use are clear, including clearly describing the intended use, which for genetic tests includes describing the variants detected by the test.

The authors of the Benayed study reported that 10 patients received targeted therapy based on identification of complex variants by the MSK-FUSION test and claimed that 80 percent of those patients had clinical benefit. FDA disagrees with the authors' conclusions that 80 percent of patients experienced clinical benefit. First, the authors considered the denominator to include only those patients who went on to receive targeted therapy (n=10) rather than all patients identified by the MSK-FUSION test as having complex variants (n=33). Second, the authors considered clinical benefit to include stable disease, which FDA does not consider to be an appropriate endpoint for therapeutic efficacy when treating cancer. Adjusting for these considerations, only 6 percent of patients identified by the MSK-FUSION test as having complex variants (2 out of 33) experienced clinical benefit, and both of these patients could have been identified for therapy with FDA-authorized tests. Only 2 of the 10 patients who received therapy

based on the MSK-FUSION test would not have otherwise been identified, and neither of those patients necessarily benefited from the therapy. Following treatment, one had progression of disease and the other had stable disease (i.e., disease with no substantial change). Thus, it cannot be concluded that patients would have been mismanaged had the IVD offered as an LDT not been available.

(Comment 35) FDA received a comment that increased FDA oversight will not result in quantitative agreement between assays, and that any implication that it will result in such agreement “is not supported by an empirical evaluation of approved, marketed tests.”

(Response 35) FDA has not implied that increased FDA oversight would ensure quantitative agreement for all tests. FDA’s discussion regarding variability between tests in the NPRM referred primarily to variability in tests’ clinical interpretation (e.g., positive or negative for the clinical condition being diagnosed by the test) based on differing results (88 FR 68006 at 68011). For example, when two different tests are both intended to determine whether a patient with cancer is eligible for a specific treatment and one result is “negative” while the other is “positive,” there is variability between those tests that represents a clinically significant problem.

For tests that provide a numerical value, there is reasonable quantitative agreement for FDA-authorized tests that are standardized (for example tests that are traceable to a reference material) or harmonized. However, not all tests are standardized or harmonized, nor do all tests provide a numerical result (for example, qualitative genetic tests).

(Comment 36) FDA received comments regarding FDA’s use of a New York Times article on non-invasive prenatal screening (NIPS) as evidence of a problem (Ref. 96). Specifically, comments stated that the article conflated screening with diagnostic testing. They asserted that the article mischaracterized false positive results as test failures and that the “problem” with this category of tests is with “the lack of understanding of its purpose and limitations by the providers and patients who were interviewed by the reporters.”

(Response 36) FDA agrees that NIPS tests, which may tell people the risk of their fetus having certain genetic abnormalities, are different from diagnostic tests used to more definitively confirm or rule out a suspected genetic abnormality. FDA agrees with comments that NIPS tests should not be used to confirm or rule out a suspected abnormality. After publication of the New York Times article, FDA issued a safety communication to explain the limitations of NIPS tests and provide information to educate both patients and healthcare providers to help reduce the inappropriate use of NIPS tests (Ref. 97). Increased oversight of NIPS tests, including an expectation of compliance with labeling requirements, can help ensure such tests are appropriately labeled with transparent information regarding performance, clear instructions, and appropriate limitations.

(Comment 37) FDA received several comments regarding experience with IVDs offered as LDTs during the COVID-19 pandemic. Some suggested that FDA's policies slowed availability of tests early in the pandemic and slowed down development of over-the-counter (OTC) home tests. Some pointed to long review times for EUA requests as indicative that FDA does not have the bandwidth to handle review of IVDs offered as LDTs. Others suggested that it is unfair to point to problems with COVID-19 laboratory-made tests as evidence of a broader problem with IVDs offered as LDTs given that COVID-19 laboratory-made tests were developed under unusual circumstances, including "overnight demands to dramatically expand testing capacity, continuous reagent shortages, [and] global supply chain disruptions." Another comment, from an AMC, reported on the AMC's own experience and that of colleagues at other AMCs, stating that "in no case that I know of was anyone submitting data that was remotely representative of what we would generally consider sufficient for an assay." The comment explained that their strategy involved submitting "minimal verification data so that we could get feedback on the initial submission...about how to proceed."

(Response 37) As an initial matter, we disagree that FDA's policies unnecessarily slowed availability of COVID-19 laboratory-based or home tests that had appropriate assurances of

safety and effectiveness. As discussed in section V.A.2, FDA has not applied the general enforcement discretion approach to LDTs used for declared emergencies because of the significant risk posed by the disease (as signified by the unusual step of issuing a declaration under section 564 of the FD&C Act) and because false results can have serious implications for disease progression and public health decision-making, as well as for the individual patient's care. For these reasons, FDA generally expected EUA authorization for COVID-19 LDTs.

Notably, FDA took steps to expedite submission and review of EUA requests for COVID-19 IVDs to help ensure that patients and providers had access to authorized IVDs. FDA made a template available in January of 2020 to help manufacturers prepare and submit EUA requests for COVID-19 IVDs, and engaged with 100 manufacturers by the end of February 2020 to discuss EUA requests and the EUA process. Early in the pandemic, FDA authorized IVDs, including several IVDs offered as LDTs, within a day of receiving complete datasets. Moreover, FDA issued enforcement discretion policies to help address access concerns as appropriate. FDA acknowledges that review times grew as a backlog of EUA requests grew, but we note that many test manufacturers offered their tests as described in these enforcement discretion policies while FDA review of their EUA requests was pending.

FDA also acknowledges that the entire healthcare community, including test manufacturers, operated under unusual circumstances that do not reflect the environment in which tests are typically developed. However, while the pandemic was an unusual circumstance, our conversations with laboratory manufacturers during that time revealed that many were unfamiliar with what constitutes appropriate analytical and clinical validation for an IVD generally. FDA's validation expectations for tests seeking EUAs were also lower than expectations for traditional marketing authorization, and many allegedly "complete" validation packages in EUA requests submitted to FDA were still insufficient. FDA appreciates that many laboratories were new to interactions with FDA and not familiar with FDA's expectations for

validation, but we note that many of these laboratories were nonetheless offering their unvalidated IVDs as LDTs for COVID-19, and in many cases for other diseases or conditions, to the public.

Moreover, the issues identified with COVID-19 IVDs offered as LDTs were similar to those that FDA has identified with IVDs manufactured by non-laboratory manufacturers. FDA's identification of these issues for IVDs offered as LDTs, by laboratories certified under CLIA, highlights the importance of FDA phasing out the general enforcement discretion approach for LDTs. Once the phaseout described in this preamble is complete, laboratory manufacturers will gain experience with FDA's general expectations for validation, providing greater assurances of safety and effectiveness for tests and making the country better prepared for future outbreaks. Further, FDA intends to publish guidance on validation of tests used after a determination and declaration under section 564 of the FD&C Act.

Finally, FDA disagrees that EUA review times for COVID-19 IVDs indicate that FDA does not have the capacity to handle review of IVDs offered as LDTs, as explained in response to comment 275.

(Comment 38) Several comments suggested that a study cited by FDA as evidence of variable performance among IVDs offered as LDTs was flawed (Pfeifer et al. (Ref. 20)). One comment suggested that FDA incorrectly described the findings of the study. Comments also referenced a recent publication that purported to be a reanalysis of the same data but was by different authors (Zehir et al. (Ref. 104)). Comments claimed that the reanalysis showed "excellent" LDT performance and that the original analysis was biased. Others questioned the use of the FDA-approved comparator in the original study. One comment suggested that FDA failed to disclose the reanalysis publication.

(Response 38) As an initial matter, FDA disagrees that the Zehir et al. study has any bearing on FDA's reliance on the Pfeifer et al. publication to support the need for this rulemaking. CAP proficiency testing programs' performance data are not appropriate

comparative results to those reported in Pfeifer et al. due to various limitations with proficiency testing programs, including that the programs are not sufficiently challenging and adequately representative of the routine conditions of clinical test use. For example, proficiency testing does not cover the entire test procedure, proficiency testing specimens that are highly contrived do not closely mimic patient specimens, proficiency testing samples include less challenging variant types and variant allele fractions, and laboratories are aware of participation in highly controlled proficiency testing exercises, which may influence how the test is performed and results obtained. Furthermore, aggregate data reported by Zehir et al. (Ref. 103) and referenced by the comments may mask individual poor performing laboratories. Please see our response to comment 34 for additional details regarding FDA's concerns with the use of proficiency testing data to evaluate the performance of IVDs. The SPOT/Dx pilot study reported in Pfeifer et al. was intended to evaluate laboratories individually, using samples that mimic as closely as possible patient samples, and compares the accuracy of LDTs with an FDA-approved CDx in a specific clinical scenario, to model an actual patient encounter (Ref. 20). Thus, it is one of the only truly reliable head-to-head comparisons between IVDs offered as LDTs and a parallel FDA-authorized IVD.

We also disagree with the assertion that SPOT/Dx was confounded by comparing the performance of IVDs offered as LDTs with that of the FDA-approved CDx because the CDx was performed as intended, and the SPOT/Dx pilot was intended to assess the performance of IVDs offered as LDTs in detecting the same variants as the FDA-approved CDx. In both the SPOT/Dx pilot study and the Zehir et al. reanalysis, testing using the CDx led to accurate reporting of all variants for both wet and dry samples while testing involving IVDs offered as LDTs did not accurately report all variants. SPOT/Dx demonstrated that using the same set of samples, intended to mimic formalin-fixed paraffin embedded samples, certain IVDs offered as LDTs would not identify the same patient population as the approved CDx. FDA notes that the SPOT/Dx working group that developed the pilot comprised many stakeholders, including NGS

laboratories, professional oncology organizations, payors, regulatory agencies, patient advocacy groups, and others. CAP specifically coordinated the Scientific and Technical Working Group and provided professional, logistical, and operational expertise in support of the pilot.

FDA disagrees with the comments' assertion that FDA incorrectly described the findings of the SPOT/Dx pilot study (Ref. 20). The description of this study in the NPRM stated that "the same samples were sent to 19 laboratories for testing using their own manufactured test, and only 7 of those laboratories correctly reported all results. For almost half of the tests studied, analytical accuracy was significantly lower than that of the parallel test approved by FDA" (88 FR 68006 at 68011). This aligns with the findings reported by the study authors that, of the 19 laboratories that analyzed both the wet and dry samples, "7 (37 percent) of 19 laboratories correctly reported all variants, 3 (16 percent) of 19 had fewer than five errors, and 9 (47 percent) of 19 had five or more errors." The authors also reported that the Praxis Extended Ras Panel correctly reported all variants for both wet and dry samples. As discussed in the NPRM (88 FR 68006 at 68010 and 68011), this study documents high variability in performance among IVDs offered as LDTs, which is reflected in the study authors' key point that "the accuracy of detection of genetic variants differed among the laboratory-developed tests (LDTs) performed by different laboratories," as well as the authors' conclusion that "variable accuracy in detection of genetic variants among some LDTs may identify different patient populations for targeted therapy" (Ref. 20).

FDA disagrees that the findings from the referenced reanalysis (Ref. 103) show "excellent" LDT performance. Despite Zehir et al.'s claims that the reanalysis demonstrated excellent laboratory performance, individual laboratories still had a significant number of errors, with only eight laboratories correctly reporting all variants in the reanalysis (compared to seven in SPOT/Dx) and four laboratories still had greater than five errors.

Finally, FDA did not fail to disclose the published reanalysis, as it was not published prior to the posting of FDA's NPRM for public inspection by the Office of the *Federal Register*

on September 29, 2023. It has since been published and, in addition to the discussion in our comment responses, is included as a reference to the rule.

(Comment 39) One comment claimed that the Friends of Cancer Research Tumor Mutational Burden (TMB) study cited by FDA as evidence of variability among laboratories' tests actually showed similar variability as that seen in two FDA-approved tests.

(Response 39) FDA acknowledges there can be variability among FDA-approved tests and that the referenced TMB study included two FDA-authorized tests, one tumor mutation profiling test that includes detection of TMB, and one CDx test for detection of TMB for identifying patients for treatment with pembrolizumab. FDA further acknowledges that the results from the laboratories performing those tests were included among the authors' conclusions regarding variability across tests. The authors of the study did not conduct an analysis to compare variability of IVDs offered as LDTs to those that are FDA-authorized nor comment on differences in variability between the two. While FDA accurately described the results of this study as finding "substantial variability among tumor mutational burden (TMB) tests manufactured by laboratories and used to identify patients with cancer most likely to benefit from immunotherapy" in the NPRM (88 FR 68006 at 68011), FDA does not mean for this to imply that the results of this study indicate greater variability in the studied IVDs offered as LDTs compared to the studied FDA-authorized tests. As such, FDA is clarifying here that the study does not support the proposition that TMB tests manufactured by laboratories have worse performance than FDA authorized TMB tests. However, other evidence in the NPRM supports this proposition as applied to tests more generally (see Refs. 20, 91 to 96, 105 to 110).

(Comment 40) One comment claimed that the publication on epidermal growth factor receptor (EGFR) testing for non-small cell lung cancer that was referenced in the PRIA is biased in multiple ways: the authors had a vested interest in the outcome, the work was funded by a company with a vested interest in the outcome, the IVD offered as an LDT was in Europe and

therefore not required to comply with CLIA, and the trial did not assess the same material extracted from residual tissue specimens with the laboratory-made and FDA-approved test.

(Response 40) FDA acknowledges that, as is clear from the study publication, the work reported in this publication: (1) was authored and funded by a company who may be a competitor with the relevant laboratory manufacturers and (2) utilized IVDs offered as LDTs in Europe, which may not be representative of IVDs offered as LDTs in the United States. This study was not included in the NPRM but was included in the PRIA. FDA no longer cites this publication in the FRIA.

(Comment 41) One comment addressed FDA's citation of Manrai et al., 2016 (Ref. 95), arguing that this publication did not show that IVDs offered as LDTs exacerbate health disparities. The comment claimed that FDA did not properly describe the findings of the publication, stating that "the message of the paper was the lack of testing in both control and diseased populations for underrepresented minorities is what led to poorer outcomes." The comment also asserted that an FDA-approved assay would have similar limitations to those described for IVDs offered as LDTs.

(Response 41) FDA cited this publication for the proposition that IVDs offered as LDTs *may* exacerbate health disparities. FDA did not contend that the publication showed that IVDs offered as LDTs do in fact exacerbate health disparities. FDA also separately cited this publication because it describes problems with IVDs offered as LDTs, regardless of any impact on health disparities (see 88 FR 68006 at 68011 (stating that the publication "reported false positive results from genetic IVDs offered as LDTs for hypertrophic cardiomyopathy in multiple patients of African American descent."))).

FDA believes it is appropriate to cite this publication to support that IVDs offered as LDTs may exacerbate health disparities for the following reasons. First, the study identified multiple persons of African or unspecified ancestry who had received false positive test results from IVDs offered as LDTs related to the historical dearth of data that include persons of diverse

racial and ethnic backgrounds, which prevented accurate variant interpretation at the time of results reporting; higher rates of these types of false results in underrepresented populations may exacerbate health disparities. Second, the paper reports on disparities that may result from errors unrelated to access to care, particularly genetic variant misclassification (a type of inaccurate test result). The authors specifically state that their findings “show how health disparities may arise from genomic misdiagnosis” (i.e., a type of inaccurate result) and describe the negative consequences of the “provision of false genetic information” not just to a patient but to their relatives as well. The authors also report that their “findings suggest that false positive reports are an important and perhaps underappreciated component” of certain tested persons. Despite the comment’s assertion that the message of this paper was that the lack of testing in underrepresented minorities is what led to poorer health outcomes, that message was not explicitly stated in the publication. Rather, the authors call for diverse genomic data in their conclusion: “the misclassification of benign variants as pathogenic that we found in our study shows the need for sequencing the genomes of diverse populations, both in asymptomatic controls and the tested patient population.”

FDA acknowledges that lack of data on the genomes of diverse populations makes demonstrating accurate genetic variant classification in diverse populations challenging. While FDA-authorized tests may face challenges due to the paucity of data from genetically diverse populations, FDA-authorized tests generally have greater transparency regarding the population(s) in which they were validated, information pertaining to device safety and effectiveness for specific demographic characteristics if performance differs within the target population, and population-specific limitations, if applicable. In addition, during FDA premarket review, FDA may ask that sponsors provide data for different intended use populations as well as diversity action plans to improve the generation of evidence regarding device performance in diverse populations. As such, in general, there is greater confidence in the accuracy and reliability of FDA authorized genetic tests, and FDA oversight of IVDs offered as LDTs may

help to advance health equity, as discussed in the NPRM and in our responses to comments in section VI.K of this preamble.

(Comment 42) FDA received a comment from a sponsor that submitted a 510(k) for an IVD offered as an LDT that was discussed in FDA's memorandum to file regarding "Examples of In Vitro Diagnostic Products (IVDs) Offered as Laboratory Developed Tests (LDTs) that Raise Public Health Concerns," which was included in the docket for this rulemaking (Ref. 16). The comment expressed concerns regarding the inclusion of this particular submission in the memorandum, contending that FDA's review of the submission was inappropriate and that the validation data submitted for this IVD offered as an LDT was sufficient. In particular, the comment stated that "leading journals" had published studies demonstrating the utility of the sponsor's techniques; that the sponsor withdrew its submission because FDA refused to use a certain "fit-for-purpose" assessment of the data; that the sponsor had demonstrated the detection limits and precision of the IVD; that quality controls embedded in the IVD provided for the identification of any interfering substances; that FDA inappropriately focused on certain details while dismissing other important information; that the review process was overly time-consuming and expensive; and that the IVD has become standard of care.

(Response 42) FDA disagrees with this comment. In relevant part, the memorandum to file stated that "[i]n 2021, FDA received a 510(k) submission from [redacted] for their [redacted] test for monitoring changes in burden of disease in pediatric and adult patients with [acute myeloid leukemia (AML)] during and after treatment. The submission did not contain adequate analytical and clinical validation studies to show the test worked as intended. For example, the sponsor did not provide any data from interference, detection limit, and reagent stability studies; did not submit data from precision studies to demonstrate the test is reliable in intended use specimens; only used one specimen to evaluate sample stability rather than the recommendation of at least ten; and included samples in the clinical study that were not the sample type intended for use with the test. The sponsor withdrew the submission after FDA raised concerns with the

inadequate validation data. Without sufficient information to demonstrate adequate validation, a test's performance is unknown, which may put patients at risk of harm due to inaccurate results. In general, inaccurate results from tests to monitor disease burden during and after treatment for AML could lead to suboptimal clinical management of patients with AML. The risk of false negative results (i.e., a patient assumed to have a more favorable prognosis based on the false negative result) could potentially result in a reduction in the level of care such as less medication use, subsequent confirmatory testing, and other possible treatment decisions. False positive results (i.e., a patient who is disease free presumed to have a hematologic malignancy based on the positive test result) could result in additional unnecessary testing" (Ref. 16).

With respect to the comment's statement that "leading journals" published studies demonstrating the utility of the sponsor's techniques, FDA notes that during review of the 510(k) submission, the sponsor referenced three publications that it claimed supported the clinical validation of the IVD. The first publication described a feasibility study and was not a validation study. The second publication described a clinical validation study that used a different version of the device than the subject device under review (i.e., the device evaluated had a different operating principle than the device under review). The sponsor did not provide information adequate to support leveraging clinical performance data from a version of the device that differed in significant ways from the subject device. In addition, there was a difference in the limit of quantitation (LoQ) reported in the publication and the LoQ estimated by precision and linearity data submitted by the sponsor, which raised significant uncertainty in the clinical validation data. The third publication was a clinical study that utilized the device to aid in the diagnosis of a different disease and was thus for a different intended use. Therefore, the data could not be leveraged to support the device's safety and effectiveness for the AML claim being sought.

FDA also disagrees with the comment's statement that FDA refused to use a "fit-for-purpose" assessment of the data. FDA's review was risk-based and intended to be consistent

with least burdensome principles. The expectations for safety and effectiveness for this test were based on the intended use of the device and in the context of special controls required for devices of this type, thereby ensuring the device performance was validated in a fashion encompassed by the fit-for-purpose concept. Throughout the review, FDA considered and proposed multiple alternatives as least-burdensome approaches.

The comment further contended that the sponsor had demonstrated the detection limit of the assay and had submitted precision studies to demonstrate test reliability. However, during FDA's review of the submission, the Agency did not agree that the detection limit of the assay could be demonstrated solely in the manner suggested by the sponsor as the output assessed by the sponsor in the studies conducted was different from the output of the device. In addition, although the sponsor had submitted multiple precision studies, the sponsor failed to provide information on how the studies were conducted and how the data were analyzed (e.g., study protocols), such that FDA could not determine whether the reported precision would be adequate to support a determination that the test was as safe and effective as the predicate device. In addition, when the sponsor provided a reanalysis of the precision data, there were unexplained deviations in results calculations, raising concerns with the reliability of the data submitted.

With respect to the comment's assertion that quality controls embedded in the IVD provided for the identification of any interfering substances, the sponsor made this assertion during FDA's review of the submission as well, in an effort to justify why studies to assess the impact of potentially interfering substances on test performance were inapplicable. However, the sponsor did not provide critical explanatory information or documentation, or any validation data to demonstrate the capability of the laboratory's continuous process controls to identify failures in instrument, reagent, or specimen integrity. FDA also disagrees that the Agency focused too heavily on certain aspects of the submission, such as cell counting, and dismissed the importance of other aspects, such as fluorescence intensity. FDA discussed fluorescence intensity with the sponsor on several occasions. The comment's assertion that FDA never asked about the results

from three clinical trials is likewise not accurate; during review of the submission, FDA made multiple requests to the sponsor for additional information on the studies submitted, and identified various concerns with the studies. Ultimately, throughout the review, FDA considered the available data and least burdensome approaches for providing the data necessary to demonstrate that the device was as safe and effective as the predicate device, considering the intended use and special controls for this device type, but the sponsor's assertions did not obviate the need for adequate clinical validation. During the review process, the sponsor acknowledged its ability to perform validation studies requested by FDA, but stated that it declined to do so.

The comment also suggested that FDA's review took too long and was too expensive, stating that the review process took 9 years and cost more than \$1,000,000. FDA acknowledges that the Agency worked with the sponsor over 9 years, but notes that much of this interaction was in the context of 6 voluntary Pre-Submissions submitted by the sponsor, beginning approximately 9 years before the 510(k) was submitted.

With respect to the comment's statement that the subject assay has become the standard of care, FDA was not able to determine whether in fact this test is now used as part of the standard of care. Regardless, a test being used as part of the standard of care is not sufficient to provide appropriate assurances regarding safety and effectiveness. Use in clinical practice does not necessarily establish that a device is appropriately safe and effective.

(Comment 43) One comment stated that FDA's memorandum regarding examples of IVDs offered as LDTs that raise public health concerns did not provide enough details to determine whether the stated problems were related to assay design or procedural issues, and noted that procedural issues are under the regulatory authority of CLIA. The comment also asserted that FDA's statement in the memorandum that FDA did not confirm the veracity of the reports suggests that FDA did not deem the public health risks severe enough to warrant investigation by the Agency at the time of submission.

(Response 43) FDA disagrees that the Agency did not deem the public health risks severe enough to warrant investigation by the Agency. The referenced statement regarding the Agency not confirming the veracity of information was specific to complaints, MDRs, and allegations, where FDA relies on information submitted by the entity filing the report. As described in that memorandum, any follow up by the Agency on the complaints, MDRs, and allegations is not included in the memorandum. As a general matter, FDA does not comment on such investigations.

FDA acknowledges that the details included in the memorandum regarding the MDRs and allegations cited therein do not indicate whether the problems were related to assay design or other aspects not covered by CLIA, due to the nature of MDRs where the information available to the Agency is the information submitted in the report and does not typically include detailed information on test design or validation of the test. The memorandum describes what was reported in the MDR or allegation. However, all of the examples from submissions FDA reviewed had issues related to analytical validation that would negatively impact the test's intended clinical use, or inadequate clinical validation that CLIA does not address. For these examples, FDA had sufficient data and information that pointed to issues CLIA would not address. Furthermore, FDA was able to confirm that the laboratories that developed 22 of the 26 IVDs offered as LDTs reviewed in these submissions were CLIA-certified laboratories. For the others that FDA was not able to confirm, those laboratories should have been CLIA certified since they were performing the tests on samples from United States subjects. Taken together, FDA identification of these issues demonstrates potential problems with the tests despite CLIA regulation.

D. FDA Authority to Regulate LDTs

1. General Comments Regarding FDA's Authority

(Comment 44) Various comments stated that FDA has statutory authority over LDTs. Other comments asserted (without specific analysis) that FDA lacks authority to finalize the proposed rule.

(Response 44) For the reasons set forth in the NPRM and this preamble, FDA agrees with the commenters who stated that FDA has this authority. FDA has long stated that LDTs, like other IVDs, are “devices” subject to applicable requirements in the FD&C Act (see 62 FR 62243 at 62249 (November 21, 1997), 65 FR 18230 at 18231 (April 7, 2000), Ref. 27, Ref. 32-33, Ref. 35, Ref. 39, Ref. 57, Ref. 97, Ref. 111-121). FDA responds to more specific jurisdictional arguments in the paragraphs that follow.

(Comment 45) Some comments suggested that FDA's failure to publicly announce its authority over LDTs closer to enactment of the FD&C Act or MDA raises questions about whether the Agency has authority over LDTs. Several comments noted that FDA did not communicate its authority over LDTs until 1992, 16 years after enactment of the MDA. Two comments suggested that FDA's position that it gained authority over IVDs, including LDTs, “when key legislation was passed” but exercised enforcement discretion constitutes “revisionist history” or an “ex post facto” narrative.

(Response 45) FDA disagrees with these comments. First, the Agency's jurisdiction depends on the scope of authority granted to it under the statute, and that jurisdiction existed (as explained in the NPRM and elsewhere in this preamble) regardless of when FDA publicly discussed it. *See Bostock v. Clayton Cty.*, 140 S. Ct. 1731, 1737 (2020) (“extratextual considerations” do not trump “the express terms of a statute”).

Second, the comments appear to take the position that FDA may not assert its statutory authority unless it issued a public statement announcing that authority within some timeframe after which Congress granted it. FDA is aware of no such obligation. On the contrary, the U.S.

Supreme Court has held that agencies are not required to prospectively announce their interpretations to the public before applying that interpretation in an individual case. *SEC v. Chenery Corp.*, 332 U.S. 194 (1947). Moreover, because FDA generally did not enforce device requirements with respect to LDTs when the MDA was passed (as a matter of practice and based on relevant public-health considerations), it would not necessarily have made sense for FDA to expend resources to issue a public statement about its authority. FDA did not put itself to that task until public-health considerations justified it in 1992. (Ref. 111). Thus, as these comments appear to concede, FDA squarely announced its understanding that LDTs are devices over 30 years ago, nearly double the 16-year period cited in these comments.

Third, to the extent that comments are suggesting that laboratories would not have understood their potential status as manufacturers around the time the MDA was passed, FDA disagrees. FDA signaled this interpretation in various contemporaneous materials. In 1973, before enactment of the MDA, FDA issued a final rule announcing regulatory requirements for IVD products, including systems, which contained no carveout or exception for laboratories (38 FR 7096, March 15, 1973). Following the MDA, FDA amended the rule to clarify that IVDs are devices, consistent with Congress's intent. 45 FR 7474, 7484 (February 1, 1980) (revising the definition to state that IVD products are "devices" rather than "drugs or devices" under the FD&C Act). Again, FDA did not create any carveout or exception for LDTs. These facts put laboratories on notice that FDA interpreted the device requirements to apply to test systems regardless of who manufactured them. In addition, 3 years earlier, in 1977, FDA issued regulations regarding device registration and listing and exempted only those clinical laboratories "whose primary responsibility to the ultimate consumer is to dispense or provide a service through the use of a previously manufactured device" (see § 807.65(i) (21 CFR 807.65(i)); 42 FR 42520 at 42528, August 23, 1977)). This exemption conveyed that: (1) FDA considered clinical laboratories to manufacture devices (otherwise this exemption would not have been necessary) and (2) some laboratories are not exempt from registration and listing (i.e.,

those who fall outside the “use of a previously manufactured device” limitation). In addition, in the context of a different exemption, the preamble to that rule emphasized that “exemption from registration does not relieve such persons from their obligation to comply with other provisions of the act or regulations” (42 FR 42520 at 42521). Thus, laboratories were on notice that FDA considered them device manufacturers subject to applicable provisions of the FD&C Act and regulations.

(Comment 46) Several comments suggested that FDA’s enforcement discretion approach for LDTs raises questions about FDA’s authority in this area. One comment stated that the commenter “believes that any authority to regulate LDTs has been waived through the agency’s actions since 1988 if they even existed when the Medical Device Amendments passed in 1976.” Another comment noted, in arguing that FDA lacks authority, that the Agency has a “history of inconsistent positions on LDTs” and “has never exercised [its] claimed authority in a comprehensive manner in the 85 years it had authority over devices.” Other comments stated that FDA’s “position on [its] authority has vacillated in significant ways, even recently.”

(Response 46) FDA disagrees that its enforcement discretion approach suggests that FDA lacks or “waived” authority over LDTs. As an initial matter, FDA is not aware of any legal support for the proposition that an agency can waive statutory authority granted to it by Congress through the exercise of enforcement discretion. Indeed, the Supreme Court has expressly distinguished an agency’s exercise of enforcement discretion--what FDA has done in the case of LDTs--from the refusal to initiate enforcement proceedings based on the agency’s conclusion “that it lacks jurisdiction”--a conclusion FDA has never reached in this context. *Heckler v. Chaney*, 470 U.S. 821, 833 n.4 (1985).

In addition, although FDA recognizes that it has initiated a number of efforts to address LDTs, as explained in section III.D.2 of the NPRM, these policy efforts do not cast doubt on FDA’s authority or its understanding of its authority (88 FR 68006 at 68016). On the contrary, FDA’s initiation of different policy approaches over the course of many years confirms that it

uniformly believed it had authority and certain discretion with respect to LDTs. Furthermore, as explained in response to comment 45, FDA interpreted laboratories to be manufacturers, and IVD products, including systems, to be devices, even before the initiation of these policy efforts. And since 1992, FDA has consistently and publicly announced that IVDs manufactured by laboratories are devices under the FD&C Act (see section III.D.1 of the NPRM, “FDA’s Longstanding Recognition That IVDs Manufactured by Laboratories Are Devices,” 88 FR 68006 at 68015-16). Thus, contrary to commenters’ suggestion, FDA has not had “inconsistent positions” but rather has consistently maintained a single position: it has authority over LDTs.

(Comment 47) One comment argued that “it has long been the mainstream view of legal experts that the FDA lacks authority to regulate LDTs in the absence of legislation to grant them such authority,” referencing a white paper coauthored by Paul Clement and Laurence Tribe as well as a June 2020 memorandum by the then-General Counsel of HHS. Another comment also quoted the HHS then-General Counsel’s June 2020 memorandum for the proposition that “the Agency’s jurisdiction to regulate these devices is not uniform and not as plenary as it is for a traditional device.”

(Response 47) FDA disagrees with the assertion that legal experts generally think FDA lacks authority over LDTs. In FDA’s experience, many legal scholars who have occasion to discuss LDTs describe them as tests treated differently as a matter of Agency discretion, rather than because FDA lacks authority.⁵³ Although the first comment relies on a document authored by Paul Clement and Lawrence Tribe as support for the proposition regarding the “mainstream view of legal experts,” these authors did not write that document in their capacity as independent legal experts, but as counsel to the American Clinical Laboratory Association (ACLA). Therefore, that document reflects the view of one interested party. To the extent that particular commenters incorporated arguments from that document, we address the substance of those arguments in our responses to the specific comments in question. In any event, FDA’s analysis is

⁵³ See, e.g., Refs. 122-124.

based upon the substantive merits of the issues, not upon surveying how many “legal experts” have advocated for or against a given view.

In addition, the June 2020 memorandum identified in the comments did not (contrary to one comment’s suggestion) take the position that FDA lacks authority to regulate LDTs in the absence of legislation. Instead, the memorandum indicated that FDA has discretion to treat LDTs as devices but that there is legal risk in taking that position absent notice-and-comment rulemaking (for further detail on the June 2020 memorandum’s position, see, for example, Ref. 125 at 2, n. 5). As noted by the second comment, the memorandum did suggest that FDA’s authority over LDTs was constrained by certain statutory limitations; the memorandum focused in particular on the following statutory language: “introduction or delivery for introduction into interstate commerce,” “commercial distribution,” “held for sale,” and “person.” HHS no longer agrees with that memorandum, which has since been superseded, for the reasons set forth in sections VI.D.3, VI.D.4, and VI.E (comment response 105) of this preamble. More generally, we note that even if FDA’s authorities were limited in the ways proposed in the June 2020 memorandum, that would not implicate the question of whether LDTs are devices and thus FDA’s authority to regulate LDTs under other relevant provisions of the statute and regulations. Not all provisions apply equally to all regulated products. For example, some statutory provisions apply depending on the specific activities of a manufacturer (see response to comment 54). Similarly, some statutory provisions impose requirements with respect to a device on certain actors but not others--for example, some provisions apply only to manufacturers and importers but not to distributors (e.g., 21 U.S.C. 360i(a)(1)) and others apply to all three (e.g., 21 U.S.C. 360h(a))--but the device is nonetheless within FDA’s jurisdiction. FDA has jurisdiction to regulate devices including LDTs, even if some subset of substantive statutory provisions do not apply to LDTs.

(Comment 48) One comment stated that “[f]alse advertising by some rogue companies overstating the benefits of their tests is the purview of the [Federal Trade Commission (FTC)], not the FDA.”

(Response 48) Although the comment appears to argue that IVDs manufactured by laboratories are not devices (and instead fall solely within an FTC-regulated category), laboratory-made IVDs are devices, as explained elsewhere in this preamble and the NPRM. Because these IVDs are devices, advertising for them does not fall within the sole purview of the FTC. Such IVDs are subject, for example, to the provisions in the FD&C Act that deem a device misbranded if its labeling (or advertising, in the case of a restricted device) is “false or misleading in any particular.” 21 U.S.C. 352(a)(1) and (q). FDA recognizes that the FTC also has authority regarding the advertising of devices. *E.g.*, 15 U.S.C. 52(a)(1) (prohibiting the dissemination of “any false advertisement...for the purpose of inducing, or which is likely to induce, directly or indirectly, ...the purchase...of...devices”). Because the two Agencies share authority, they have long worked together to effectively coordinate and use their authorities in complementary ways, particularly mindful of each Agency’s substantive expertise, such as FDA’s scientific expertise. Thus, the FTC is not the sole regulator of device advertisements.

(Comment 49) Two comments drew an analogy between the preparation of a laboratory test and the preparation of a restaurant meal. One comment stated that while FDA regulates the ingredients of a restaurant meal, such as pasta, it does not regulate the preparation of a restaurant meal, and the same should be true for laboratory tests. Another comment stated that restaurant recipes are like laboratory testing procedures and should be regulated in the same manner.

(Response 49) Food and devices present different public health considerations and are subject to different requirements under the FD&C Act, including differing premarket review requirements, so FDA oversight of restaurants should not be understood to determine FDA’s authority over, or approach to, laboratory tests. Furthermore, these comments appear to take as their premise that restaurants are exempt from the FD&C Act, but that is not the case. FDA has

jurisdiction over “food,” a term defined broadly at 21 U.S.C. 321(f), and restaurants are subject, for example, to the prohibition on doing an act with respect to a food if such act is done while the food is held for sale after shipment in interstate commerce and results in it being adulterated or misbranded (21 U.S.C. 331(k)).

(Comment 50) One comment argued that if the Supreme Court overturns or narrows the *Chevron* doctrine through its decision in *Loper Bright Enterprises v. Raimondo*, that would “further undermine FDA’s authority to regulate LDTs and further place in question the validity of a final LDT rule.”

(Response 50) Because the FD&C Act confers clear authority on FDA to regulate IVD products, without any exception for products made by laboratories, the *Chevron* doctrine is not necessary to resolve any question of FDA’s authority over LDTs. FDA’s reasoning for this position, taking into account the traditional tools of statutory construction, is set forth in the following responses to comments 51-54.

2. Application of the Device Definition to LDTs

A number of comments argued that LDTs are not devices within the meaning of 21 U.S.C. 321(h)(1) because they are intangible services rather than tangible or material objects. Comments raised arguments related to the plain language, canons of construction, legislative history, and other provisions of the FD&C Act to support this position.

(Comment 51) Several comments took the position that because the device definition does not contain the terms “in vitro diagnostic product” (as defined in § 809.3), “system,” “assay,” “test,” or “laboratory developed test,” it does not encompass these articles. Some stated that these terms are broader than the terms that do appear in the definition, including “in vitro reagent,” “instrument,” and “similar or related article,” and concluded that they therefore fall outside the definition. One comment stated that because Congress presumably was aware that diagnostic tests are “key elements of medical diagnoses” when it enacted the MDA, if Congress had intended to cover such tests, it would have done so expressly. Several comments stated that

Congress's decision not to include the term "system" in the device definition in 1976, following issuance of the IVD regulations in 1973, undermines the Agency's reliance on that concept. One commenter also noted that the concept of an LDT was not discussed in congressional hearings prior to the passage of the MDA, suggesting that Congress did not intend for LDTs to be included.

(Response 51) FDA disagrees with the position that the device definition does not include IVD systems because it does not contain the terms "system," "assay," "test," or "laboratory developed test." As explained in the NPRM, IVD systems fell within the device definition (which included the terms "apparatus" and "contrivance") even before passage of the MDA (88 FR 68006 at 68017). In FDA's 1973 rulemaking, which occurred 3 years before the MDA's enactment, the Agency publicly announced its view that IVD systems fell within the device and drug definitions and thus within its authority. If Congress had disagreed with FDA's interpretation, it had the opportunity to clarify that in the MDA, but it did not do so. Instead, it retained the same terms from the device definition in the 1938 Act, without any exemption for "systems," "assays," "tests," or "laboratory developed tests." This sequence of events indicates that despite numerous opportunities to do so, over decades' worth of subsequent legislation concerning devices, Congress did not disagree with FDA's interpretation that IVD systems fall within its authority.

In fact, Congress clarified in the MDA that IVD systems are devices and not drugs. To do so, it added the terms "in vitro reagent" and "other similar or related articles" to the device definition. *See* S. Rep. No. 93-670 at 16 (January 29, 1974) (explaining, with respect to nearly identical language, that "[t]he Committee recognizes that there is confusion at the present time about whether certain articles are to be treated as devices or drugs under the Food, Drug and Cosmetic Act. Therefore, the Committee reported bill has carefully defined 'device' so as to specifically include implants, in vitro diagnostic products, and other similar or related articles."). The purpose of adding the term "in vitro reagent" was not to narrow FDA's authority over IVD

products (again, Congress had much clearer ways to accomplish that); instead, the goal was to clarify that all in vitro diagnostic products were devices rather than drugs. *Id.* (explaining that the term “device” includes “in vitro diagnostic *products*”) (emphasis added). Other evidence in the legislative history confirms that Congress intended for FDA to regulate IVD systems as devices, as explained in response to comment 53. More recently, in the Protecting Access to Medicare Act of 2014 (PAMA) (passed in 2014), Congress enacted provisions that support an interpretation that LDTs are subject to FDA regulation. 42 U.S.C. 1395m-1(d)(5) & (d)(5)(B).

FDA also disagrees with the comment that suggested that Congress would have discussed LDTs in congressional hearings if it had intended for LDTs to be included in the definition. The topics covered in congressional hearings do not trump the plain text of the device definition, which encompasses LDTs. *See Bostock v. Clayton Cty.*, 140 S. Ct. 1731 at 1754 (“Judges are not free to overlook plain statutory commands on the strength of nothing more than suppositions about intentions or guesswork about expectations.”). Also, it would not be reasonable to expect that Congress would have discussed every conceivable device during congressional hearings.

(Comment 52) Many comments stated that tests made by laboratories, or some subset of such tests termed “LDTs,” are not devices under the FD&C Act because the device definition is limited by its plain language to physical objects or material things, and tests made by laboratories are intangible methods, services, procedures, or processes. One comment stated that a device within the definition has “mass and volume” and “can be touched and held.” Another comment relied on a canon of construction that words grouped together in a list should be given related meaning, and stated that because, according to the comment, the terms “instrument,” “implement,” “machine,” “implant,” and “in vitro reagent” refer to tangible objects, the terms “apparatus” and “contrivance” should also be understood to be tangible objects. The same comment noted that an “article” is defined as a “particular material thing” in the Oxford English Dictionary (OED). Several comments stated that courts have construed the term “article” to mean a material thing.

(Response 52) The FD&C Act defines a device, in relevant part, as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is...intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.” 21 U.S.C. 321(h)(1)). FDA does not agree that this definition is limited by its plain language to physical objects or material things, but even if it were, a test system is a physical object and a material thing.

As an initial matter, FDA does not read the definition of device to encompass only physical objects. The definition includes terms such as “contrivance,” whose plain meaning goes beyond objects that can be “touched and held.” Contrivance, Merriam-Webster.com (last accessed January 5, 2024) (defining “contrivance” as “a thing contrived” and “an artificial arrangement or development,” among other things). (Ref. 126). (*See also* Ref. 127 (defining “contrivance” as “an arrangement or thing in which the foregoing action or faculty is embodied; something contrived for, or employed in contriving to effect a purpose.”)) Although commenters advocate for a narrow interpretation of the device definition, the Supreme Court has specifically considered and rejected a narrow reading of the FD&C Act, instead embracing broad constructions of the FD&C Act based on the Court’s understanding of its text, congressional intent, and remedial purpose. *See United States v. Bacto-Unidisk*, 394 U.S. 784, 798 (1969) (“Congress fully intended that the [FD&C] Act’s coverage be as broad as its literal language indicates.”).⁵⁴ Software is an example of an article that cannot be “touched and held” but falls within the device definition. FDA has long interpreted software to be a device, see, e.g., 52 FR

⁵⁴ *See also United States v. Dotterweich*, 320 U.S. 277, 280 (1943) (“The purposes of [the FD&C Act] thus touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection. Regard for these purposes should infuse construction of the legislation if it is to be treated as a working instrument of government and not merely as a collection of English words.”); *United States v. 25 Cases*, 942 F.2d 1179, 1182 (7th Cir. 1991) (quoting 79 Cong. Rec. at 4841 (1935)) (“the language [of the bill] is broad enough to cover any device of which the Food and Drug Bureauchooses to take jurisdiction”); *United States v. Diapulse Corp. of America*, 457 F.2d 25, 27-28 (2d Cir. 1972) (“[t]he reach of the Act is broad”); *Clinical Reference Lab. v. Sullivan*, 791 F. Supp. 1499, 1508-09 (D. Kan. 1992), *rev’d in part on other grounds sub nom U.S. v. Undetermined No. of Unlabeled Cases*, 21 F.3d 1026 (10th Cir. 1994) (“congressional reportsindicate approval of the Supreme Court’s method in *Bacto-Unidisk* of broadly defining terms within the [FD&C Act]”).

36104, September 25, 1987, and Congress reinforced that interpretation in the 21st Century Cures Act (Cures Act) (Pub. L. 114-255). The Cures Act, enacted in 2016, amended the FD&C Act to exclude certain software functions from the statutory “device” definition unless certain criteria are met. *See* 21 U.S.C. 360j(o). Congress would have had no need to make this amendment to the FD&C Act if the device definition did not already cover software, which is a thing that cannot be “touched and held.” This underscores that a plain reading of the device definition may include things that cannot be “touched and held.”

Regardless, a test system manufactured by a laboratory is a physical product and a material thing. As explained in the NPRM, a test system is a set of components--such as reagents, instruments, and other articles--that function together to produce a test result (88 FR 68006 at 68017). No comment disputed that these individual components are physical or tangible, and there is no reason to think that uniting those physical objects in a system takes away from their physical or material nature. The instrument clause of the device definition clearly encompasses collections of this sort because it includes the term “apparatus,” which Merriam-Webster defines as “a set of materials or equipment designed for a particular use” (Ref. 128. *See also* Ref. 129-130). The fact that there is human involvement to fulfill the intended use of the system does not exclude it from the definition of a device. Such involvement is neither unique to LDTs nor unusual for devices more generally, as the examples offered in comment response 66 illustrate.

In short, the statute makes clear that test systems, including those manufactured by laboratories, are devices. To argue otherwise not only would be inconsistent with the FD&C Act’s plain text, but also would be at odds with the way FDA has understood and regulated IVDs (and other devices) for at least half a century. *See* 38 FR 7096 at 7098, *see* 62 FR 62243 at 62249 (November 21, 1997), 65 FR 18230 at 18231 (April 7, 2000), Ref. 27, Ref. 32-33, Ref. 35, Ref. 39, Ref. 57, Ref. 97, Refs. 111 to 121. Indeed, under the commenters’ construction of the FD&C Act, FDA would not be able to regulate any test systems at all, such as a COVID-19 test for at-

home use: the Agency could oversee the safety and effectiveness of the individual test components in the context of their individual intended uses, but it could not evaluate the safety and efficacy of the COVID-19 test system as a whole, including the accuracy and reliability of the test results yielded when those individual components are used together. Such a construction defies the basic theory and premise of FDA's existing IVD program, which is to ensure that tests work. Nothing in the text or history of the FD&C Act justifies the commenters' proposed interpretation of the definition. On the contrary, the device definition specifically includes "any component, part, or accessory," showing that the mere fact that an article, such as a COVID-19 test system, has individual components does not defeat the possibility that the article is a "device." The legislative history also supports that Congress intended for FDA to regulate such systems, as discussed in response to comment 53. And Congress, which has been aware of FDA's interpretation for over 50 years (see 38 FR 7096), has never expressed disagreement with it. *See, e.g., United States v. Tuent Livestock*, 888 F. Supp. 1416, 1423 (S.D. Ohio 1995) (upholding FDA interpretation of statutory term "food" based, among other things, on the fact that "Congress has been aware of the FDA's understanding and practice concerning live animals for almost twenty-five years, yet has in no way acted to limit the agency's jurisdiction").

Furthermore, at least two Federal statutes contemplate that tests manufactured by laboratories can be subject to FDA regulation. First, CLIA refers to "laboratory examinations and procedures" that have been "approved by the Food and Drug Administration for home use" as among the types of tests a laboratory with a CLIA certificate of waiver can perform. 42 U.S.C. 263a(d)(3). Second, in PAMA, Congress expressly recognized that "a clinical diagnostic laboratory test...offered and furnished only by a single laboratory and not sold for use by a laboratory other than the original developing laboratory (or a successor owner)," a description that may include an LDT, can be "cleared or approved by the Food and Drug Administration." 42 U.S.C. 1395m-1(d)(5) and (d)(5)(B). These provisions refute the comments' suggestion that tests developed by laboratories never fall within the definition of a device.

Various comments focused specifically on the term “article” in the device definition, citing narrow descriptions of the term “article” in a dictionary or in case law to support a narrow understanding of the term “device.” For example, one comment indicated that the term “article” is limited to a “particular material thing” based on a definition in the OED, arguing that the definition of “device” cannot include intangible objects. FDA disagrees that this OED definition narrows the meaning of “article” in the FD&C Act’s device definition. As an initial matter, other dictionary definitions of the term “article” are not so limited. See, e.g., Merriam-Webster.com (Merriam Webster Collegiate Dictionary), article (“a member of a class of things”) (Ref. 131). More important, the text of the FD&C Act indicates that “article” is not so limited. As explained above, Congress has made clear that as used in the device definition, the term article includes software, an intangible thing. It has also made clear that the device definition encompasses clinical diagnostic laboratory tests, as just discussed.

With respect to comments’ citations to cases interpreting the term “article,” FDA notes that none of these cases interpret language in the FD&C Act. Because these cases involve different legal schemes, contexts, and history, they are of limited relevance. Regardless, FDA has reviewed the cases and has concluded that they do not counsel in favor of a different understanding of the device definition as applied to LDTs.

Comments cited three cases: *ClearCorrect Operating, LLC v. ITC*, 810 F.3d 1283 (Fed. Cir. 2015), petition for rehearing en banc denied, 819 F.3d 1334 (Fed. Cir. 2016); *Wilton Meadows Ltd. P’ship v. Coratolo*, 14 A.3d 982 (Conn. 2011); and *Fortin v. Marshall*, 608 F.2d 525 (1st Cir. 1979). In *ClearCorrect*, the Federal Circuit determined that the term “articles” in the Tariff Act does not include digital data, relying on certain dictionary definitions contemporaneous with passage of the 1922 Tariff Act, among other things. This case is particularly inapposite because, as discussed previously, the FD&C Act specifically lists (to name one example) a “contrivance,” as within the device definition (unlike the Tariff Act, which does not further define the term “articles”), and Congress has endorsed the view that the device

definition in the FD&C Act (both as drafted in 1976 and currently) includes software functions. Regardless, an IVD system falls within the *ClearCorrect* court’s understanding of an article because it is comprised of material things, as discussed earlier in this comment response. In *Fortin* and *Wilton Meadows*, courts interpreted the term “article” to exclude services (air transportation services in the former case and nursing home services in the latter). However, FDA’s position is not that laboratory services are articles but that in vitro diagnostic products used in laboratories (such as test systems) are articles. Courts have agreed that medical services and articles used in medical services are distinguishable for purposes of FDA regulation. *See, e.g., United States v. Regenerative Sciences*, 741 F.3d 1314, 1319 (D.C. Cir. 2014). And the *Wilton Meadows* court itself acknowledged this distinction, 14 A.3d at 987 (holding that the term “article” does not include nursing home services but “could reasonably be construed to include food, medicine or many other items that are associated with nursing home care,” although upon review of relevant “extratextual sources,” it did not).

(Comment 53) Several comments asserted that the legislative history of the MDA bolsters the interpretation that the definition of “device” under 21 U.S.C. 321(h)(1) means physical objects. For example, these comments pointed to use of the terms “products,” “machines” and “articles” in congressional reports to argue that Congress only intended for physical objects to be devices.

(Response 53) At the outset, FDA notes that even if it were true that the legislative history suggested a narrow understanding of the device definition, that history would not trump the definition’s plain text, which encompasses LDTs, as explained in comment response 52. *See Bostock v. Clayton Cty.*, 140 S. Ct. 1731 at 1737 (“When the express terms of a statute give us one answer and extratextual considerations suggest another, it’s no contest. Only the written word is the law.”). Moreover, FDA does not agree that the legislative history suggests a narrow understanding of the device definition. Comments point to passing references to terms such as “products,” “machines” and “articles” in the legislative history, but these terms, such as the term

“article,” do not necessarily refer solely to tangible objects, as discussed in the previous comment response. Likewise, “product” commonly refers to things that are either tangible or intangible, insurance and software being examples of the latter. Regarding software, the FD&C Act uses the term “product” to specifically refer to “software” in section 520(o)(2). This is consistent with dictionary definitions of “product.” *See, e.g., Merriam-Webster.com* (Merriam Webster Collegiate Dictionary), product (“(1): something produced” “(2): something (such as a service) that is marketed or sold as a commodity”) (Ref. 132). The legislative history’s passing references to “machines” also could not have been intended to limit the scope of the device definition to tangible objects. The instrument clause of that definition, section 201(h)(1) of the FD&C Act, is not limited to machines. Rather, it refers to “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory.” In accordance with this definition, FDA regulates as devices a wide variety of products--such as surgical instruments, surgical masks, and blood collection containers--that are not “machines.” In addition, the legislative history does not indicate that Congress intended for these references to limit the scope of FDA’s authority; in fact, the legislative history also includes terms that cut in the opposite direction, such as a reference to a “diagnostic service,” as discussed later in this comment response.

Regardless, as explained in response to comment 52, LDTs are physical objects. Generally, they are systems consisting of a combination of physical objects. FDA has not identified evidence in the legislative history to suggest that when IVD components are combined as intended, the resulting in vitro diagnostic product falls outside FDA’s jurisdiction; rather, the legislative history states the opposite. For example, a House report issued months before enactment of the MDA noted a district court’s skepticism of FDA authority over a “pregnancy detection kit” and then emphasized the need for “more comprehensive authority,” suggesting that the Committee agreed that this type of kit (or combination of components) should fall within FDA’s authority. H.R. Rep. 94-853 at 9 (February 29, 1976). A Senate report signaled

Congress's intent that FDA regulate a test system (described as a "diagnostic service" in the report) under which an "operator" used various physical components--a "Blood Specimen Carrier," a "wand," "metal plates," and a machine known as the "Radioscope"--to determine the "identity, kind, location, and significance of any disease present." S. Rep. 94-33 at 4-5 (March 11, 1975). The Committee described the system in detail, including how the individual components were used, and explained that practitioners "received, for a fee, a diagnosis blank filled in with the diseases which the patient was supposed to have." *Id.* It noted with concern that the "service was incapable of distinguishing the blood of animals or birds from that of man, or that of the living from the dead." *Id.* at 5. The Committee's emphasis on faulty results makes clear that it was focused on the harms from the test system, not from any one individual component. (Although one commenter argued that the relevant "device" in this passage of the Senate Report was the Radioscope, that interpretation fails to account for the Committee's overall focus on the results, which were attributable to the combination of components.) The discussions in these reports reflect the degree of focus on IVDs at the time and show that, contrary to some commenters' suggestions, the MDA was enacted precisely with test systems in mind. The Committees' support for FDA authority over IVD systems is particularly notable given that FDA had, by regulation, announced that a "system" was a type of IVD only a few years before passage of the MDA. *See* 38 FR 7096. If Congress has disagreed with FDA's position, it presumably would have said so.

In sum, FDA does not agree that the legislative history casts doubt on its authority over LDTs; instead, it supports it. *See Clinical Reference Lab. v. Sullivan*, 791 F. Supp. 1499, 1508-09 (D. Kan. 1992) ("congressional reports [associated with the MDA]...indicate approval of the Supreme Court's method in *Bacto-Unidisk* of broadly defining terms within the [FD&C Act]").

(Comment 54) Some comments stated that various provisions of the FD&C Act do not apply in the context of LDTs, which they contended supports their interpretation that LDTs do not fall within the device definition. These comments cited: (1) provisions referencing interstate

commerce or movement in interstate commerce, commercial distribution, and “held for sale,” (2) requirements to repair, replace, or refund the purchase price of a device under 21 U.S.C. 360h(b); (3) provisions related to packaging; (4) packing, storage, and installation requirements at 21 U.S.C. 351(h), 360b, and 360j(f)(1); (5) import and export provisions at 21 U.S.C. 381; and (6) labeling requirements, such as those at 21 U.S.C. 352(a), (f). These comments concluded that FDA authority over LDTs is incompatible with the statute as a whole. Several comments also suggested that FDA regulations undermine the Agency’s position, including the reference to “in-process devices, finished devices and returned devices” at § 820.3(r) and the UDI requirements at part 801.

(Response 54) As an initial matter, FDA disagrees with the premise of these comments that if some particular provisions in the FD&C Act do not apply to a system which meets the statutory definition of “device,” that means FDA lacks authority over that system. That premise is incompatible with the FD&C Act itself, which contains detailed provisions laying out the scope of the Agency’s authority, the Agency’s obligations, private party obligations, and private party exemptions. Congress included, for example, express statutory exclusions from certain requirements for certain healthcare personnel (such as “practitioners licensed by law to prescribe or administer drugs or devices and who manufacture...drugs or devices solely for use in the course of their professional practice” under 21 U.S.C. 360(g)(2)). It would be incongruous to conclude that it also intended, without saying so, to exclude a whole type of healthcare product or institution (namely, a laboratory). Instead, courts “assume that Congress meant what it said, and said what it meant.” *See Aqualliance v. U.S. Bureau of Reclamation*, 856 F.3d 101, 105 (D.C. Cir. 2017). The comments’ interpretive approach also is inconsistent with how the Supreme Court has counseled interpretation of the FD&C Act. *See United States v. Bacto-Unidisk*, 394 U.S. 784, 798 (1969) (“[R]emedial legislation such as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act’s overriding purpose to protect the public health.”). And it runs counter to Congress’s understanding of the MDA as

expressed in the legislative history. *See* H.R. Rep. 94-853 at 13 (“Because the Committee recognizes...that, in general, authority under the [FD&C Act] to regulate food, drugs, cosmetics, and devices is too often vague thus lending itself to interpretive regulation having the force of law, the Committee has attempted to design device authority such that the law and the intent of the Congress is clear.”).

Moreover, in the case of LDTs, the alleged “inapplicability” of many of the provisions identified by comments arises from a laboratory’s own choice not to engage in certain activities that would be governed by such provisions, not from some fundamental incompatibility between the FD&C Act and LDTs. For example, even if a given laboratory chooses not to package or ship an IVD, that is not a reason to conclude that it, or the devices it makes, are excluded from the scope of the statute altogether. It simply means the laboratory is not engaged in conduct--such as packaging--that triggers a particular statutory requirement--such as the requirement that packaged devices bear certain information in their label under 21 U.S.C. 352(b).

Under commenters’ logic, any manufacturer could narrow the scope of her or his operations, such that only some provisions of the FD&C Act applied, and then assert that none of its activities are “what Congress had in mind when it drafted the statute” (i.e., that none of its activities are within FDA’s jurisdiction). FDA disagrees with this logic. That would run counter to the statute’s text and would cause negative public-health outcomes. If an entity is engaged in activities subject to the FD&C Act, even if those activities are limited in scope, the entity is subject to the FD&C Act--though obviously the nature of those activities will determine which provisions of the statute apply. A manufacturer’s choice to engage in only a limited number of activities to which the FD&C Act is applicable should not mean that the FD&C Act does not apply at all.

FDA also has the following responses regarding specific provisions identified by commenters as inapplicable:

- For responses to comments regarding FD&C Act provisions that reference interstate commerce, commercial distribution, and “held for sale,” see sections VI.D.3 and VI.D.4 of this preamble.
- To the extent that commenters argued that the repair, replacement, and refund provisions in 21 U.S.C. 360h(b) do not apply to LDTs because they cannot be repaired, replaced, or refunded, FDA disagrees. A faulty IVD system could be repaired, for example, by repairing a faulty component, such as an instrument. The system could also be replaced with another IVD system, such as one from a conventional IVD manufacturer. Or the purchase price of the system could be refunded to the same extent and in the same manner as for most other devices that are used in medical practice.
- With respect to packaging, although it is true that laboratories making LDTs generally do not package those LDTs, the FD&C Act does not assume that regulated articles are packaged. On the contrary, the FD&C Act expressly contemplates that some drugs and devices will *not* be packaged, as it imposes certain label requirements only “[i]f [the device is] in a package form.” 21 U.S.C. 352(b)) (emphasis added).
- The provisions in 21 U.S.C. 351(h) and 360j(f)(1) do not contemplate that all devices will be packed, stored, and/or installed. Rather, these statutory provisions empower FDA to establish requirements governing these activities, to the extent they occur, and also require entities to comply with FDA requirements when applicable. *See* 21 U.S.C. 360j(f)(1) (authorizing the Secretary to “prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, pre-production design validation..., packing, storage, and installation of a device conform to current good manufacturing practice”); 21 U.S.C. 351(h) (device adulterated if “the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or installation are not in conformity with applicable requirements”). It is not the case that all these activities must occur in order for an article to be a device. For example, a cotton swab or a tongue

depressor intended for a use specified in the device definition is not “installed” but is indisputably a device. Neither the FD&C Act nor FDA regulations assume that all these activities will occur with respect to every device. *See, e.g.,* 21 U.S.C. 360e(c)(1)(C) (requiring premarket approval applications to contain “a full description of the methods used in, and the facilities or controls used for, the manufacture, processing, and, *when relevant,* packing and installation of, such device”) (emphasis added); § 820.1(a)(1) (“If a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged.”). Therefore, FDA disagrees that the potential inapplicability of these statutory provisions to some laboratories signals a broader mismatch between the FD&C Act and LDTs. Finally, although a comment referenced 21 U.S.C. 360b in connection with packing, storage, and installation, that provision relates to new animal drugs and not to devices.

- Import and export are not necessary for an article to be a device. FDA regards arguments concerning the import and export provisions at 21 U.S.C. 381 to be similar to arguments about physical shipment of an article in interstate commerce. Please see section VI.D.3 of this preamble for a detailed response to those arguments.
- Labeling requirements, such as those at 21 U.S.C. 352(a) and (f), do apply to LDTs. Although laboratories generally choose not to package LDTs or place them in a container, LDTs are accompanied by “written, printed, or graphic matter” that falls within the definition of labeling at 21 U.S.C. 321(m). Therefore, the labeling requirements at 21 U.S.C. 352(a) and (f) apply to LDTs.
- The comments citing FDA regulations appear to argue that despite FDA’s publicly stated view that LDTs are devices, certain regulations governing device packages or returned devices may not apply to LDTs, which calls into question FDA’s view of its authority. FDA disagrees with that reasoning. FDA has stated its interpretation that LDTs are

devices on many occasions in clear terms and that interpretation is not undermined if some regulations do not apply to LDTs. See 62 FR 62243 at 62249 (November 21, 1997), 65 FR 18230 at 18231 (April 7, 2000), Refs. 27, 32 and 33, 35, 39, 57, 97, 111 to 121). In any event, the regulations the comments point to are not necessarily inapplicable to LDTs. First, the terms “in-process devices” and “finished devices” in the definition of “product” at § 820.3(r) apply to LDTs. An LDT can be “in-process,” for example, when system components are in process, such as when a laboratory manufacturer is sourcing and qualifying critical reagents such as primers and probes or antibodies for their test system. In addition, FDA recognizes that the UDI requirements at part 801 generally apply to “labels” and “device packages,” and that laboratories generally do not package their IVDs, such as test systems. However, this is not necessarily the case for all laboratories’ IVDs and does not mean that laboratories are incapable of compliance with UDI requirements. For the reasons previously stated, FDA does not agree that these UDI requirements have any broader meaning with respect to FDA’s authority over LDTs.

3. Interstate Commerce and “Held for Sale”

(Comment 55) Several comments asserted that FDA lacks authority to regulate LDTs under the FD&C Act because many of FDA’s authorities to regulate devices, such as the premarket notification provision in section 510(k) of the FD&C Act (21 U.S.C. 360(k)), require introduction or delivery for introduction into interstate commerce and, according to the comments, LDTs do not meet this element. One comment argued that in addition to section 510(k), the FD&C Act’s premarket approval and De Novo classification provisions are limited to devices that are or will be introduced or delivered for introduction into interstate commerce, citing sections 513(c)(2)(C)(ii), 513(f)(1), 515(b)(1), and 515(i)(1) of the FD&C Act.

(Response 55) We disagree that introduction or delivery for introduction into interstate commerce is required for FDA jurisdiction of devices, including LDTs, under the FD&C Act. The FD&C Act’s definition of a “device” subject to FDA’s jurisdiction does not include an

interstate commerce element. Whether a particular provision of the FD&C Act requires a connection to interstate commerce goes to the reach of *that specific provision*, not of the device definition or of the Act as a whole. If an FD&C Act provision does not contain an interstate commerce element, “interstate commerce” imposes no limit on FDA’s powers beyond the constitutional minimum.

Section 510(k) of the FD&C Act illustrates this point. That provision states that a person who is required to register and “proposes to begin the introduction or delivery for introduction into interstate commerce” of a device “shall” submit a premarket notification. The inclusion of an interstate commerce element in section 510(k) of the FD&C Act means that the requirements of *that section* do not apply where that element is not satisfied. It does not mean that FDA lacks jurisdiction to enforce *other* device provisions of the FD&C Act that do not include such an element.⁵⁵

Contrary to the assertion in comments that “many” of the FD&C Act’s device requirements require introduction or delivery for introduction into interstate commerce, relatively few of the device provisions in the FD&C Act and FDA regulations include a specific interstate commerce element, and most of the device-related prohibited acts do not. See, *e.g.*, 21 U.S.C. 331(e) (prohibiting the failure to establish or maintain any record, or make any report, required under the device adverse-event reporting requirements without reference to interstate commerce); 21 U.S.C. 331(p) (prohibiting the failure to register a device establishment without reference to interstate commerce); 21 U.S.C. 331(q)(1) (prohibiting the failure to comply with device investigational use requirements without reference to interstate commerce); 21 U.S.C. 331(f)(3) (prohibiting the doing of any act which causes a device to be a counterfeit device, or the sale or dispensing, or holding for sale or dispensing, of a counterfeit device without reference

⁵⁵ Additionally, as discussed in the NPRM, section 510(k) of the FD&C Act does not *preclude* regulated entities from submitting premarket notifications even if the device is not introduced into interstate commerce (88 FR 68006 at 68020). Therefore, laboratories may utilize the less burdensome 510(k) process to market their LDT even assuming the device is not introduced or delivered for introduction into interstate commerce. Regardless, the inclusion of an interstate commerce element in section 510(k) in no way affects FDA’s overall authority to regulate IVDs manufactured by laboratories.

to interstate commerce). For further discussion, see the NPRM (88 FR 68006 at 68019-20). Additionally, the FD&C Act gives FDA authority to take action, without satisfying any particular interstate commerce element, when there is a violation of device requirements. For example, FDA has the authority to seize any “adulterated or misbranded device” without reference to an interstate commerce element (21 U.S.C. 334(a)(2)). Thus, FDA does not somehow lose jurisdiction if a particular device has not been introduced or delivered for introduction into interstate commerce.

Further, Congress clearly intended that FDA have jurisdiction over devices that violate the FD&C Act even if they are not introduced or delivered for introduction into interstate commerce. For example, as discussed in the NPRM, Congress intentionally revised the aforementioned seizure provision of the FD&C Act, section 304, to ensure that FDA could take action against devices without satisfying any particular interstate commerce element. For further discussion, see the NPRM (88 FR 68006 at 68020). Additionally, one of the key prohibited acts on which FDA relies, section 301(k) of the FD&C Act (21 U.S.C. 331(k)), contains an interstate commerce element, but it does not require a *complete* violative device to have itself been introduced or delivered for introduction into interstate commerce. That provision prohibits “the doing of any...act with respect to, a...device...if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.” Courts have held that even if a product is wholly manufactured and sold intrastate, the interstate commerce element in this provision is satisfied if a component used in manufacturing the product has traveled in interstate commerce. (See, e.g., *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1320–21 (D.C. Cir. 2014) (upholding FDA enforcement action under section 301(k) of the FD&C Act because a drug component had traveled in interstate commerce); *Baker v. United States*, 932 F.2d 813, 814-15 (9th Cir. 1991); *United States v. Dianovin Pharm., Inc.*, 475 F.2d 100, 102-103 (1st Cir. 1973)). At least some components of test systems, such as reagents and instruments, are usually shipped in interstate

commerce even if the system itself is designed, manufactured, and used within the laboratory. And section 709 of the FD&C Act (21 U.S.C. 379a) establishes a presumption that any required connection with interstate commerce exists for enforcement actions, meaning that the burden is on regulated parties to demonstrate, for example, that no component of a system traveled across State lines. (“In any action to enforce the requirements of this Act respecting a device...the connection with interstate commerce...shall be presumed to exist.”). Thus, under the FD&C Act, FDA has authority over devices even assuming they are not introduced or delivered in completed form for introduction into interstate commerce.

FDA also disagrees with the comment’s apparent presumption that, if a device is not subject to 510(k) requirements (because that provision’s interstate commerce element is not satisfied), then it must not be subject to any of the FD&C Act’s other requirements for marketing a device. As explained in the rest of this response, the relevant statutory text contains no such limitation.

Section 513(f)(1) of the FD&C Act applies to devices intended for human use that were “*not* introduced or delivered for introduction into interstate commerce for commercial distribution before [May 28, 1976].” (emphasis added). Under sections 513(f)(1) and 515(a), such devices fall into class III by operation of law, and must have an approved PMA, unless either: (1) they are exempt as investigational devices under section 520(g) of the FD&C Act (21 U.S.C. 360j(g)) or (2) they satisfy one of the criteria established in section 513(f)(1)(A)-(C) (21 U.S.C. 360c(f)(1)(A)-(C)).⁵⁶

References in sections 513(c)(2)(C)(ii), 515(b)(1), and 515(i)(1) of the FD&C Act to devices that *were* “introduced or delivered for introduction into interstate commerce for commercial distribution before [May 28, 1976]” do not impose a general interstate commerce limitation on the FD&C Act’s PMA requirements or the De Novo provisions. Rather, these

⁵⁶ Those criteria are substantial equivalence under section 513(i), reclassification under section 513(f)(3), and De Novo authorization under section 513(f)(2) of the FD&C Act.

sections use that language to identify the preamendments devices that are subject to specific processes under the FD&C Act.

The FD&C Act's De Novo and reclassification provisions (sections 513(f)(2) and (f)(3) of the FD&C Act, respectively) are also not limited to devices that are or will be introduced or delivered for introduction into interstate commerce. The De Novo provisions provide an alternative process for classifying new devices into class I or II where there is no legally marketed device upon which to base a substantial equivalence determination (section 513(f)(2) of the FD&C Act). Indeed, as mentioned above, De Novo is available as a non-PMA marketing pathway for certain devices that were “*not* introduced or delivered for introduction into interstate commerce for commercial distribution before [May 28, 1976].” (emphasis added). Manufacturers may also utilize the reclassification process in section 513(f)(3) of the FD&C Act, which likewise applies to devices “*not* introduced or delivered for introduction into interstate commerce for commercial distribution before [May 28, 1976]” (emphasis added) (see sections 513(f)(1) and (3)).

In sum, a device that is not subject to the premarket notification requirements under section 510(k) of the FD&C Act because it does not satisfy that provision's interstate commerce element is not thereby exempted from other requirements under the FD&C Act that do not include such an element.

(Comment 56) A comment asserted that FDA's interpretation of interstate commerce deviates from the plain language definition of the term and that FDA's concept of interstate commerce in section IV.B.3.a. of the NPRM (88 FR 68006 at 68019 and 68020) is so expansive as to negate the entirety of the meaning of the word interstate. Further, the comment asserted that if Congress did not intend to restrict FDA's authority to interstate commerce, it would not have used the term in legislation.

(Response 56) FDA did not provide a specific interpretation of the term “interstate commerce” in the NPRM but rather, we explained that interstate commerce is not a prerequisite

to FDA device jurisdiction (beyond the constitutional minimum). To the extent the comment is asserting that interstate commerce is a prerequisite to FDA device jurisdiction, FDA disagrees. As explained in the NPRM and in response to comment 55, in the FD&C Act there are a limited number of provisions applicable to devices that include a specific interstate commerce element (88 FR 68006 at 68019-20). Where a provision applicable to devices includes an interstate commerce element, the particular interstate commerce element must be met in order for FDA to exercise authority under that provision. However, there are many provisions applicable to devices that do not include an interstate commerce element. Where a provision applicable to devices does not include an interstate commerce element, the provision applies without satisfying any particular interstate commerce element. “[Where] Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.” *See, e.g., Russello v. United States*, 464 U.S. 16, 23 (1983) (quoting *United States v. Wong Kim Bo*, 472 F.2d 720, 722 (CA5 1972)). Additionally, as discussed in the NPRM and in response to comment 55, Congress intentionally revised section 304 of the FD&C Act (seizure provisions) to ensure that FDA could take action against devices without satisfying any particular interstate commerce element (88 FR 68006 at 68020; H.R. Rep. No. 94–853 (1976), at 15). Thus, the statutory text of the FD&C Act, caselaw construing that text (such as *United States v. Walsh*, 331 U.S. 432, 434-36 (1947), discussed in the NPRM (88 FR 68006 at 68020)), and the legislative history of the MDA clearly support that interstate commerce is not a prerequisite to FDA jurisdiction over devices under the FD&C Act (beyond the constitutional minimum).

(Comment 57) One comment asserted that the NPRM was dismissive of concerns that Congress, by granting FDA the statutory authorities relied on here, may have exceeded its authority under the Interstate Commerce Clause of the U.S. Constitution, adding that some current justices of the U.S. Supreme Court might not agree that Congress may constitutionally authorize FDA to regulate purely intrastate operations.

(Response 57) The legal position FDA described in the NPRM and reflected in the final rule is fully consistent with current Interstate Commerce Clause jurisprudence, including numerous cases decided over decades by the U.S. Supreme Court. *See, e.g., Gonzales v. Raich*, 545 U.S. 1, 17-18 (2005).

As an initial matter, many laboratories that at first glance might appear to be operating exclusively within a single state are in fact operating interstate. Their online advertising may attract patients, the human samples they test may have been collected, the components they purchase to assemble their LDTs may have been shipped, and the test reports they generate may go to ordering physicians, from out-of-state. So not all laboratory manufacturers have operations that are purely intrastate.

But, even if a laboratory's operations are purely intrastate, Congress can still regulate the laboratory's activities under the Interstate Commerce Clause. The Supreme Court's "case law firmly establishes Congress' power to regulate purely local activities that are part of an economic 'class of activities' that have a substantial effect on interstate commerce." *Gonzales v. Raich*, 545 U.S. at 17. Congress "may regulate these intrastate activities based on their aggregate effect on interstate commerce." *Taylor v. United States*, 579 U.S. 301, 303 (2016). When a laboratory offers a test for purchase and use by healthcare providers and patients for diagnosis or treatment, it is engaged in economic activity. And that economic activity, in the aggregate, has a substantial effect on interstate commerce. As explained in the FRIA, FDA's primary estimated market revenue for IVDs offered as LDTs for 2023 is, in 2022 dollars, approximately \$20 billion. IVDs offered as LDTs divert patients and providers from using IVDs not offered as LDTs, whose market FDA estimates at 65 percent of all IVDs (Ref. 10). And the test results obtained from IVDs offered as LDTs will lead patients and providers to choose to undergo or forgo a variety of health treatment decisions, with clear effects in both directions on the markets for the relevant treatments.

(Comment 58) A comment argued that LDTs are not “held for sale” under section 301(k) of the FD&C Act because there is no transfer of title or possession of an LDT to the ordering physician, and that this view comports with case law, which extends FDA’s jurisdiction to regulate drugs and devices after release by the original manufacturer, but only insofar as such regulated products are being delivered or transferred to another ultimate consumer. The comment also argued that *United States v. Regenerative Scis., LLC*, 741 F.3d 1314 (D.C. Cir. 2014), is inapplicable to LDTs because that case involved a drug-cell mixture administered to a patient for treatment, and LDTs are not transferred to anyone but performed by the manufacturer. The comment further argued that “held for sale” does not include use of a device to facilitate the work of a healthcare professional where that device is not transferred to the patient, citing *Shahinian v. Kimberly-Clark Corp.*, No. 14-CV-8390, 2017 WL 11595343 (C.D. Cal. March 7, 2017). Additionally, the comment argued that in cases cited by FDA in its response to a citizen petition from ACLA and in a memorandum by the then-General Counsel to HHS, the regulated drug or device product was delivered or transferred from one party (typically a doctor) to an ultimate consumer (typically a patient), and that this does not occur with LDTs.

(Response 58) FDA disagrees with the comment. Section 301 of the FD&C Act identifies prohibited acts that are intended to provide protection against adulterated and misbranded devices all the way to the consumer or patient. For example, section 301(a) addresses acts early in the distribution chain, by prohibiting “[t]he introduction or delivery for introduction into interstate commerce” of an adulterated or misbranded device (21 U.S.C. 331(a)). Separately, section 301(k) of the FD&C Act addresses circumstances later in the distribution process, in which the defendant does an act that results in the adulteration or misbranding of a device that is held for sale. Specifically, this section prohibits “the doing of any...act with respect to, a...device...if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded” (21 U.S.C. 331(k)). Courts have adopted a broad interpretation of the phrase “held

for sale” in section 301(k) of the FD&C Act. This interpretation is based on the 1948 Supreme Court decision, *United States v. Sullivan*, 332 U.S. 689, in which the Court explained: sections 301(a)-(c) of the FD&C Act “alone would not supply protection all the way to the consumer. The words of paragraph (k) ‘while such article is held for sale after shipment in interstate commerce’ apparently were designed to fill this gap and to extend the Act’s coverage to every article that had gone through interstate commerce until it finally reached the ultimate consumer.” *Id.* at 696-97.

LDTs are “held for sale” under section 301(k) of the FD&C Act. Among other things, laboratories generally sell their LDTs. Similar to other prescription products, a physician orders a test (which may or may not be an LDT) and the patient (or another party such as the patient’s insurer) pays for it. With LDTs, patients and their healthcare providers are the ultimate consumers. LDTs are used on patients, specifically their specimens (as is the nature of in vitro diagnostic products), and the LDT output--the test results--are provided to healthcare professionals and/or patients for use in diagnosing or treating patients.

Consistent with section 301(k) of the FD&C Act’s purpose, courts have held that devices used in the diagnosis or treatment of patients may properly be considered “held for sale” within the meaning of the FD&C Act, even where the device itself is not delivered or transferred to a patient. *See, e.g., United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (2d Cir. 1975) (the Diapulse machine, which was held by practitioners and “used in the treatment of patients, may properly be considered ‘held for sale’ within the meaning of the [FD&C Act], 21 U.S.C. § 331(k).” (citations omitted)); *United States v. Articles of Device (Acuflex; Pro-Med)*, 426 F. Supp. 366, 368 n.3 (W.D. Pa. 1977) (“Therefore, by their use in diagnosis [the electric acupuncture devices] were held for sale after interstate shipment.”); *United States v. Device Labeled “Cameron Spitler Amblyo-Sytonizer,” etc.*, 261 F. Supp. 243, 246 (D. Neb. 1966) (“The court is also of the opinion that the devices were misbranded while being held for sale. Although the claimant never sold the devices in the commercial sense, the device was used in the

claimant's treatment of patients.''). This interpretation of section 301(k) of the FD&C Act by the courts is consistent with the FD&C Act's intent to supply protection "all the way to the consumer." The view asserted by the comment is not only inconsistent with the case law, but also would leave a serious gap in protecting patients under the FD&C Act. For example, under the comment's view, devices such as x-ray systems, MRI systems, excimer lasers, and proton therapy beams could never fall within section 301(k) of the FD&C Act because these devices are not delivered or transferred to a patient, even though they are used on patients. Whether a device is physically transferred/delivered to a patient or used on a patient without physical transfer/delivery, the public health interest in safe and effective devices is the same.

Although some of the cases discussing section 301(k) of the FD&C Act involved a product that was delivered or transferred to a patient, that does not mean that these cases stand for the proposition that delivery or transfer to a patient must occur in order for section 301(k) to apply. For example, in *United States v. Regenerative Scis., LLC*, 741 F.3d 1314 (D.C. Cir. 2014), cited in one of the comments, the D.C. Circuit did not state that an article is held for sale only if there is physical delivery or transfer to a patient. Indeed, it did not address the "held for sale" requirement at all. On appeal the issue concerning section 301(k) of the FD&C Act was whether the defendant's entire Mixture product had to be shipped in interstate commerce in order to fall within section 301(k), which applies "after shipment in interstate commerce." *Id.* at 1320. The court held "that, by virtue of its use of doxycycline, [a component shipped in interstate commerce,] the Mixture is within the scope of drugs--and, by extension, biological products, see 42 U.S.C. § 262(j)--regulated by [21 U.S.C.] § 331(k)." *Id.* at 1321. Contrary to the comment's assertion, the D.C. Circuit's holding applies to LDTs because, among other things, LDTs are generally manufactured with components that are shipped in interstate commerce. Additionally, the district court's opinion in the same case *did* address the "held for sale" requirement, and endorsed FDA's interpretation. The district court stated: "Defendants create the cell product, the 'drug' in this case, and use it to treat their patients. Such conduct satisfies the 'held for sale'

requirement of the statute.” *United States v. Regenerative Scis., LLC*, 878 F. Supp. 2d 248, 258. Both courts determined that the defendants who manufactured the Mixture fell within the scope of section 301(k) of the FD&C Act, because the Mixture was made with doxycycline that had been shipped in interstate commerce and the defendants used the Mixture to treat patients. Similarly, laboratories that manufacture LDTs with any component that has been shipped in interstate commerce and use their LDTs in the diagnosis or treatment of patients fall within the scope of section 301(k). 21 U.S.C. 331(k).

Additionally, the comment misconstrues *Shahinian v. Kimberly-Clark Corp.*, No. 14-CV-8390, 2017 WL 11595343 (C.D. Cal. March 7, 2017). Although not explicitly stated, it appears that the court considered the surgical gowns not to be “held for sale” by the surgery center because the surgery center purchased the surgical gowns for its own personal consumption.

In contrast, laboratories are not manufacturing LDTs solely for their own personal consumption. Rather, laboratories manufacture LDTs for healthcare providers and patients. Consistent with the case law discussed above, LDTs are generally held for sale under section 301(k) because LDTs are generally sold and used on patients, specifically their specimens (as is the nature of in vitro diagnostic products), and the LDT output--the test results--are provided to healthcare professionals and/or patients for use in diagnosing or treating patients.

(Comment 59) A comment argued that even if LDTs were “held for sale,” section 301(k) of the FD&C Act only applies while LDTs are held for sale “after shipment” in interstate commerce, and LDTs are never shipped in interstate commerce, but rather performed only within the laboratory in which they are developed.

(Response 59) FDA disagrees with the comment. The comment’s assertion--that section 301(k) of the FD&C Act only applies while LDTs are held for sale after the LDT is shipped in interstate commerce--is contrary to the case law. For example, as discussed in response to comment 58, the appellants in *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, raised this issue, arguing that section 301(k) did not apply because the entire Mixture product was not

shipped in interstate commerce. Id. at 1320. The court disagreed, holding “that, by virtue of its use of doxycycline”—a component shipped in interstate commerce--“the Mixture is within the scope of drugs--and, by extension, biological products, see 42 U.S.C. § 262(j)--regulated by [21 U.S.C.] § 331(k).” Id. at 1321. The court noted that other circuits had come to the same conclusion, citing *Baker v. United States*, 932 F.2d 813, 814 (9th Cir. 1991) (holding that section 301(k) of the FD&C Act’s “ ‘shipment in interstate commerce’ requirement is satisfied even when only an ingredient is transported interstate.”); and *United States v. Dianovin Pharmaceuticals, Inc.*, 475 F.2d 100, 103 (1st Cir. 1973) (holding that the company’s “use of components shipped in interstate commerce to make vitamin K for injection brought their activities within [21 U.S.C.] § 331(k).”). Thus, even if the LDT itself is not shipped in interstate commerce, LDTs generally are manufactured with components (e.g., reagents and instruments) that are shipped in interstate commerce, and as discussed in response to comment 58, generally LDTs are held for sale under section 301(k) of the FD&C Act.

4. Commercial Distribution

(Comment 60) Some comments asserted that FDA lacks authority to regulate LDTs under the FD&C Act because certain device provisions under the FD&C Act, such as the premarket notification provision in section 510(k) of the FD&C Act, require “commercial distribution” and that LDTs do not meet this element. For example, several comments argued that LDTs are not in commercial distribution because there is no transfer of title with an LDT, and the test is not distributed to the clinician or the patient. A comment further argued that “commerce” refers to “the exchange or buying and selling of commodities especially on a large scale and involving transportation from place to place” and that “distribution” requires a “delivery” or “conveyance” of a good from a main source. Additionally, the comment alleged that the preamble to part 807 took pains to emphasize that commercial distribution is satisfied only where the product at issue is transferred to an unaffiliated third party, claiming that this is the reason why § 807.3(b)(1) specifically exempts the “[i]nternal or interplant transfer of a device between establishments

within the same parent, subsidiary, and/or affiliate company,” and that this is also the reason why the preamble to the analyte specific reagent (ASR) rule expressly distinguished between “ASR’s that move in commerce” and “tests developed in-house by clinical laboratories or ASR’s created in-house and used exclusively by that laboratory for testing services.” (62 FR 62243 at 62249, November 21, 1997). Additionally, a comment argued that in Compliance Policy Guide (CPG) § 300.600 (Commercial Distribution with Regard to Premarket Notification (Section 510(k))) (1978, reissued 1987) (Ref. 133), FDA interpreted commercial distribution to require actual or anticipated delivery of the device to purchasers or consignees and that in *United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 993-95 (W.D. Mich. 1985), a court upheld this interpretation.

(Response 60) FDA disagrees with these comments. As discussed in the NPRM, LDTs generally are in commercial distribution (88 FR 68006 at 68020-21). Under our longstanding interpretation, “commercial distribution” does not require the physical transfer of an object, nor does it require transfer of title. Instead, the legislative history of the MDA, FDA’s near contemporaneous regulation, and at least one judicial decision reflect that the phrase “commercial distribution” means “on the market.” See H.R. Rep. No. 94–853 at 36 (Feb. 29, 1976) (“ ‘Commercial distribution’ is the functional equivalent of the popular phrase ‘on the market.’ ”); 41 FR 37458 at 37459, September 3, 1976 (in the preamble to proposed part 807, FDA equated “commercial distribution” with the phrase “on the market”); and *United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 994-95 (upholding as reasonable FDA’s interpretation of “commercial distribution” to mean, “in its popular sense, ‘on the market’”). For further discussion, see the NPRM (88 FR 68006 at 68020). Because LDTs generally are “on the market,” they are for commercial distribution. For example, like manufacturers of other IVDs do, laboratories often promote their LDTs on their websites and hold or offer them for sale.

Additionally, the dictionary definitions of “commercial,” “distribute” and “distribution” are not limited to physical transfer of an object. The dictionary defines “commercial” to mean “of or relating to commerce,” providing examples of “commercial regulations” and “commercial services,” thus making it clear that the term “commercial” is not limited to “the exchange or buying and selling of commodities especially on a large scale and involving transportation from place to place” as suggested in the comment (Ref. 134). Regardless, the manufacture of LDTs generally involves components, such as reagents and instruments, that are purchased by and transported to the laboratory, and thus, involves commerce even under the more limited definition described in the comment. Moreover, the dictionary definitions of “distribute” and “distribution” include “supply for sale” and “the marketing or merchandising of commodities” (Refs. 135 and 136).⁵⁷ Thus, the plain meanings of “commercial,” “distribute,” and “distribution” are not limited to physical transfer of an object, and are consistent with FDA’s longstanding interpretation of “commercial distribution.”

FDA’s interpretation of “commercial distribution” is also consistent with the FD&C Act’s overriding purpose to “protect the public health by ensuring that...there is reasonable assurance of the safety and effectiveness of devices intended for human use.” Section 1003(b)(2)(C) of the FD&C Act (21 U.S.C. 393(b)(2)(C)). Moreover, FDA’s interpretation of “commercial distribution” is consistent with section 301(k) of the FD&C Act which is intended to supply protection all the way to the consumer. As discussed in our responses to comments in section VI.D.3, the case law on section 301(k) of the FD&C Act supports FDA’s jurisdiction over medical products that never leave a physician’s office, and that are used in the diagnosis or treatment of patients even where the product itself is not delivered or transferred to a patient. *See, e.g., United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (the Diapulse machine, which was held by practitioners and “used in the treatment of patients, may properly be considered ‘held for sale’ within the meaning of the [FD&C Act], 21 U.S.C. § 331(k).” (citations omitted));

⁵⁷ The definition of “commodity” includes “an economic good” and “something useful or valued” (Ref. 137).

United States v. Articles of Device (Acuflex; Pro-Med), 426 F. Supp. 366, 368 n.3 (“Therefore, by their use in diagnosis [the electric acupuncture devices] were held for sale after interstate shipment.”); *United States v. Device Labeled “Cameron Spittler Amblyo-Syntonzizer,” etc.*, 261 F. Supp. 243, 246 (“The court is also of the opinion that the devices were misbranded while being held for sale. Although the claimant never sold the devices in the commercial sense, the device was used in the claimant’s treatment of patients.”).

However, even assuming LDTs were not in commercial distribution, this would not preclude FDA jurisdiction over these devices. As an initial matter, even assuming that certain provisions in the FD&C Act do not apply to a particular device, that does not mean FDA lacks authority to regulate the device under the FD&C Act. As discussed in the NPRM, “commercial distribution” appears in certain device provisions of the FD&C Act, including section 510(k), but as with “interstate commerce,” the presence of this term in certain device provisions does not bear on the Agency’s overall jurisdiction (88 FR 68006 at 68019-21). For example, “commercial distribution” is not needed to trigger or enforce the PMA requirements. Specifically, section 515(a)(2) of the FD&C Act requires, without reference to commercial distribution, an approved PMA for any device that is class III under section 513(f) of the FD&C Act (which applies to all postamendments devices) unless it is exempt under section 520(g) of the FD&C Act, and section 501(f)(1)(B) of the FD&C Act deems adulterated, without reference to commercial distribution, any device that is classified into class III under section 513(f) of the FD&C Act and is required to have an approved PMA under section 515(a) of the FD&C Act, unless it is exempt under section 520(g) of the FD&C Act. Simply put, any requirement of commercial distribution is conspicuously absent from the statutory provisions that require an approved PMA for a postamendments class III device and that render the device adulterated in its absence. Further, FDA may initiate seizure of an adulterated device regardless of whether the device is in commercial distribution (21 U.S.C. 334(a)(2)(D) (stating that any adulterated device “shall be liable to be proceeded against at any time on libel of information and condemned in any district

court of the United States...within the jurisdiction of which they are found,” without reference to “commercial distribution”).

The fact that Congress chose to include commercial distribution as an element only in certain device provisions but omitted it in others further supports that Congress did not intend for commercial distribution to be a prerequisite for device jurisdiction under the FD&C Act.

“[Where] Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.” *See, e.g., Russello v. United States*, 464 U.S. 16, 23 (quoting *United States v. Wong Kim Bo*, 472 F.2d 720, 722). When Congress enacted the MDA, it could have made commercial distribution an overarching element for device jurisdiction, but instead Congress chose to include this element only in a limited number of device provisions.

Regarding the regulatory exclusion from commercial distribution in § 807.3(b)(1) for “[i]nternal or interplant transfer of a device between establishments within the same parent, subsidiary, and/or affiliate company,” the preambles to the regulation support that this was intended to exclude such transfers as such devices were not on the market at that point. In the preamble to proposed part 807, FDA explicitly equated “commercial distribution” with “on the market.” 41 FR 37458 at 37459 (“The Amendments contain special provisions relating to the classification of devices not in commercial distribution (i.e., not actually on the market) prior to May 28, 1976”). Further, commenters understood “commercial distribution” to mean “on the market.” *See* 42 FR 42520 (with regard to the internal/interplant transfer exclusion in the “commercial distribution” definition, commenters recommended that transfers between a foreign subsidiary and domestic parent also be excluded as “premarket notification in such a situation would not serve any useful purpose since the device will not go ‘on the market’ at that point.”). Thus, the exclusion in § 807.3(b)(1) is consistent with FDA’s longstanding interpretation of “commercial distribution.”

Regarding the CPG on commercial distribution and *United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, neither the CPG nor the court in this case limited “commercial distribution” to delivery. The CPG is clearly directed to devices that were not delivered. Specifically, the CPG identifies certain factors that FDA considers in determining whether a device is in commercial distribution before May 28, 1976, “even though no units of the device had been delivered to purchasers or consignees.” (Ref. 133). The factor in the CPG that the manufacturer had, before May 28, 1976, accepted or been prepared to accept at least one purchase order “*generally* with delivery to occur immediately or at a promised future date” indicates that delivery is typical but not necessary. *Id.* (emphasis added). Regardless, given that the CPG clearly covers devices that were not delivered, it reflects FDA’s view that delivery is not required for commercial distribution. Additionally, in *United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 993-95, the court upheld FDA’s interpretation of commercial distribution, stating “This explanation, together with the agency’s compliance policy guide...is a reasonable interpretation of the phrase ‘commercial distribution’.” The court was referring to the explanation in FDA’s letter to the firm that, among other things, “indicated that the agency views ‘commercial distribution’ to mean, in its popular sense, ‘on the market’, pursuant to H.R. 94-853, 94th Cong. 2d Sess. 36 (1976).” *Id.* at 994.

Regarding the preamble to the ASR rule, FDA’s limitation of the scope of the ASR rule to “the classification and regulation of ASR’s that move in commerce, not tests developed in-house by clinical laboratories,” was a statement that those products were outside the scope of the rule and not a statement that there was no commercial distribution or that they were outside of FDA’s jurisdiction or authority to regulate. 62 FR 62243 at 62249 (“The focus of this rule is the classification and regulation of ASR’s that move in commerce, not tests developed in-house by clinical laboratories....”). In fact, FDA made clear in the preamble to the ASR rule that “FDA believes that clinical laboratories that develop [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act.” *Id.*

(Comment 61) A comment argued that neither the FD&C Act nor FDA's own interpretation of the statute supports an interpretation that a device not subject to section 510(k) may be independently subject to the PMA requirements in section 515 or the De Novo provisions in section 513(f)(2) of the FD&C Act. The comment argued that this is because submission of a PMA under section 515 or a De Novo request under section 513(f)(2) satisfies the requirement to submit a 510(k) premarket notification, which generally applies to all devices unless subject to a specific exemption. As support, the comment points to § 807.81, which states that a premarket notification is not required for a device for which a PMA, or for which a reclassification petition under section 513(f)(2) of the FD&C Act, is pending before FDA. The comment also refers to the preamble to proposed part 807 in which the Agency stated that "[a] premarket notification under § 807.81 is not required for a device for which a premarket application under section 515 of the act, or for which a petition to reclassify from class III to class I or II under section 513(f)(2) of the act, is pending before FDA. For such devices, the other submissions will serve the purpose of a notification under section 510(k) of the act." 41 FR 37458 at 37460. Additionally, the comment refers to the preamble to the final rule setting out part 807 in which FDA explained "[i]f a premarket approval application has been submitted, a premarket notification submission would not be required since FDA would already be advised of the intent to market." 42 FR 42520 at 42523. Another comment also argued that it "defies logic that Congress would create a system to regulate LDTs where foundational provisions would not apply." The comment also alleged that the principal pathway to market for devices would be unavailable to LDTs, and claimed that the tens of thousands of LDTs that FDA estimated to be eligible for the 510(k) pathway in the PRIA would be subject to the lengthier, more expensive PMA and De Novo pathways.

(Response 61) The comment suggests that the fact that there are exemptions from the 510(k) requirements in the FD&C Act and in FDA regulations supports the conclusion that a device must be subject to the 510(k) requirements in order to be subject to the PMA

requirements. FDA disagrees. Exemptions from the 510(k) requirements in the FD&C Act and FDA regulations are provided for various reasons, e.g., because a 510(k) submission is not necessary to provide for reasonable assurance of safety and effectiveness as reflected in section 510(m) of the FD&C Act or because a 510(k) submission is not necessary where another submission informs the Agency of the intent to market the device as reflected in § 807.81(b)(1) and the accompanying preambles. The fact that these exemptions from 510(k) requirements exist do not signify that a device must be intended for “introduction or delivery for introduction into interstate commerce for commercial distribution” under section 510(k) of the FD&C Act in order for FDA to have jurisdiction over the device or for the PMA requirements to apply. This is supported by the device framework in the FD&C Act where all postamendments devices are class III by operation of law and subject to the PMA requirements, without satisfying any particular interstate commerce or commercial distribution element, unless one of the criteria under section 513(f)(1) of the FD&C Act is met or the device is exempt under section 520(g) of the FD&C Act (section 513(f)(1) of the FD&C Act). This is also supported by the numerous other provisions applicable to devices that do not require these elements, including the seizure provision in section 304(a)(2) which was amended through the MDA. The legislative history of the MDA reinforces that under section 304(a)(2) of the FD&C Act, FDA has the authority to seize adulterated and misbranded devices without satisfying any particular interstate commerce element (see H.R. Rep. 94–853 at 15 (Congress made clear that it was amending this seizure provision to “permit seizure of devices without reference to interstate commerce” because “whether or not a medical device actually crosses state lines has nothing to do with the principal intent of this proposal: to assure the safety and effectiveness of medical devices.”)).

Further, the 510(k) and PMA requirements are separate and distinct as reflected by the different charges under the FD&C Act. Specifically, the failure to provide a premarket notification as required under section 510(k) of the FD&C Act misbrands the device (section 502(o) of the FD&C Act), and the failure to obtain approval of a PMA as required under section

515 of the FD&C Act adulterates the device (section 501(f)(1) of the FD&C Act). Indeed, FDA routinely cites both charges in warning letters issued to manufacturers that appear to be marketing a device that FDA did not review (see <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>). Thus, the FD&C Act supports that a device may be subject to the PMA requirements regardless of whether the device is subject to the 510(k) requirements and the fact that there are exemptions from 510(k) requirements do not lead to a contrary conclusion.

We note that the De Novo provisions in section 513(f)(2) of the FD&C Act exist simply to provide another pathway to classify a postamendments device (which is class III by operation of law under section 513(f)(1) of the FD&C Act) into class I or II. A manufacturer is not required to follow the De Novo pathway but may instead submit a reclassification petition under section 513(f)(3) of the FD&C Act.

Regarding the comment claiming that it “defies logic that Congress would create a system to regulate LDTs where foundational provisions would not apply,” we assume the comment is referring to the 510(k) requirements as this comment was made in the context of referring to other premarket pathways. We addressed this above and in other responses in this preamble.

Regarding the comment alleging that the principal pathway to market for devices would be unavailable to LDTs, we assume the comment is referring to the 510(k) pathway. As we explained in the NPRM (88 FR 68006 at 68020), section 510(k) of the FD&C Act does not preclude regulated entities from submitting premarket notifications even assuming their devices are not introduced or delivered for introduction into interstate commerce for commercial distribution. Thus, such regulated entities may still obtain a substantial equivalence determination through the submission of a 510(k) as a substantial equivalence determination is one way for a device that is otherwise class III by operation of law to be classified into class I or II (section 513(f)(1) of the FD&C Act).

Regarding the comment claiming that the tens of thousands of LDTs that FDA estimated to be eligible for the 510(k) pathway in the PRIA would be subject to the lengthier, more expensive PMA and De Novo pathways, as discussed in the paragraph above, LDTs may be eligible for the 510(k) pathway. Further, given that a substantial equivalence determination through a 510(k) submission is less burdensome than a PMA or De Novo submission, such regulated entities have an incentive to follow this less burdensome path to market (see 88 FR 68006 at 68020). Thus, the 510(k) pathway should play the same role in device reclassification regardless (88 FR 68006 at 68020).

(Comment 62) One comment argued that the presence of “commercial distribution” in the 510(k) and certain other specific device provisions of the FD&C Act bears on FDA’s overall jurisdiction because statutes must be read as a whole, citing *Territory of Guam v. United States*, 141 S. Ct. 1608, 1613 (2021), and that a statute’s language has meaning only in context, citing *Graham Cnty. Soil & Water Conservation Dist. v. United States ex rel. Wilson*, 545 U.S. 409, 415 (2005). The comment further stated that consequently, the words of a statute must be read in their context and with a view to their place in the overall statutory scheme, citing *Sturgeon v. Frost*, 577 U.S. 424, 438 (2016).

(Response 62) As explained in more detail in response to comment 60, FDA disagrees that the inclusion of commercial distribution as an element in certain device provisions in the FD&C Act bears on FDA’s overall jurisdiction of devices or on the applicability of those provisions in the FD&C Act in which Congress did not include commercial distribution as an element. However, even assuming “commercial distribution” were necessary for a device to be within FDA’s jurisdiction under the FD&C Act, this would not affect FDA’s jurisdiction over LDTs because LDTs are generally in commercial distribution, and therefore, LDTs generally would meet such an element. *See* NPRM (88 FR 68006 at 68021) and response to comment 60.

(Comment 63) A comment asserted that there is not much support for “commercial distribution” meaning “on the market.” Specifically, the comment argued that the cited

legislative history is a statement in one committee report, and that an isolated statement in a committee report does not represent an authoritative interpretation of a congressional enactment, citing *NLRB v. Health Care & Retirement Corp. of Am.*, 511 U.S. 571, 582 (1994). The comment also argued that the case cited in the NPRM, *United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, deferred to an FDA letter citing the committee report in the course of improperly deciding a genuine issue of material fact on summary judgment.

Another comment argued that the aforementioned case arose from a traditional device manufacturer's introduction without premarket notification of a prosthetic ligament device, and that the parties' only dispute turned on whether the defendant's product was the same or different from a pre-1976 version of the product. The comment further alleged that the government itself "argue[d] that the FDA's definition of 'commercial distribution' has only minor relevance to this action...since the device in question did not exist prior to enactment of the [MDA]," and the district court fully agreed. Another comment argued that the case cited in the NPRM, *United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 994-95, fails to support that no transfer, movement, transportation, or exchange of title between unaffiliated parties is required to trigger statutory provisions requiring commercial distribution.

(Response 63) FDA disagrees with the comments. As discussed in response to comment 60, the plain meanings of "commercial," "distribute," and "distribution" support FDA's interpretation that "commercial distribution" in the relevant provisions of the FD&C Act means "on the market." This interpretation has been endorsed by at least one judicial decision, as explained in more detail below, and is reinforced by a House Report issued 3 months before the MDA that contained an unusually clear statement on the intended meaning of commercial distribution. H.R. Rep. No. 94-853 at 36 (" 'Commercial distribution' is the functional equivalent of the popular phrase 'on the market.' "). See also *Garcia v. United States*, 469 U.S. 70, 76 (1984) (the Court has "repeatedly stated that the authoritative source for finding the Legislature's intent lies in the Committee Reports on the bill, which '[represent] the considered

and collective understanding of those Congressmen involved in drafting and studying proposed legislation.”) (citation omitted).

FDA’s interpretation of “commercial distribution” is also consistent with the FD&C Act’s overriding purpose to “protect the public health by ensuring that...there is reasonable assurance of the safety and effectiveness of devices intended for human use.” Section 1003(b)(2)(C) of the FD&C Act. Moreover, as discussed in response to comment 60, FDA’s interpretation is consistent with section 301(k) of the FD&C Act which is intended to supply protection all the way to the consumer, and under which courts have upheld FDA’s jurisdiction over medical products that never leave a physician’s office, and that are used in the diagnosis or treatment of patients even where the product itself is not delivered or transferred to a patient. *See, e.g., United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (the Diapulse machine, which was held by practitioners and “used in the treatment of patients, may properly be considered ‘held for sale’ within the meaning of the [FD&C Act], 21 U.S.C. § 331(k).” (citations omitted)); *United States v. Articles of Device (Acuflex; Pro-Med)*, 426 F. Supp. 366, 368 n.3 (“Therefore, by their use in diagnosis [the electric acupuncture devices] were held for sale after interstate shipment.”); *United States v. Device Labeled “Cameron Spittler Amblyo-Syntonizer,” etc.*, 261 F. Supp. 243, 246 (“The court is also of the opinion that the devices were misbranded while being held for sale. Although the claimant never sold the devices in the commercial sense, the device was used in the claimant’s treatment of patients.”).

The case cited by the comment to support the assertion that a committee report does not represent an authoritative interpretation of a congressional enactment is inapposite. In that case, which involved the interpretation of a phrase in the definition of “supervisor” in the National Labor Relations Act, the Court found the legislative history to be unpersuasive where the interpretation asserted by the National Labor Relations Board (NLRB) was inconsistent with the plain meaning of the phrase and court precedent. *NLRB v. Health Care & Ret. Corp. of Am.*, 511 U.S. 571, 578-79 (1994). Additionally, the Court noted that the legislative history relied on by

the Board was not contemporaneous as it related to the 1974 amendments to the National Labor Relations Act that amended other sections of the statute but not the provision at issue which was enacted in 1947. *Id.* at 581-82. Thus, the Court stated: “the isolated statement in the 1974 Committee Report does not represent an authoritative interpretation of the phrase ‘in the interest of the employer,’ which was enacted by Congress in 1947.” *Id.* at 582. In contrast, FDA’s interpretation of commercial distribution is consistent with the plain meaning of the terms. Moreover, the legislative history that provides additional support for the Agency’s interpretation is contemporaneous to the enactment of the relevant statutory language.

Additionally, FDA maintains that *United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990 supports the Agency’s reasonable interpretation of “commercial distribution.” In this case, which involved summary judgment motions filed by both the government and claimant, one of the charges was that the device was misbranded under section 502(o) of the FD&C Act because the claimant did not submit a 510(k) for the device. *Id.* at 992-97. The court stated that “[w]hether the device was in commercial distribution before May 28, 1976, was a factual issue” because it pertained to whether an exemption from the 510(k) requirements would apply. *Id.* at 993-94. This factual issue was “hotly debated” by the parties and given that “commercial distribution” was a key element of the exemption, the court considered the Agency’s interpretation of the term and the relevant CPG in deciding the issue. *Id.* at 994-95. Ultimately, the court agreed with the government that the seized device was not in commercial distribution prior to May 28, 1976, because it was not the same as the device that was manufactured prior to May 28, 1976. *Id.* at 995 (“I find myself in agreement with the Government that the device which it has seized is not the same device manufactured by Meadox prior to enactment of the amendments.”). The court did not address the argument that the definition of “commercial distribution” has only minor relevance but regardless, the meaning of “commercial distribution” was still relevant given that “commercial distribution” was an element

of the exemption; therefore, it was appropriate for the court to consider the meaning of the term and to uphold FDA's interpretation.

Although *An Article of Device Consisting of 1,217 Cardboard Boxes* was not specifically about transfer, movement, transportation, or exchange of title between unaffiliated parties, FDA referenced this case to support its longstanding interpretation of "commercial distribution" to mean "on the market." It is clear in this case that the court upheld this interpretation.

(Comment 64) One comment argued that clinical laboratories cannot be considered manufacturers within the scope of the FD&C Act or key regulatory requirements because "distribution" of a device in interstate commerce is a threshold requirement for the applicability of many of the key regulatory requirements applicable to device manufacturers, including the requirements for medical device reporting, correction and removal reporting, and registration and listing, citing as an example, the definition of "manufacturer" in part 806 which includes "distribution" or "commercial distribution."

(Response 64) FDA disagrees with the comment. Although the definition of "manufacturer" in various regulations includes "distribution," "distribution" is not a required element of the definition. For example, § 806.2(h) defines "manufacturer" to mean "any person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological, or other procedures. The term *includes* any person who: (1) [r]epackages or otherwise changes the container, wrapper, or labeling of a device in furtherance of the distribution of the device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user or consumer; (2) [i]nitiates specifications for devices that are manufactured by a second party for subsequent distribution by the person initiating the specifications; or (3) [m]anufactures components or accessories which are devices that are ready to be used and are intended to be commercially distributed and are intended to be used as is, or are processed by a licensed practitioner or other qualified person to meet the needs of a particular patient" (emphasis added). Although the definition lists three specific types of persons, the term

“includes” indicates that the list is not intended to be exhaustive or limit the first part of the definition. The term “includes” means, among other things, “to take in or comprise as a part of a whole or group.” (Ref. 138). Thus, the specific list is intended to be part of the whole or group described in the prior sentence of the “manufacturer” definition, i.e., “any person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological, or other procedures.” In other words, any person who engages in any of these activities is a manufacturer under part 806 and subject to the requirements therein.

(Comment 65) A comment claimed that the use of “distributed” in section VI.B.3 (“distributed outside that laboratory”) of the NPRM, which describes certain settings where limited QS requirements may be implemented, is inconsistent and illogical, and asserted that the Agency uses expansive definitions only when it supports its own claims for increased regulatory authority.

(Response 65) FDA disagrees with the comment. Words can have different meanings depending on their context. For example, the dictionary provides multiple definitions of “distribute” and “distribution.” (Refs. 135 and 136). As explained in response to comment 60, “distribute” and “distribution” in the context of the term “commercial distribution” include “supply for sale” and “the marketing or merchandising of commodities,” consistent with FDA’s interpretation of “commercial distribution” to mean “on the market.” However, in other contexts, “distribute” and “distribution” can have different meanings. In section VI.B.3 of the NPRM (88 FR 68006 at 68025), FDA was using “distributed” consistent with the meaning “to give out or deliver....” (Ref. 139). FDA believes it was obvious the Agency was not using the term consistent with commercial distribution as FDA was not saying that the IVD could not be on the market. However, to avoid potential confusion about this subset of IVDs for which FDA intends to enforce only certain QS requirements, FDA has decided to use “transferred” instead of “distributed” in section V.C of this preamble.

5. Asserted Distinctions from Devices

A number of comments argued that laboratory activities, tests, or both have unique characteristics that distinguish them from devices and device manufacturers. Many comments argued that these characteristics mean that LDTs are “services” or “processes” not subject to FDA jurisdiction.

(Comment 66) A number of comments argued that laboratory tests should not be understood to be devices because there is a strong human professional component to the performance of these tests. One comment stated, for example, that “[t]he quality of [an LDT] procedure depends not only on the tangible components of a cancer genomics assay such as the reagents, and platforms and software but quite heavily on the qualifications, expertise, and experience of the operator both at the level of test performance and interpretation.” Several comments stated that “LDTs are comprised of not only medical products, but also analytic processes.” Many comments emphasized the expertise and training of laboratory professionals who perform tests, including that they may be “doctoral-level” and “board-certified,” and may have “specialty training to implement and run assays, interpret results, and ensure that clinicians understand them.” One comment distinguished between laboratory tests that, in the commenter’s view, are subject to FDA’s jurisdiction--tests in which the device “does all the work”--and those that are not, such as tests that involve a “complex interplay between highly trained personnel, at multiple steps throughout the process.” One comment suggested that LDT system components do not make up a system at all, stating that an LDT “is a protocol or process by which a laboratory uses various tools--some of which are individually regulated as devices--to derive a test result for a patient,” similar to “a surgery” that is “performed by a physician using various tools (scalpels, sutures, etc.).” The comment stated that LDTs “do not become devices because they use devices.”

(Response 66) FDA does not agree that the involvement of qualified personnel in the administration of laboratory tests eliminates FDA’s jurisdiction over IVDs, including LDTs.

The comments argue that test systems manufactured by laboratories are distinct from “devices” because professional users play a significant role in the achievement of the systems’ intended uses, but that fact is not unusual or unexpected for devices. Devices are often complex and difficult to use; many contain a range of features, parts, and accessories, and functions that necessitate extensive user instructions to enable healthcare professionals to administer the device safely and effectively. Some devices are so difficult to use that FDA requires manufacturers to provide end-user training for them. *See, e.g.,* 21 CFR 870.5700(b)(5); 876.4340(b)(9); 884.4050(b)(5); 892.5725(b)(2). For this reason, human factors testing can be a core element of device design and important area of review during device premarket review. *See, e.g.,* Ref. 140.

The devices that require sophisticated user involvement regularly consist of disparate components that must be organized, manipulated, and evaluated by healthcare professionals, just like the complex laboratory test systems described in the comments. Sometimes, healthcare professionals must use the disparate components to build the device in accordance with the manufacturer’s instructions for use. For example, FDA regulates a type of device known as a “thoracolumbosacral pedicle screw system” consisting of “multiple components,” such as screws, plates, rods, and connectors, that “allow the surgeon to build an implant system to fit the patient’s anatomical and physiological requirements.” 21 CFR 888.3070(a); *see also* 21 CFR 870.1350(a) (identifying as a device a “catheter balloon repair kit,” which includes the materials, such as glue and balloons, necessary to repair or replace a catheter balloon). These systems are still “devices” even though significant healthcare practitioner involvement is required to effectuate their intended use.

FDA regulation of such devices is important--even in the context of use by highly trained and expert users--because, among other things, FDA regulation helps assure the safe and effective design of the device, which is separate from the safe and effective use of a device. For example, if a stent has a serious design defect, a cardiologist implanting the stent cannot necessarily assure the safety and effectiveness of the procedure no matter how great her stent

implantation expertise. Similarly, if a laboratory test system lacks clinical validity (for example, it identifies a gene that has no clinical meaning), the test will not provide meaningful diagnostic information no matter how great the expertise or experience of the professionals performing the test.

Taken to its logical conclusion, commenters' argument would mean that few or no test systems intended for laboratory use (even those made by non-laboratories) would be devices, because most such systems consist of different components that must be organized and managed by expert personnel performing the test, in accordance with a manufacturer's instructions for use. No comments appeared to embrace the conclusion that even these sorts of systems are not devices, which would run counter to 50 years of established IVD regulation and enforcement. It would also mean that none of the device types described earlier in this comment response are actually "devices," contrary to decades of FDA regulation of those articles.

FDA also emphasizes that the fact that these systems are devices does not mean that the use of the devices--i.e., the performance of a test--in accordance with a manufacturer's instructions for use is a "device." Those two things are distinct. *See, e.g., United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1319 (distinguishing FDA regulation of a defendant's "Mixture" product from "the procedures used to administer the Mixture") (citation omitted).

FDA recognizes that extensive training and clinical knowledge can be required to perform laboratory tests, and does not seek in any way to diminish that expertise required for, or the important public-health contributions associated with, laboratorians performing testing. The fact that an entire statute was enacted to govern laboratory operations and laboratory personnel--CLIA--is evidence of the degree of complexity, technical skill, and experience required to perform many laboratory tests. But FDA believes that expertise in performing tests is not the same thing as expertise in designing and developing tests. For example, the set of skills required to develop a test that accurately detects COVID-19 is not the same as the set of skills required to correctly perform a test that accurately detects COVID-19. FDA's responsibility under the

FD&C Act is to help ensure that such tests are designed in a way that, when they are performed as the manufacturer intends, they can produce accurate and reliable results, and that responsibility exists whether or not the test is designed by a laboratory.

(Comment 67) Various comments argued that design and development by laboratories should be viewed as distinct from design and development by other IVD manufacturers because laboratories provide medical care or employ medical experts. For example, one comment argued that LDTs are neither “products” nor “manufactured” because they may be developed in medical care settings. Another comment stated that LDTs “do not fit into the category of medical devices” because “[t]he development and usage of LDTs are heavily reliant on the expertise of professional laboratory personnel.”

(Response 67) As an initial matter, FDA does not agree that IVDs offered as LDTs are necessarily designed and manufactured under circumstances that are distinct from other IVDs. As explained in the NPRM, FDA’s understanding is that many test systems offered as LDTs are designed at Fortune 500 and other large companies by a “development team,” similar to how systems from conventional IVD manufacturers are designed (88 FR 68006 at 68018) (see also Ref. 141). And in FDA’s experience, the individuals on these development teams (as well as individuals developing laboratory test systems at smaller laboratories) generally have the same training and expertise as those employed by a conventional manufacturer. Usually, this training is scientific or technical in nature rather than medical in nature. Therefore, FDA disagrees that the background and training of the individuals who develop LDTs is necessarily a distinguishing feature of these devices.

In any event, whether an article meets the definition of a “device” in the FD&C Act does not turn on who manufactures the article or where it is manufactured. Thus, even assuming that LDTs were always designed by healthcare professionals in medical care settings, those facts would not affect whether the LDT is a device under the plain language of the statutory definition. Other provisions in the FD&C Act confirm this fact because they exempt healthcare

professionals who manufacture devices solely for use in the course of their professional practice from certain requirements. *See, e.g.,* 21 U.S.C. 360(g)(2). These exemptions would be superfluous if licensed healthcare professionals operating in medical care settings could not “manufacture” “devices” in the first place. For additional discussion of these exemptions, see our response to comment 77.

(Comment 68) Various comments took the position that LDTs are services and not devices because they are tailored to patients. For example, comments stated that LDTs “are informed by the clinical needs of the individuals we treat,” address patients’ “unique needs,” and “can be adjusted to the specific needs of the patient.”

(Response 68) FDA does not agree that the fact that LDTs can be customized to patients is a reason to conclude that they are not devices. The FD&C Act does not require mass production, marketing, or use in order for an article to be a “device.” On the contrary, the FD&C Act contains special provisions for “custom devices,” thus recognizing that an article can be tailored to patients and still be a device. *See* 21 U.S.C. 360j(b) (exempting devices that have been designed and manufactured to suit the unique needs of a physician or patient from certain requirements). The legislative history for these provisions reinforces that they were intended to cover the circumstances in which devices are “ordered from manufacturers by members of the health professions to conform to their own special needs or to those of their patients” as well as when “health professionals themselves develop or alter devices to serve such needs.” H.R. Rep. 94-853 at 44. Thus, the provisions were designed for exactly the types of circumstances asserted to exist with certain LDTs. Furthermore, Congress limited the applicability of the exemptions to premarket approval and performance standards, meaning that custom devices are not entirely exempt from the FD&C Act. *Id.* (explaining that “[custom] devices are not exempt from otherwise applicable provisions...such as provisions with respect to investigational use, banning, restriction, adulteration or misbranding”). Reading the definition of “device” to exclude customized devices would render these provisions superfluous.

(Comment 69) One comment stated that LDTs are distinct from other IVDs because they “are not produced or marketed for use outside of the originating laboratory.” The comment stated that “[t]he lack of marketing and sales to other laboratories further differentiates LDTs from IVDs--a distinction that is crucial to understanding why LDTs do not fit into the category of medical devices.”

(Response 69) FDA recognizes that LDTs are designed, manufactured, and used within a single laboratory (without being sold for use outside that laboratory), but that fact does not mean these IVDs are not devices. The statute defines a “device,” in relevant part, as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is...intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.” 21 U.S.C. 321(h)(1). The definition does not exclude an article produced, sold, and used in a single location, and reading in such a limitation would undermine Congress’s purpose in the MDA to assure the safety and effectiveness of devices (see response to comment 53).

(Comment 70) One comment suggested that LDTs are not devices because they have purposes that are distinct from other IVDs. The comment stated that the “primary role of LDTs is to detect and/or quantify substances within the human body, aiding in disease detection, health condition assessment, monitoring of drug treatments and other testing processes” and that “over 83 percent of LDTs offered by NILA [National Independent Laboratory Association] and AAB [American Association of Bioanalysts]-member laboratories serve these purposes.”

(Response 70) FDA disagrees that LDTs have purposes that are distinct from other IVDs. The detection and/or quantification of substances within the human body to aid in “disease detection, health condition assessment, monitoring of drug treatments and other testing processes” is consistent with the intended uses of non-LDT IVDs, and articles intended for such uses generally fall within the device definition because they are intended for use in “the diagnosis of disease or other conditions” and/or “the cure, mitigation, treatment, or prevention of

disease.” Many FDA-authorized IVDs are indicated for use in conjunction with clinical assessments and not as the sole basis for clinical decisions, and IVDs offered as LDTs are not unique in that respect (see our response to comment 196 for examples of IVDs that fit this description). Therefore, even assuming the comment’s factual assertions are correct that these are the primary intended uses of LDTs, these uses are not distinct from the intended uses of other IVDs, and they do not distinguish LDTs from devices.

(Comment 71) Several comments argued that test development activities occurring in a laboratory are distinct from conventional IVD manufacturing. One comment asserted, for example, that the laboratory validation is distinct because “[v]alidation of each clinical test requires specific equipment and personnel that is unique to the lab and test being performed.” Another comment stated that “LDTs are developed specifically for use by the laboratory that created them, or laboratories under the same ownership/control,” which promotes “great consistency in performance” and more limited “potential for user error” compared with manufacturing by non-laboratories. A separate comment argued that “Quality Management applied to procedures have to be inherently different from those applied to products and need to consider the entire laboratory and not just individual procedures.” The same comment stated that LDT development is unique because “the primary output of a test development process is a standard operating procedure document, which is essentially a set of instructions to appropriately qualified individuals.”

(Response 71) With respect to comments’ factual assertions about laboratory test development, FDA does not necessarily agree⁵⁸, but even assuming those assertions are correct,

⁵⁸ In particular, FDA disagrees that the need for specific equipment and personnel for validation is unique to laboratory manufacturers. Validation of each clinical test, regardless of whether that test is manufactured by a laboratory or a non-laboratory manufacturer, may require equipment and personnel to perform the validation that is specific or unique to the type of test being performed. FDA also disagrees that developing a test for use in a single laboratory or laboratories under common ownership/control necessarily promotes “great consistency in performance” or more limited “potential for user error.” Elsewhere in this preamble, FDA has described examples of problematic tests that were designed or used in a single laboratory. In addition, standard operating procedures for LDTs must include instructions that specify the components for use (this may include specifically naming components that are procured or specifications for components that may be otherwise procured). This is no different from IVD kit instructions that list components that are necessary but not provided.

FDA disagrees that they would mean that laboratory test development is distinct from device manufacturing. As explained in the NPRM and elsewhere in this preamble, IVDs manufactured by laboratories are devices. Under FDA regulations, any “person who designs, manufactures, fabricates, assembles, or processes a finished device” is a manufacturer (§ 820.3(o)). Thus, laboratories that design, manufacture, fabricate, assemble, or process IVDs are manufacturers subject to FDA requirements.

Furthermore, laboratory IVD development is fully amenable to regulation under FDA’s CGMP requirements for devices (the QSR) even if that development occurs in a single laboratory. These requirements are flexible and recognize that manufacturing circumstances may vary. For example, the QSR requires design validation that “ensure[s] that devices conform to defined user needs and intended uses” and “include[s] testing of production units under actual or simulated use conditions” for most devices (§820.30(g)). This requirement does not prescribe a single, rigid approach to validation; instead, under the QSR, a manufacturer’s design validation obligations vary based on specific user needs and actual or simulated use conditions. In addition, the FD&C Act and FDA regulations provide for the issuance of “exemption[s]” and “variance[s]” from the QSR to account for unique circumstances in manufacturing. 21 U.S.C. 360j(f)(2)(A); § 820.1(e).

With respect to one comment’s statement that laboratories primarily produce “standard operating procedure document[s]”--and to the extent that the comment was suggesting that such documents are incongruous with FDA manufacturing requirements--FDA disagrees. First, we disagree that laboratories only produce standard operating procedure documents; laboratories produce test systems, which are the devices that generate results and implicate patient health and safety. For example, when a laboratory develops a test for measurement of hormone levels using mass spectrometry, they must source or manufacture calibrators and qualify a mass spectrometry instrument in order to perform that test. These calibrators and instrument, along with other components, comprise a test system. Second, the QSR specifically requires the development of

documents, including procedures, laying out the design of a test (§ 820.30(d) (requiring device design output to be documented, reviewed, and approved before release)). Thus, this type of work is directly contemplated under the QSR. We note that even if laboratories were only engaged in design activity, they would still be manufacturers under the QSR (§ 820.3(o) (“manufacturer” includes those “perform[ing] the function[] of...specification development”)).

(Comment 72) One comment stated that an individual laboratory should not be considered a manufacturer because the instruments, software, and many reagents used in IVD testing are not manufactured by the laboratory. In addition, the comment stated that “the term manufacture doesn’t necessarily apply to the process individual laboratories use to assemble reagents for use in running an IVD test” because they “are not sold to other entities, do not leave the laboratory, take no part in interstate commerce, and may be individually labeled for their many uses within the laboratory environment.”

(Response 72) If a laboratory manufactures a test system, it is a manufacturer, even if it does not manufacture the components of that system (such as instruments, software, and reagents). In addition, FDA notes that entities who “assemble[]” devices constitute manufacturers (§ 820.3(o)). Laboratories do this by sourcing individual components and combining them to assemble a single test system with a specific intended use. For example, a laboratory that develops a PCR-based, targeted genetic test for Factor V Leiden thrombophilia must source or manufacture primers and probes and validate a PCR instrument to assemble their test. These primers, probes and instrument together, along with other components, comprise a test system with a specific intended use that is independent of each individual component’s intended use. Under the FD&C Act and FDA regulations, manufacturing is not limited to devices that are sold to other entities, leave a laboratory, take part in interstate commerce, or are labeled for different uses. *See generally* 21 U.S.C. 360j(f); part 820. FDA addresses interstate-commerce arguments in more detail in section VI.D.3 of this preamble.

(Comment 73) One comment argued that FDA regulations recognize that laboratories are performing services, and not manufacturing devices, based on the language in § 807.65(i) that exempts clinical laboratories from registration and listing under certain circumstances.

(Response 73) This comment misunderstands the legal framework behind the exemption at § 807.65(i). Contrary to the comment's suggestion, § 807.65(i) is premised on the position that laboratories are device manufacturers. If they were not device manufacturers, there would have been no need to exempt them from the registration and listing requirements because those requirements only apply to those who own or operate establishments engaged in the "manufacture, preparation, propagation, compounding, or processing" of a device. *See* 21 U.S.C. 360(b)(2), (c), (i), and (j). In other words, FDA issued § 807.65(i) because it understood laboratories to be engaged in the "manufacture, preparation, propagation, compounding, or processing" of a device and concluded laboratories engaged in limited activities falling within that description should be exempt from the registration and listing requirements. Specifically, FDA decided that laboratories "whose primary responsibility to the ultimate consumer is to dispense or provide a service through the use of a previously manufactured device" should not have to register and list.

As noted in response to comment 45, this exemption means not only that FDA considers clinical laboratories to manufacture devices, as just explained, but also that only certain laboratories should be exempt from registration (i.e., those "whose primary responsibility to the ultimate consumer is to dispense or provide a service through the use of a previously manufactured device"). Laboratories who go beyond that do not fall within the exemption. Furthermore, even for those laboratories who fall within § 807.65(i), the exemption does not confer broad immunity on laboratories or suggest they are not manufacturing devices. In the preamble to the registration and listing rule, for example, FDA emphasized (in the context of a different exemption) that "exemption from registration does not relieve such persons from their obligation to comply with other provisions of the act or regulations" (42 FR 42521, August 23,

1977). Although FDA acknowledges that the exemption implicates listing and the 510(k) premarket notification requirements because those requirements are tied to registration, it does not implicate the premarket approval or investigational use requirements, for example.

Thus, § 807.65(i) confirms, rather than undermines, the position that laboratories are manufacturers and that they are subject to a variety of requirements under the FD&C Act.

6. Practice of Medicine

(Comment 74) Several comments asserted that FDA cannot regulate the “practice of medicine,” which (in the commenters’ view) includes all laboratory testing activities, but did not cite a specific source of authority for either the general assertion about FDA authority or the specific assertion about laboratory testing activities. To support the position that laboratory development falls within the “practice of medicine,” comments emphasized: (1) the training, board certifications, technological expertise, and medical judgment required for these activities, (2) that medical specialties associated with laboratory testing are sometimes defined to include the “develop[ment of] new testing methods,” (3) that the focus of laboratorians is on patient care, and (4) the involvement of a treating physician in ordering a test and receiving results. Some comments explained why, in the commenters’ opinion, this type of “practice of medicine” limitation on FDA’s authority is justified, including the fact that laboratories consider many factors in developing an LDT, such as clinical need, accuracy, and cost-effectiveness to the patient, and ensure “quality” in a more comprehensive sense than does FDA.

(Response 74) FDA does not agree that an atextual “practice of medicine” limitation precludes FDA regulation of all laboratory testing activities. The statute does not contain such a limitation, and FDA “assume[s] that Congress meant what it said, and said what it meant.” *See Aqualliance v. U.S. Bureau of Reclamation*, 856 F.3d 101 at 105. Instead, Congress enacted a narrower provision, entitled “Practice of Medicine,” that spells out in clear terms what conduct within the practice of medicine falls outside FDA’s statutory authority. That provision states, in relevant part: “Nothing in this [Act] shall be construed to limit or interfere with the authority of a

health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship,” with several explicit limitations (21 U.S.C. 396).⁵⁹ In general, the provision codifies FDA’s longstanding recognition of the fact that healthcare providers prescribe and use medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their particular patients.⁶⁰ It thus limits FDA’s oversight of certain practitioners’ “prescrib[ing] or administer[ing]” of a “legally marketed device,” but it does not reach all the activities that fall within commenters’ broad conception of the practice of medicine--including, notably, the manufacturing of a device. The fact that Congress assigned specific meaning to the “practice of medicine” and laid out, in statutory text, exactly how that concept should apply in the context of FDA regulation belies the notion that there is some additional “practice of medicine” limitation on the Agency.

Other statutory provisions confirm that understanding. In particular, if there were some generalized “practice of medicine” limitation that foreclosed FDA regulation of activities in a medical context, Congress would not have needed to issue exemptions specific to physician manufacturing. But the FD&C Act does contain exemptions for licensed practitioners who manufacture devices “solely for use in the course of their professional practice.” *See, e.g.*, 21 U.S.C. 360(g)(2). A generalized “practice of medicine” limitation would render these provisions superfluous. The exemptions are also limited in scope and do not, by their express terms, apply to all manufacturing by licensed practitioners. *Id.* (limiting exemption to “use in the course of [the practitioner’s] professional practice”); *see also* H.R. Rpt. 94-853 at 24 (stating, with respect to the adverse-event reporting exemption, that “[o]bviously, physicians and other licensed

⁵⁹ The rest of 21 U.S.C. 396 provides: “This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.” These limitations show that this provision does not operate as an across-the-board bar on FDA regulation of the prescribing or administration of legally marketed devices.

⁶⁰ *See* Ref. 17 at 17 (“January 2017 Memorandum”).

practitioners are not exempt from these requirements if their use of a device extends beyond ordinary professional practice into commercial activity”). A generalized “practice of medicine” prohibition would read out those limitations.

As explained in response to comment 66, FDA recognizes that laboratories employ expert, trained personnel. We also recognize that laboratories prioritize the care of patients, may specialize in the development of testing methods, and may work closely with treating physicians. But these facts do not mean that, as a legal matter, FDA lacks authority over the IVDs manufactured by laboratories. The FD&C Act by its very nature affects medical practice. Cf. *United States v. 9/1 Kg. Containers*, 854 F.2d 173, 176 (7th Cir. 1988) (“Congress gave the FDA comprehensive powers to license the manufacture of drugs and limit their sales. To regulate drugs is to be ‘involved’ in the ‘practice of the healing arts.’”). Thus, the fundamental question is the scope of authority Congress delegated, and the limitations it enacted, relevant to medical practice. As already explained, the FD&C Act contains no generalized limitation on FDA regulation of devices in a medical context. Cf. *United States v. Regenerative Scis.*, 741 F.3d 1314, 1320 (construing the FD&C Act not to apply to otherwise prohibited activities, because they were undertaken by doctors, would “create an enormous gap in the FDCA’s coverage”).

(Comment 75) One comment stated that Congress did not intend for FDA to regulate the “practice of medicine,” which (in the commenter’s view) included all laboratory testing activities, as shown by: (1) legislative history for the FD&C Act, including legislative history associated with the 1938 Act and the 1962 Kefauver-Harris Amendments, (2) section 214 of the Food and Drug Administration Modernization Act (FDAMA), and (3) section 1111 of the Food and Drug Administration Amendments Act (FDAAA).

(Response 75) As explained in response to comment 74, FDA does not agree that there is a generalized, atextual “practice of medicine” limitation on FDA’s authority in ways other than those enumerated in the statute. The statute contains specific provisions related to healthcare practitioners’ “prescrib[ing] or administer[ing]” a legally marketed device and “manufactur[ing]”

a device “solely for use in the course of their professional practice,” and those provisions represent Congress’s considered judgment about the scope of conduct that falls outside FDA authority. *See West Virginia Univ. Hospitals, Inc. v. Casey*, 499 U.S. 83, 98 (1991) (“The best evidence of [Congress’s] purpose is the statutory text adopted by both Houses of Congress and submitted to the President.”).

Comments cite statements in the legislative history related to the 1938 Act and the 1962 Kefauver-Harris Amendments, but (among other things) those sources predate the MDA and FDAMA, when Congress specifically considered the practice of medicine in the device context and translated those considerations into legislative text. *See* 21 U.S.C. 360(g)(2), 360i(c)(1), 374(a)(2)(B), 396.

FDA agrees that section 214 of FDAMA, codified at 21 U.S.C. 396, reflects Congress’s intent to protect certain practitioner prescribing and administration activities, but the provision does not extend to laboratory manufacturing of IVDs, including LDTs. The purpose of the provision is to “ensure[] that once the FDA permits a device to be marketed for one use, health care practitioners have the flexibility to draw on their expertise to prescribe or administer the device” for other uses for a specific patient. *Judge Rotenberg Educ. Ctr., Inc. v. United States*, 3 F.4th 390, 395 (D.C. Cir. 2021); *see also* Conf. Rep. 105-399 at 97 (November 9, 1997) (provision intended to cover “off-label use of a medical device by a physician using his or her best medical judgment in determining how and when to use the medical product for the care of a particular patient”). It applies only in the context of use of a “legally marketed device”—that is, a device that is already manufactured and lawfully on the market—and only applies to “prescrib[ing] or administer[ing]...within a legitimate health care practitioner-patient relationship.”

The comment also cites section 1111 of FDAAA, 42 U.S.C. 247d–5a (2007), but that provision was repealed in 2016 by the Cures Act (Pub. L. 114-255, 130 Stat 1033 at 1121 “Section 1111 of the Food and Drug Administration Amendments Act of 2007 (42 U.S.C. 247d–

5a), relating to identification of clinically susceptible concentrations of antimicrobials, is repealed.”). In any event, that provision directed FDA to identify and periodically update “clinically susceptible concentrations” of antimicrobial drugs and did not address FDA’s regulation of IVDs.

(Comment 76) Various comments cited the role of state authorities, such as State laws and medical boards, in support of their conclusion that FDA cannot regulate the “practice of medicine,” which (in the commenters’ view) included all laboratory testing activities. Several commenters asserted, for example, that the practice of medicine is regulated by state medical boards rather than FDA. Comments also argued that the proposed rule is inconsistent with existing state medical practice acts, such as a Utah law’s definition of the practice of medicine. One commenter indicated that state law definitions of the practice of medicine should inform the applicability of 21 U.S.C. 396. Finally, one comment suggested that state tort law provides adequate oversight, noting that certain pathologists “bear legal responsibility for the design and performance of LDTs” and “purchase medical malpractice insurance to cover these activities.”

(Response 76) The scope of FDA’s authority is defined by Federal law. *See, e.g., City of Arlington v. Fed. Comm’n Comm’n*, 569 U.S. 290, 297 (2013) (Agencies’ “power to act and how they are to act are authoritatively prescribed by Congress.”). Thus, the FD&C Act vests FDA with authority and dictates how that authority intersects with the “practice of medicine” (see our response to comment 52 for a discussion of FDA’s authority and our response to comment 74 for a description of this intersection). To the extent that comments were suggesting that State law defines those authorities and limitations, FDA disagrees.

Comments appear to take the view that State law controls based on an assumption that state and Federal authorities cannot share jurisdiction, but that is not the case. Congress regularly enacts laws governing entities or activities that are also regulated under State law, and when it does so, the two regimes can coexist. *See Wyeth v. Levine*, 555 U.S. 555, 579 (2009) (“FDA [has] long maintained that state law offers an additional, and important, layer of consumer

protection that complements FDA regulation.”). At least one comment indicated that there is a “conflict” between the State laws cited in the comments and this rulemaking, but the comment did not give any basis for the alleged conflict. State medical boards can perform their oversight function--and State law definitions of the “practice of medicine” can inform the application of State law--concurrent with FDA’s exercise of its own authority under Federal law. Several comments inferred conflict from State law definitions, but if a State law defines particular activities to fall within the practice of medicine, that does not mean that FDA oversight of those same activities is impermissible, just as CMS’s administration of CLIA with respect to laboratory activities that fall within the State’s “practice of medicine” is not impermissible. *See Pharm. Mfrs. Ass’n v. FDA*, 484 F. Supp. 1179, 1187-88 (D. Del.), *aff’d*, 634 F.2d 106 (3d Cir. 1980) (“The fact that the practice of medicine is an area traditionally regulated by the states does not invalidate those provisions of the [statute] which may at times impinge on some aspect of a doctor’s practice.”). Even assuming there were a conflict, it is Federal law, not State law, that would trump. Const. Art. VI, Cl. 2 (“[T]he Laws of the United States... shall be the supreme Law of the land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.”).

FDA also does not agree that it should read State law definitions of the “practice of medicine” into 21 U.S.C. 396. Section 396 does not prohibit regulation of the “practice of medicine” in general terms, nor does it explicitly or implicitly incorporate State law to define the scope of FDA authority. Instead, that provision carves out a specific and defined scope of physician conduct that falls outside FDA’s statutory authority. *See* Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine* (February 21, 2004) (Provisions such as 21 U.S.C. 396 “endorse deference to professional autonomy rather than the primacy of state regulation.”) (Ref. 142). Under the statute’s plain language, State law does not control the analysis of FDA authority--nor would it be sensible to apply State law in this way given differences in definitions of the “practice of medicine” across the states. *See United States*

v. Regenerative Scis., LLC, 741 F.3d 1314, 1319 (“[A]ppellants are wrong to suggest that the scope of the FDCA depends on state-by-state definitions of the ‘practice of medicine.’”).

Finally, the presence of State tort law is not a reason to conclude that FDA lacks authority over IVDs manufactured by laboratories. The FD&C Act was enacted against the backdrop of State regulation and common-law liability. *Wyeth v. Levine*, 555 U.S. 555 at 566. Congress delegated power to FDA based on a view that the then-existing controls, including state controls, were not adequate to protect the public from dangerous products. *Id.* As explained in response to comment 53, Congress then increased FDA’s powers over devices in the MDA based on concerns about unsafe and ineffective devices on the market, all while state tort liability continued. *See Medtronic, Inc. v. Lohr*, 518 U.S. 470, 475-76 (1996). These facts show that the FD&C Act is not constrained by, but rather provides an extra layer of public-health protection over, state tort law.

(Comment 77) Two comments argued that the statutory exemptions for licensed practitioners who manufacture products solely for use in the course of their professional practice apply for laboratories, or some subset of laboratories. One comment asserted that the exemptions apply to corporate and hospital laboratories that employ licensed practitioners, because construing the exemption to exclude corporate entities would impose liability on a solo practitioner’s personal service corporation and would “conflict[] with baseline common-law principles” related to vicarious immunity. The same comment suggested that these statutory exemptions also should be construed to constitute an exemption from other “more burdensome and costly provisions” under the FD&C Act and FDA regulations.

(Response 77) The statutory exemptions cited by comments exempt covered practitioners from several specific requirements: (1) establishment registration requirements (this exemption, by operation of law, also constitutes an exemption from listing and 510(k) requirements); (2) adverse-event reporting requirements; and (3) an expansive FDA inspection that “extend[s] to all things” within a relevant factory, warehouse, establishment, or consulting laboratory. 21 U.S.C.

360(g)(2), 360i(c)(1), 374(a)(2)(B). These exemptions apply when a “practitioner[]” (1) is “licensed by law to prescribe or administer” a device, such as an IVD, (2) “manufacture[s]” that device, and (3) does so “solely for use in the course of their [or his] professional practice.” The exemptions are only relevant when a particular individual meets all three criteria. The language is precise and limited in scope; the possessive terms “their” and “his,” for example, make clear that the exemption applies only to specific individuals, not institutions. Thus, to the extent that comments are arguing that the exemptions apply to: (1) all activities of a laboratory that employs such an individual or (2) any laboratory activities in which personnel collectively meet the criteria (e.g., one individual is licensed to administer the device and others manufacture the device), FDA disagrees. By their plain terms, the exemptions do not apply to an institution or an entity; they apply only to an individual practitioner who meets all criteria. And construing the exemptions to apply more broadly would create a significant loophole: every device manufacturer could escape the relevant requirements simply by hiring the right personnel. That is not a rational understanding of Congress’s intent: as one committee report made clear, the exemption was not intended to apply to “commercial activity.” H.R. Rpt. 94-853 at 24. This evidence of congressional purpose underscores the plain language of the statute.

FDA also disagrees that exemptions from certain requirements in the FD&C Act should be read as exemptions from all, or any other, requirements of the FD&C Act. Congress included the licensed-practitioner exemption for certain requirements and excluded it from others. This means that Congress knew how to apply the exemption when it wanted to, and did so only in particular circumstances. Interpreting the exemption to apply to other requirements, not specified by Congress, would directly conflict with Congress’s intent as expressed through the statutory text. Courts have come to the same conclusion. *See Cowan v. United States*, 5 F. Supp. 2d 1235, 1240 (N.D. Okla. 1998) (“[T]he ‘medical practice exemption’ referenced by Plaintiff is a very limited exemption from the registration requirements of the FDCA. Plaintiff’s assertion that this exception provides a broad-based exemption to all physicians from the requirements of the Food,

Drug, and Cosmetic Act is incorrect.”); *cf. United States v. Algon Chem., Inc.*, 879 F.2d 1154, 1160 (3d Cir. 1989) (“the medical practitioner exemptions by their terms afford no more than the right to be free from inspection and registration requirements when veterinarians and other practitioners compound medicine with legally acquired materials, not the right to acquire unapproved drug substances”).

One comment argued that it is not reasonable to say that a licensed practitioner acting within the scope of the exemption is exempt from “basic” requirements such as registration, listing, and adverse-event reporting but still subject to “more burdensome” requirements, like De Novo review and premarket approval. FDA disagrees. De Novo review generally applies when FDA lacks experience with a device type, and premarket approval applies to class III devices, the highest-risk devices regulated by FDA. It is entirely reasonable for Congress to conclude that an exemption should apply with respect to some FD&C Act requirements but not with respect to FDA’s premarket review of devices that are unknown or “present[] a potential unreasonable risk of illness or injury,” for example. *See* 21 U.S.C. 360c(a)(1)(C). FDA also notes that although the comment suggested that the FD&C Act exempts licensed practitioners who are manufacturing solely within the course of their professional practice from “inspection[s],” that is not the case. The licensed-practitioner inspection provision limits the scope of FDA’s inspection--so that the inspection does not “extend to all things therein”--but it does not eliminate FDA’s authority to inspect (21 U.S.C. 374(a)(1)-(2)). In any event, reading these exemptions into other provisions of the FD&C Act would amount to rewriting the FD&C Act, which FDA cannot do.

(Comment 78) Several comments argued that activities regulated under CLIA constitute the “practice of medicine,” implying that they are outside the scope of FDA’s authority.

(Response 78) CLIA does not constrain FDA’s authority over devices, including LDTs, and that fact is true regardless of whether the activities regulated under CLIA are described as “the practice of medicine.” For further discussion of CLIA, please see section VI.D.8 of this preamble.

7. Right of Healthcare Providers to Practice Medicine

(Comment 79) One comment asserted that there is a right--based on several provisions of the Constitution--of healthcare providers to practice their profession without unwarranted interference. Specifically, the comment asserted that: the First Amendment guarantees the freedom of expression and the right to petition, which implicitly supports healthcare providers' rights to advocate for their patients and express concerns about regulations they view as capricious; the Fourth Amendment guards against unreasonable searches and seizures, which can be related to the privacy of patient records and the autonomy of healthcare providers in their practice; and the 14th Amendment ensures that no state may deprive any person of life, liberty, or property without due process of law. The comment asserted that, because the right to practice medicine is constitutionally protected, any limitation on that right must withstand strict scrutiny. The comment asserted that the LDT rule fails strict scrutiny because there is "nothing narrow" in FDA's approach to LDTs.

(Response 79) We disagree with this comment. First, this rule does not purport to regulate healthcare providers' practice of their profession. As the phaseout of the general enforcement discretion approach is implemented, laboratories that manufacture IVDs offered as LDTs generally will be expected to comply with several pre- and post-market submission and reporting requirements applicable to devices for humans (including premarket notification/PMA requirements (as applicable), registration and listing, labeling requirements, reporting requirements regarding adverse events and corrections and removals, QS requirements, and certain IDE regulations), but this phaseout policy relates to statutory and regulatory requirements applicable to medical devices and the conduct of manufacturers and distributors, not healthcare providers. The medical profession is, of course, regulated, particularly under state law, but neither the amendment to § 809.3 nor the phaseout policy regulates healthcare providers acting in that capacity.

Second, we disagree with the assertion that there is a constitutional right to practice medicine subject to regulation only under strict scrutiny. The comment did not support its conclusory assertion of a constitutional right to practice medicine with any case law citations, and we are not aware of any. *See, e.g.,* Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. Kan. L. Rev. 149, 192 (2004) (“[F]ederal expressions of deference to professional medical autonomy are rooted in politics rather than constitutional law.”) (Ref. 142). The comment’s citation to various rights protected by the Constitution does not help bolster the argument. The right to petition, like other parts of the First Amendment, provides an “assurance of a particular freedom of expression.” *McDonald v. Smith*, 472 U.S. 479, 482 (1985). Nothing in this rule limits healthcare providers’ ability to advocate for their patients and express concerns about regulations they view as capricious--in fact, that is just what the commenter did in submitting a comment on the proposed rule. Similarly, although “private medical records warrant some privacy protection under the Fourth Amendment,” *Big Ridge, Inc. v. Fed. Mine Safety & Health Review Comm’n*, 715 F.3d 631, 648 (7th Cir. 2013), the comment failed to identify anything in the rule that constitutes a search or seizure of medical records or impinges on patients’ privacy.

Procedural due process guarantees “the opportunity to be heard at a meaningful time and in a meaningful manner” “before an individual is finally deprived of a property interest.” *Mathews v. Eldridge*, 424 U.S. 319, 333 (1976) (cleaned up). Substantive due process protects rights that are “deeply rooted in this Nation’s history and tradition” and “implicit in the concept of ordered liberty” “such that neither liberty nor justice would exist if they were sacrificed.” *Washington v. Glucksberg*, 521 U.S. 702, 721 (1997) (cleaned up). Nothing in this rule implicates either doctrine; the comment did not identify anything in the rule that would cause a deprivation of life, liberty, or property without notice and opportunity for hearing or any infringement on a fundamental right.

Third, even if strict scrutiny were applied, that test would be satisfied here because the government has a compelling interest in protecting the public health, and premarket review and related requirements are narrowly tailored to achieve that result, as further explained elsewhere (see response to comment 93). The comment did not support its conclusory assertion to the contrary.

8. CMS/CLIA

(Comment 80) Several comments argued that Congress delegated the regulation of IVDs offered as LDTs not to FDA but to CMS, and that the enactment of CLIA is evidence that Congress did not intend for such IVDs to be subject to the device authorities of the FD&C Act. Some argued that the FD&C Act's failure to specifically call out IVDs offered as LDTs, in contrast with CLIA's specific provisions regarding the regulation of laboratories, demonstrates that Congress intended IVDs offered as LDTs to be solely regulated by CMS under CLIA.

(Response 80) FDA does not agree that Congress intended for IVDs offered as LDTs to be regulated solely by CMS under CLIA. CMS's CLIA authorities complement, rather than replace, FDA's regulation of laboratory-manufactured IVDs as devices under the FD&C Act. CMS determines whether a laboratory meets CLIA requirements, which is a specific role distinct from FDA's statutory responsibilities. FDA's device authorities under the FD&C Act are intended to help ensure that devices, including IVDs offered as LDTs, have appropriate assurance of safety and effectiveness. CMS's authorities under CLIA, by contrast, focus on the proficiency with which laboratories perform the testing activities. Unlike FDA can do under the FD&C Act, CMS does not regulate critical aspects of laboratory test development; does not evaluate the performance of a test before it is offered to patients and healthcare providers; does not assess clinical validity (i.e., the accuracy with which a test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient); does not regulate certain manufacturing activities, such as design controls and acceptance activities; does not

provide human subject protections for patients who participate in clinical trials of tests; and does not require adverse event reporting.

The lack of language in the FD&C Act specifically mentioning IVDs offered as LDTs does not change this conclusion. Congress did not define the scope of FDA's device authority by enumerating every device type subject to that authority; instead, it wrote a broad device definition at 21 U.S.C. 321(h)(1), which captures a wide range of articles without listing each one. FDA's device authorities thus are not limited to those few device types specifically mentioned in the FD&C Act. To the contrary FDA can, and does, regulate hundreds of device types that are not specifically mentioned in the FD&C Act. The controlling question is whether a product meets the FD&C Act's definition of device, and under the plain language of the statute as well as FDA's long-standing position this inquiry is resolved in the affirmative for IVDs offered as LDTs.

As explained in the NPRM, CLIA does not expressly repeal FDA's authority, nor was FDA's authority repealed by implication, and the comments do not demonstrate otherwise (88 FR 68006 at 68019). "An implied repeal will only be found where provisions in two statutes are in irreconcilable conflict, or where the latter Act covers the whole subject of the earlier one and is clearly intended as a substitute." *Branch v. Smith*, 538 U.S. 254, 273 (2003) (cleaned up). Here, as CMS itself has explained, "the regulatory schemes of the two agencies are different in focus, scope and purpose" and "are intended to be complementary" (Ref. 26). As explained above, CLIA puts a focus on the proficiency with which laboratories perform clinical testing, and the FD&C Act puts a focus on the tests themselves. CMS and FDA have different areas of expertise, and CLIA does not address a wide range of activities regulated under the FD&C Act, such as clinical validation and design activities. Thus, "CLIA does not preempt the FDA's authority to regulate facilities like [Clinical Reference Laboratory]. When two statutes are 'capable of co-existence, it is the duty of the courts, absent a clearly expressed congressional intent to the contrary, to regard each as effective.'" *Clinical Reference Lab.*, 791 F. Supp. at 1509

(quoting *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1018, (1984)), aff'd in part and rev'd in part on other grounds sub nom. *United States v. Undetermined No. of Unlabeled Cases*, 21 F.3d 1026 (10th Cir. 1994).

(Comment 81) Some comments stated that CLIA's legislative history does not mention FDA jurisdiction over LDTs, or that it characterized CLIA as directing HHS "to regulate all laboratories under a single statute," arguing that this is evidence that Congress did not intend for LDTs to be subject to the device authorities of the FD&C Act.

(Response 81) FDA disagrees with the comments' characterization of CLIA's legislative history. As FDA has noted, CLIA serves a distinct role from FDA oversight and establishes requirements for laboratories and laboratory personnel pertaining to operations, inspections, and certification, with a focus on the proficiency with which laboratories conduct clinical testing, rather than on the test systems themselves, and its legislative history reflects this. The full context surrounding the enactment of CLIA reveals that Congress was not focused on the oversight of test systems themselves but rather on whether laboratory personnel were performing their jobs in a setting and in a manner that helped ensure accurate, reliable, and timely patient test results. CLIA's enactment was prompted in large part by Congress's concern with the low quality of cytology services associated with Pap testing for cervical cancer. For example, the Senate Report accompanying the bill noted: "In too many instances, such errors [in pap smear testing] are the result of overworked and under-supervised cytotechnologists charged with the crucial responsibility of examining and categorizing cervical slides." S. Rep. No. 100-561, at 27 (1988). This concern led Congress to conclude that "lack of quality assurance and quality control in the medical testing industry is pervasive." *Id.* at 20. Congress reaffirmed this intent in 1997 when it noted that "[t]he purpose of CLIA quality control, proficiency testing, and personnel requirements is to ensure consistent, reliable, and appropriate *use* of a test system⁶¹ by users of

⁶¹ It is our understanding that CMS's role is, in part, to determine and ensure that a laboratory is following the manufacturer's instructions for a test (including how the test kit is stored, what specimens are used, how the

the test.” H.R. Rep. No. 105-310, at 76 (1997) (emphasis added). CMS has interpreted its authority consistent with this congressional intent, stating in the preamble to the final rule implementing the 1988 CLIA: “CLIA specifically requires the regulation of the provision of laboratory services. On the other hand, CLIA and those implementing regulations are not intended to affect FDA’s existing jurisdiction under the [FD&C Act] to regulate as devices, products used by providers of laboratory services.” (57 FR 7002 at 7010). CLIA’s legislative history thus reflects a distinct and complementary role for CMS in the regulation of IVDs offered as LDTs.

(Comment 82) Some comments argued that CLIA’s quality control and assurance provisions are incompatible with or duplicative of, or were intended to apply to laboratories in place of, FDA’s QS requirements, and therefore IVDs offered as LDTs cannot be regulated as devices.

(Response 82) FDA disagrees. CLIA’s quality control and assurance provisions do not supplant FDA’s QS requirements, because FDA and CMS regulation, including these requirements, are complementary. Although the phaseout policy described in section V.C acknowledges that compliance with CLIA requirements provides certain quality assurances, FDA’s QS requirements are neither duplicative of, nor incompatible with, CLIA. As noted in response to comment 12, the portion of CLIA that addresses quality systems relates to laboratory operations, laboratory personnel, and requirements for laboratory procedures relevant to testing. FDA’s QS requirements are focused on the IVD offered as an LDT, including design control and validation, complaint handling, and other requirements intended to ensure that the IVD has appropriate assurance of safety and effectiveness for its intended use.

Moreover, nothing in CLIA suggests that Congress intended it to supersede FDA’s ability to apply its QSR to IVDs offered as LDTs. As described in more detail in response to comment

specimens are stored, how the test is interpreted, and other aspects of the manufacturer’s instructions). This is distinct from regulation by FDA, which focuses on the test itself and its manufacture.

80 and in the NPRM, CLIA does not expressly repeal FDA’s authority, nor was FDA’s authority repealed by implication (88 FR 68006 at 68019).

(Comment 83) FDA received comments asserting that IVDs offered as LDTs cannot be regulated under FDA’s device authorities, because the application of FDA labeling requirements and prohibitions to these test systems would prevent manufacturers from complying with CMS’s CLIA regulations requiring laboratories to offer consultation on interpreting test results and to provide pertinent updates on testing information that affect test results or their interpretation.

(Response 83) FDA disagrees that these policies are in conflict. CMS’s CLIA consultation regulations, 42 CFR 493.1445(e)(9) and 493.1457(d), provide that laboratory directors and clinical consultants must “[e]nsure that consultation is available to the laboratory’s clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions.” As noted in more detail in response to comment 93, a laboratory director or clinical consultant’s ability to comply with the cited regulatory requirements is unaffected by FDA’s oversight of LDTs. Premarket review for LDTs is intended to help assure that LDTs generate accurate and reliable test results. As noted in response to comment 93, FDA does not generally consider professional advice regarding a patient’s results as evidence of a new intended use, and nothing in this rule is intended to change this practice.⁶² FDA recognizes that laboratory directors and clinical consultants help with interpretation and consulting to the healthcare provider, and they can and do give recommendations that are not limited to the content of FDA-required labeling.⁶³

CMS’s CLIA test report requirements provide, in relevant part, that “[p]ertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results.” 42 CFR 493.1291(e). As further explained in CMS’s

⁶² In contrast, if a laboratory offers a test on its website for an unapproved use, FDA would likely consider that offer to be evidence of a new intended use.

⁶³ For products not subject to premarket approval, but instead subject to premarket notification (510(k)) requirements or exempt from premarket review, we use the term *FDA-required labeling* to include labeling that provides adequate directions for use and other information required to appear on the label or in labeling.

interpretive guidelines: “When the laboratory changes methods, establishes a new procedure or refers tests to another laboratory, the laboratory must make the updated information concerning parameters such as patient preparation, preservation of specimens, specimen collection, or new ‘normal’ ranges or units of measure available to its clients.” CMS Manual Pub. 100-07. (Ref. 143). This requirement would not conflict with FDA requirements associated with certain labeling changes as the comment asserts. As noted above, interpretations and recommendations are not limited to the content of FDA-required labeling.

(Comment 84) Some comments argued that IVDs offered as LDTs are not devices because the CLIA regulatory requirement for the establishment of performance specifications for tests that are not cleared or approved by FDA, 42 CFR 493.1253, indicates that such test systems are not intended to be regulated by FDA.

(Response 84) FDA disagrees that the regulation of LDTs as devices is inconsistent with the CLIA regulatory requirements for the establishment of performance specifications for tests that are not FDA-approved or -cleared. The CLIA regulation provides, “[e]ach laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval” must establish performance specifications for certain performance characteristics specified in the regulation. *See* 42 CFR 493.1253(b)(2). Although the regulation uses the term “not subject to FDA clearance or approval,” the purpose of the regulation is not to state what tests are and are not devices that are required to undergo FDA premarket review (which would not be within CMS’s expertise). It merely differentiates those tests that have not undergone FDA premarket review and thus must adhere to certain additional CLIA requirements. The regulation was issued in 2003--long after FDA had publicly stated that IVDs offered as LDTs fall within the device authorities of the FD&C Act--but its preamble does not discuss any intent to overrule FDA on this issue (see 68 FR 3640 at 3707). Instead, statements from CMS both preceding and following issuance of the CLIA regulation indicate that IVDs offered as LDTs are devices. *See* 57 FR 7002 at 7010 (“CLIA and those implementing

regulations are not intended to affect FDA’s existing jurisdiction under the [FD&C Act] to regulate as devices, products used by providers of laboratory services”); CMS, “Laboratory Developed Tests (LDTs) Frequently Asked Questions” (Ref. 26). (“Similar to other in vitro diagnostic tests, LDTs are considered ‘devices,’ as defined by the FFDCFA, and are therefore subject to regulatory oversight by FDA.”). Tests might not have undergone premarket review for a number of reasons, including a test not requiring premarket review due to its classification (or exemption from 510(k)) or a test being marketed without premarket authorization as a result of an FDA exercise of enforcement discretion.

(Comment 85) A comment argued that the CLIA regulation requiring laboratory directors to ensure quality laboratory services for “all aspects of test performance,” 42 CFR 493.1407(e)(1), includes both analytical and clinical performance, and therefore FDA cannot regulate IVDs offered as LDTs. Another comment stated that CLIA assessments administered through CLIA-approved accrediting agencies, such as CAP, COLA, and the Joint Commission, account for clinical validity, and that laboratories whose tests are approved by NYS CLEP must show clinical validity.

(Response 85) The comments are incorrect about the scope of CLIA regulation. CMS has stated explicitly that the “CLIA program does not address the clinical validity of any test” (Ref. 26). The NYS CLEP requirement to demonstrate clinical validity does not limit FDA’s authority over laboratory-manufactured IVDs, as State requirements cannot preempt Federal law. Further, as noted in response to comment 12, FDA and CMS enforce two different regulatory schemes, and there are many aspects of IVDs offered as LDTs that CMS does not regulate under CLIA, including, but not limited to, design control and validation and other requirements intended to ensure that the IVD has appropriate assurance of safety and effectiveness for its intended use.

(Comment 86) One comment argued that Congress’s establishment of a reimbursement system for laboratory tests that lack FDA clearance or approval, including section 216 of PAMA and CMS’s reliance on Palmetto GBA’s MolDX Program for local coverage determinations,

indicates that Congress did not intend for IVDs offered as LDTs to be regulated as devices under the FD&C Act.

(Response 86) FDA disagrees that the Medicare payment requirements established under section 216 of PAMA evidence a congressional intent to exclude IVDs offered as LDTs from FDA's device authorities, and, to the contrary, believes the requirements support an interpretation that such test systems are devices under the FD&C Act. PAMA established Medicare payment requirements for certain "advanced diagnostic laboratory tests" (ADLTs), which the statute defines as "a clinical diagnostic laboratory test covered under this part that is offered and furnished only by a single laboratory and not sold for use by a laboratory other than the original developing laboratory (or a successor owner)" and meets one of the following criteria: "(A) The test is an analysis of multiple biomarkers of DNA, RNA, or proteins combined with a unique algorithm to yield a single patient-specific result. (B) The test is cleared or approved by the Food and Drug Administration. (C) The test meets other similar criteria established by the Secretary" (*see* 42 U.S.C. 1395m-1(d)(5)). As ADLTs are developed, offered, and furnished by a single laboratory they may include IVDs offered as LDTs. If ADLTs that are IVDs offered as LDTs were not subject to the FD&C Act's device authorities, FDA would have no jurisdiction to clear or approve the tests. If FDA lacked jurisdiction to clear or approve the tests, Congress would not have enacted 42 U.S.C. 1395m-1(d)(5)(B), which includes FDA clearance or approval as a criterion for an ADLT and, thus, a basis for Medicare payment. Two allegedly conflicting statutes must be interpreted "to give effect to each if [one] can do so while preserving their sense and purpose." *Watt v. Alaska*, 451 U.S. 259, 267 (1981). Because excluding IVDs offered as LDTs from FDA's device authorities could render part of PAMA's payment scheme a dead letter, this principle applies here.

PAMA's inclusion of criteria other than FDA clearance or approval within the definition of an ADLT does not suggest that IVDs offered as LDTs are not devices under the FD&C Act. Nor does the fact that the MolDX program--which evaluates certain tests to determine whether

the test meets Medicare's reasonable and necessary criteria--may list tests that are not cleared or approved by FDA. As noted in the response to comment 84, regarding the lack of a conflict with 42 CFR 493.1253(b)(2), the marketing of a laboratory-manufactured IVD without FDA clearance or approval in certain situations is not incompatible with its regulation as a device by FDA.

(Comment 87) FDA received comments asserting that the application of registration requirements and fees under FDA's device authorities to IVDs offered as LDTs would be duplicative of such requirements under CLIA.

(Response 87) FDA disagrees that such requirements are duplicative, as they go to different regulators for different activities. As noted in response to comment 12, FDA's device authorities and CMS's CLIA authorities are complementary, not duplicative. CMS determines whether a laboratory and its personnel meet CLIA requirements, whereas FDA's statutory mandate is to review and evaluate the tests themselves, including IVDs offered as LDTs, to ensure that they have appropriate assurance of safety and effectiveness for their intended use.

(Comment 88) Some comments, citing *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000), argued that FDA jurisdiction over IVDs offered as LDTs is precluded by the supposed inconsistency of FDA regulation of LDTs as devices with the regulatory structures for reimbursement for ADLTs and the regulation of clinical laboratories set forth in CLIA.

(Response 88) FDA disagrees that *FDA v. Brown & Williamson* precludes FDA jurisdiction. In that case, the Supreme Court found that FDA's regulation of tobacco products as devices contravened the intent of Congress. The Court explained that Congress enacted six pieces of legislation, outside of the FD&C Act, regarding tobacco and human health, and did so against the "backdrop of the FDA's consistent and repeated statements that it lacked authority under the [FD&C Act] to regulate tobacco absent claims of therapeutic benefit by the manufacturer." *Id.* at 144. The Court also concluded that the FD&C Act's mandate to ensure products are safe and effective for their intended use would require the removal of tobacco

products from the market. *See id.* at 133–39. Because such a “ban would contradict Congress’ clear intent as expressed in its more recent, tobacco-specific legislation,” the “inescapable conclusion” was that tobacco products without therapeutic claims did not “fit” within the FD&C Act’s regulatory scheme for medical products. *Id.* at 143.

That is not the case here. FDA’s regulation of LDTs as devices will not result in a categorical ban on LDTs. Moreover, FDA has long understood and publicly maintained that LDTs are devices, and Congress has not manifested a contrary intent. Indeed, as noted in response to comment 86, Congress has since enacted legislation that assumes LDTs are subject to FDA approval or clearance. As explained in response to comments 82-87, FDA regulation of IVDs offered as LDTs does not conflict with either the regulation of clinical laboratories under CLIA or the provisions for reimbursement for ADLTs cited in the comments to this rulemaking. The lack of a conflict here makes this situation clearly different from that in *FDA v. Brown & Williamson*.

Moreover, to the extent that the supposed inconsistencies are based on CMS regulations, and not Federal statutes, *FDA v. Brown & Williamson* is inapposite. There, the Court turned to six pieces of Federal legislation outside of the FD&C Act in order to determine whether Congress intended tobacco products to be regulated as devices under the FD&C Act. *See id.* at 137–38. Here, comments citing to individual CMS regulations or the presence of unapproved, uncleared LDTs in the MolDX program are not compelling because, unlike statutes, those sources do not shed light on Congress’s intent in enacting the FD&C Act or its amendments.

(Comment 89) One commenter argued that because the performance of a test is a “service” or “examination” regulated under CLIA, even if a laboratory engages in IVD manufacturing or development activities, those activities should be understood to be governed by CLIA and not the FD&C Act because “the lab’s primary responsibility is still to perform the service.”

(Response 89) FDA does not agree that a laboratory's "primary responsibility" is relevant to FDA's jurisdiction or that a laboratory engaged in both manufacturing an IVD and performing a medical service has greater or "primary" responsibility for performing the medical service such that it is no longer obligated to comply with requirements related to manufacturing the IVD. The mere fact that laboratories conduct a CMS-regulated activity--performing a test--does not exempt them from other relevant statutory or regulatory authorities related to test manufacturing or design.

(Comment 90) One comment stated that, generally, Congress has appropriated sufficient funds for CMS to regulate clinical laboratories under CLIA, but it has not provided FDA with adequate funds to exercise regulatory authority over LDTs. This asserted disparity in funding, the comment argued, is evidence that Congress did not intend for FDA to have authority over LDTs.

(Response 90) FDA fails to see how the amount of funds appropriated to CMS that are available to implement CLIA and the amount of funds appropriated to FDA that are available to regulate devices reflects a congressional intent that these tests are not regulated as devices under the FD&C Act. FDA's device program is funded through a combination of budget authority and user fees. As enforcement discretion is phased out, FDA will receive user fees associated with establishment registrations and premarket submissions for IVDs offered as LDTs. As with all products FDA regulates, FDA intends to prioritize its available resources to oversee LDTs in a risk-based manner. Even if FDA were not provided adequate funds, the Supreme Court recently acknowledged that funding does not always match apparent statutory mandates. *See Biden v. Texas*, 142 S. Ct. 2528, 2535 (2022) ("The INA states that if 'an alien seeking admission is not clearly and beyond a doubt entitled to be admitted, the alien shall be detained for a proceeding.' Due to consistent and significant funding shortfalls, however, DHS has never had 'sufficient detention capacity to maintain in custody every single person described in section 1225.'" (cleaned up)). Moreover, FDA's jurisdiction over devices and other products is established in the

FD&C Act, and is not based on annual funding decisions and the relative amount of funding appropriated.

(Comment 91) One comment suggested that, rather than regulate IVDs offered as LDTs under the FD&C Act, FDA should consult with CMS and CDC on an alternative approach whereby CLIA regulations are updated with additional requirements for validation of IVDs offered as LDTs, including modifications to authorized IVDs and novel LDTs.

(Response 91) While FDA has consulted with CMS and CDC on the topic of IVDs offered as LDTs, including as part of this rulemaking, FDA disagrees that an alternative approach through updating CLIA regulations would suffice. As discussed in more detail in response to comment 10, CMS determines whether a laboratory and its personnel meet CLIA requirements, whereas FDA's statutory mandate is to review and evaluate the tests themselves, including IVDs offered as LDTs, to ensure that they have appropriate assurance of safety and effectiveness for their intended use. FDA has the resources and expertise to assess whether tests work for their intended clinical purpose; CMS does not.

9. Major Questions Doctrine

(Comment 92) Various comments argued that this rulemaking implicates the “major questions doctrine” under *West Virginia v. EPA*, 142 S. Ct. 2587 (2022). These comments asserted that: (1) the rulemaking presents the type of “extraordinary case” in which courts should hesitate before concluding that Congress granted the relevant authority to an agency and (2) the FD&C Act lacks the “clear congressional authorization” necessary to conclude that Congress granted this authority to FDA. To support their position, these comments generally focused on the facts that: (1) Congress previously has considered but declined to enact bills related to LDTs; (2) LDTs are a topic of congressional debate and therefore, in the commenters' view, a matter for Congress; (3) the claimed authority would affect a significant number of parties, “would have a major impact on the delivery of healthcare,” and would “alter the market”; and (4) the Agency's approach would require billions of dollars in spending each year. Some comments also pointed

to “the overall FDCA regulatory scheme” and “subsequent legislation specific to clinical laboratories” (i.e., CLIA). Several comments analogized to other cases such as *FDA v. Brown and Williamson Tobacco Corp.*, 529 U.S. 120, *Utility Air Regulatory Group v. EPA*, 573 U.S. 302 (2014), and *United States v. Franck’s Lab, Inc.*, 816 F. Supp. 2d 1209 (M.D. Fla. 2011).

(Response 92) FDA does not agree that it lacks authority for this rulemaking under the major questions doctrine. First, we do not agree that the major questions doctrine applies, because this is not the type of “extraordinary case” in which there is “reason to hesitate” before concluding that Congress intended to confer on FDA authority over laboratory-manufactured IVDs. Second, even if a court were to hold that the major questions doctrine applies, the FD&C Act supplies clear congressional authorization.

a. This rulemaking is not “extraordinary” for purposes of the major questions doctrine.

As explained by the Supreme Court, the major questions doctrine does not apply to every agency action, or even every agency action that involves significant costs and benefits and congressional interest. Rather, it applies only in those “extraordinary cases” in which “the history and the breadth of the authority that the agency has asserted, and the economic and political significance of that assertion, provide a reason to hesitate before concluding that Congress meant to confer such authority.” *West Virginia v. EPA*, 142 S. Ct. 2587 at 2608 (cleaned up). The Court has indicated that whether there is a “reason to hesitate” depends on specific “circumstances” and “common sense as to the manner in which Congress would have been likely to delegate.” *Id.* at 2609 (cleaned up). It has identified specific factors that can signal such an extraordinary case, such as whether:

- The Agency appears to be assuming “extravagant” or “broad and unusual” power--as measured in terms of cost, politics, or policy, for example--that Congress would have been “highly unlikely” to leave to Agency discretion. *Id.* at 2608-09, 2612 (internal quotations omitted).

- The asserted authority relies on an “ancillary,” “rarely...used” or otherwise “modest” statutory provision. Id. at 2609-10 (internal quotations omitted).
- The Agency, through statements or practice, previously appeared to view the relevant language more narrowly, such that the Agency’s new view seems “unheralded” or “newly discovered.” Id. at 2610, 2612 (internal quotations omitted).
- Implementation of the Agency’s decision will require “technical and policy expertise” not traditionally within the Agency’s wheelhouse. Id. at 2612 (internal quotations omitted).
- There is inconsistency between the asserted authority and the larger statutory scheme--for example, Congress has not “conferred a like authority” on the Agency elsewhere in the statute. Id. at 2613.

Under the major questions doctrine, the Court has described these factors as indicating that Congress may not have meant to confer the power claimed by the Agency.

Application of the factors here shows that courts should not hesitate before concluding that Congress granted FDA authority over laboratory-manufactured IVDs, consistent with the statute’s plain language. In this rulemaking, FDA is not asserting any “new” authority at all. Over 30 years ago, FDA unambiguously stated that it has authority over laboratory-made IVDs, (Ref. 111), and in the last decade, it has applied that authority to hundreds of laboratory-made IVDs, including LDTs, without legal challenge (see, e.g., Refs. 144 to 155). This Rule clarifies the statutory definition of a “device,” which is not an “ancillary” provision of the FD&C Act but rather the bedrock definition that governs the application of each device provision that FDA administers. As explained elsewhere in this preamble, the device definition encompasses diagnostic test systems, so there is nothing “unusual” or “extravagant” about concluding that it reaches test systems made by laboratories. In fact, that understanding is in lockstep with FDA’s statutory mandate and the other authorities it implements, is consistent with FDA’s longstanding approach, and makes the most of FDA’s expertise. What would be “unusual” is to read an

atextual laboratory exemption into the FD&C Act--thus elevating laboratories above any other type of manufacturer--of entirely amorphous breadth and scope. *See Bostock v. Clayton Cty.*, 140 S. Ct. 1731 at 1749 (inferring from “broad language” “Congress’s ‘presumed point [to] produce general coverage--not to leave room for courts to recognize ad hoc exceptions.’”) (quoting A. Scalia & B. Garner, *Reading Law: The Interpretation of Legal Texts* 101 (2012)). In the following paragraphs, FDA addresses each of the major questions factors to show why this is not an “extraordinary case” under that doctrine.

First, FDA is not asserting “extravagant” or “broad and unusual” power that Congress would have been “highly unlikely” to leave to Agency discretion. Congress enacted the MDA “to provide for the safety and effectiveness of medical devices intended for human use” without qualification. Medical Device Amendments of 1976, Pub. L. 94-295 (May 28, 1976) (purpose clause). In that legislation, it tasked FDA with overseeing the safety and effectiveness of all devices used in the United States--a substantial delegation that, according to FDA’s estimates, encompasses a \$374.5 billion industry today. Although FDA has estimated that this rule will have important public health impacts, the costs of the rule are not “extravagant” or “unusual,” particularly when viewed in the context of FDA’s regulatory responsibility for devices overall. And device regulation is just one small part of FDA’s overall remit: as of January 2024, FDA-regulated products accounted for about 21 cents of every dollar spent by U.S. consumers, and FDA had responsibility for “more than \$3.6 trillion in consumption of food, medical products, and tobacco.”⁶⁴ Given the breadth and scope of FDA’s overall mandate, and its mandate with respect to devices, there is no reason to doubt that the mandate includes the subset of IVDs that are manufactured by laboratories, and the economic impact of this rule alone does not provide a reason to hesitate under the major questions doctrine.⁶⁵

⁶⁴ Ref. 156.

⁶⁵ One commenter’s discussion of the major questions doctrine emphasized the Agency workload under the NPRM. Even assuming that were a relevant factor, the Agency’s workload for purposes of this rule is not so great that it raises a question about whether Congress intended to confer authority on FDA to regulate laboratory-manufactured IVDs. As stated, FDA’s regulation of devices is just one small part of FDA’s overall remit; and the regulation of the

FDA also does not agree that “political significance” is a compelling factor here. Many comments pointed to recent legislative proposals related to IVDs, such as the Verifying Accurate, Leading-Edge IVCT Development Act of 2023 (VALID Act), H.R. 2369, 118th Cong. (2023). Some comments portrayed the VALID Act as a proposal to grant FDA new authority over LDTs, or interpreted Congress’s decision not to enact the VALID Act as evidence that FDA lacks authority to issue the rule. These characterizations do not accurately describe the VALID Act. Congressional deliberations over the VALID Act involved the question whether a whole new statutory scheme, instead of the device framework in the FD&C Act, should apply to IVDs. Under the VALID Act, all IVDs, including LDTs, would have been carved out from the definition of a “device”--a step that would not have been necessary were they not covered by the existing definition--and would have been subject to a novel statutory framework including, for example, a new statutory approval standard, new types of premarket review (such as “technology certification”), and different QS requirements. Thus, contrary to commenters’ suggestions, the fact that Congress has not passed that bill does not represent a decision that FDA lacks authority over LDTs, but rather that Congress has not chosen to create a statutory scheme for IVDs that is different than for all other devices. Around the same time, Congress also considered, but did not pass, a bill that, as summarized by Congressional Research Service, would have “shift[ed] the regulation of laboratory-developed testing procedures from the Food and Drug Administration (FDA) to the Centers for Medicare & Medicaid Services (CMS).”⁶⁶ In not passing that bill, Congress opted to maintain the longstanding, well-understood status quo: that IVDs, including LDTs, are devices subject to device requirements under the FD&C Act. Congress’s consideration of these bills does not show that there is an open question whether Congress conferred this

subset of IVDs that are manufactured by laboratories is just one part of that broader regulatory authority over devices.

⁶⁶ See Congressional Research Service summary, Verified Innovative Testing in American Laboratories (VITAL) Act, S. 1666, 117th Cong. (introduced May 18, 2021), available at <https://www.congress.gov/bill/117th-congress/senate-bill/1666>.

authority on FDA under the FD&C Act; instead, it provides additional evidence affirming that LDTs fall within FDA's existing authority.

In any event, even if a court were to find the foregoing economic and political facts relevant under the major questions doctrine, FDA does not agree that they are sufficient to implicate that doctrine. The Court's major-questions cases examine a variety of factors to determine whether there is a "reason to hesitate" before concluding that Congress meant to confer the power claimed by the Agency. For example, in *West Virginia*, the Court cited a range of factors to conclude that the rulemaking there presented a "major question." The Court did not rest the decision solely on the "billions of dollars in compliance costs," *EPA v. West Virginia*, 142 S. Ct. 2587 at 2604, and the fact that Congress had "consistently rejected proposals" to create a cap-and-trade scheme for carbon, *id.* at 2614. Instead, it devoted much attention to other factors, such as those described in the remaining paragraphs of this comment response. This fact suggests that economic and political factors, even where applicable, are not enough. And the other hallmarks of an "extraordinary case" are absent here.

For example, FDA's asserted authority does not rely on an "ancillary," "rarely...used" or otherwise "modest" statutory provision, but on the meaning of "device," which defines the scope of articles subject to device requirements under the FD&C Act. Congress knew this definition would play a central role in the application of FDA's authorities, so it gave the provision special attention in 1976, adding new terms and carefully distinguishing "devices" from "drugs." *See*, e.g., H.R. Rep. 94-853 at 13-15. Given the detailed nature of the definition and Congress's care in drafting it, this provision is very different from the "vague statutory grant" at issue in *West Virginia*, which, in the Court's view, was susceptible of interpretation in a manner that went "beyond what Congress could reasonably be understood to have granted." *EPA v. West Virginia*, 142 S. Ct. 2587 at 2609, 2614. Here, the definition's text is reasonably understood to reflect the true scope of FDA's authority as intended by Congress. *See id.* at 13 ("[T]he Committee has attempted to design device authority such that the law and the intent of the Congress is clear.");

see also *United States v. Bacto-Unidisk*, 394 U.S. 784, 798 (1969) (“Congress fully intended that the [FD&C] Act’s coverage be as broad as its literal language indicates.”).

FDA is not exercising “newly uncovered” or “unheralded” authority. *West Virginia v. EPA*, 142 S. Ct. 2587 at 2610, 2614. FDA publicly communicated its view that test systems are subject to the Agency’s authority over 50 years ago, see 38 FR 7096; that laboratories are subject to the Agency’s authority almost 50 years ago, see 42 FR 42521; and that laboratory “in house” tests are devices nearly 30 years ago, see 62 FR 62249. And in the years since, FDA has consistently reiterated these assertions (see NPRM section III.D.1., “FDA’s Longstanding Recognition That IVDs Manufactured by Laboratories Are Devices” 88 FR 68006 at 68015-16). Over the last 10 years, FDA has applied its device authorities to hundreds of laboratory-manufactured tests. For example, dating back to at least 2014, it has granted premarket approval to IVDs offered as LDTs,⁶⁷ and during the COVID-19 public health emergency, the Agency issued EUAs for scores of IVDs offered as LDTs (see Ref. 18). All of these activities were predicated on the legal conclusion that test systems manufactured by laboratories are devices. See 21 U.S.C. 360e (premarket approval authority applicable to devices); 21 U.S.C. 360bbb-3 (EUA authorities applicable to drugs, devices, or biological products). Thus, this is not a situation in which “the want of assertion of power by those who presumably would be alert to exercise it” raises a question about “whether such power was actually conferred.” *Id.* at 2608. FDA has repeatedly expressed its view of its authority, including in public statements and through public actions, and its consistent position over decades--without congressional intervention--suggests that there is no “reason to hesitate” here. See, e.g., *United States v. Tuente Livestock*, 888 F. Supp. 1416, 1423 (S.D. Ohio 1995) (upholding FDA interpretation based on, among other things, the fact that “Congress has been aware of the FDA’s understanding and

⁶⁷ Ref. 157.

practice concerning live animals for almost twenty-five years, yet has in no way acted to limit the agency's jurisdiction").⁶⁸

Implementation of this Rule involves technical and policy expertise traditionally within FDA's wheelhouse. FDA has amassed significant experience and expertise regulating IVDs (including test systems) over the course of five decades. This work is squarely within the expertise of FDA's OHT7. OHT7 employs staff across a wide range of disciplines to evaluate test systems and other IVDs, including the principles of their operation and the analytical validity, clinical validity, and safety data behind them. As explained in the NPRM, FDA's work in this area does not meaningfully differ whether an IVD comes from a laboratory or another manufacturer (88 FR 68006 at 68014) (see also responses to comments 67 and 71). Applying this sort of technical and scientific knowledge to devices is a quintessential function performed by FDA, and undoubtedly an area where FDA has "comparative expertise." *Id.* at 2613. Indeed, no other Federal Agency is similarly equipped to do it. These facts underscore the conclusion that FDA has a legitimate role to play--and value to add--in overseeing laboratory-made IVDs. They also reinforce the commonsense point that laboratory-manufactured IVDs fall within the basic mandate of the FD&C Act. Here, FDA is exercising authority, applying expertise, and serving its public-health mission in exactly the ways that are contemplated under the FD&C Act.

Finally, the FD&C Act as a whole supports the conclusion that the Agency has authority for this rulemaking. Congress enacted both the FD&C Act and the MDA with public-health protection in mind. See *United States v. Sullivan*, 332 U.S. 689, 696 (1948) ("[T]he Act as a whole was designed primarily to protect consumers from dangerous products."); *Medtronic, Inc.*

⁶⁸ One commenter attempted to discredit FDA's statement of authority in one preamble (62 FR 62243) on the basis that FDA lacked "any supporting analysis," among other things. But FDA is aware of no basis for the position that the major-questions doctrine requires an Agency to produce a detailed legal analysis in order to show its historical view. As the Supreme Court has described it, the question is whether the Agency's asserted authority is "unheralded," "newly uncovered," or "not previously exercised," *West Virginia v. EPA*, 142 S. Ct. 2587 at 2610, 2614, and that is not the case here. FDA also notes that the statement identified by the commenter was just one in a long line of public statements (see NPRM section III.D.1., "FDA's Longstanding Recognition That IVDs Manufactured by Laboratories Are Devices" 88 FR 68006 at 68015-16), and it was not the first statement of FDA's authority over laboratory-manufactured IVDs. See, e.g., (Ref. 111). Draft CPG: Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation (Aug 3, 1992) (stating that laboratory "home brew" products "are subject to the same regulatory requirements as any unapproved medical device").

v. *Lohr*, 518 U.S. 470, 476 (“In response to the mounting consumer and regulatory concern, Congress enacted the statute at issue here: the Medical Device Amendments of 1976.”). Congress tasked FDA with protecting the public with respect to certain defined categories of articles--as relevant here, “devices”--and sought to avoid “language which afforded loopholes for the escape of the unscrupulous.” S. Rep. 74-361 at 2 (March 13, 1935). Given that risky products could originate from all corners of the country by all manner of “persons,” see 21 U.S.C. 321(e), Congress did not key the “device” definition to any particular type of entity and did not limit FDA’s enforcement authorities to particular actors, see 21 U.S.C. 331 (listing “prohibited acts” generally without reference to the identity of an actor). Instead, it delegated broad authority and crafted exemptions from certain requirements as appropriate. *See, e.g.*, 21 U.S.C. 360(g)(2), 360i(c)(1), 374(a)(2)(B) (even licensed practitioners are subject to the FD&C Act, though their activities may be exempt). Consequently, the best reading of the FD&C Act is that it contains no carveout for laboratories, and Congress has enacted legislation supporting that interpretation. *See* 42 U.S.C. 1395m-1(d)(5)(B) (certain tests developed by laboratories subject to FD&C Act). With respect to commenters’ assertions regarding specific provisions of the FD&C Act and the enactment of CLIA, FDA has addressed those elsewhere in this preamble (see response to comment 54 and sections VI.D.3, VI.D.4, and VI.D.8 of this preamble).

Some commenters also analogized FDA’s proposed action to those in *FDA v. Brown and Williamson Tobacco Corp.*, 529 U.S. 120 and *Utility Air Regulatory Group v. EPA*, 573 U.S. 302. But important factors influencing the Court’s opinions in those cases are not present here. For instance, here, there is no inconsistency between the FD&C Act and FDA’s regulation of laboratories as “device” manufacturers. *See Brown and Williamson*, 529 U.S. 120 at 125 (FDA “may not exercise its authority in a manner that is inconsistent with the administrative structure that Congress enacted into law.”) (internal quotations omitted); *Utility Air Regulatory Group*, 573 U.S. 302 at 321 (Agency interpretation “would be inconsistent with--in fact, would overthrow--the Act’s structure and design.”). Indeed, FDA has regulated in this way for years,

and FDA has never disclaimed authority over laboratory-manufactured IVDs. In addition, this final rule will not have the type of “calamitous consequences” that have caused the Court to consider other regulatory actions to be “incompatible with the substance of Congress’ regulatory scheme.”⁶⁹ 573 U.S. 302 at 322. Quite the opposite: FDA believes that a continuation of the status quo--or a construction of the FD&C Act that incorporates an atextual exemption for laboratories--would have serious consequences for the public, which is why FDA is issuing this rule.⁷⁰

b. Even if the major-questions doctrine applies, the FD&C Act supplies “clear congressional authorization” for this rulemaking. In response to comment 52, FDA explained that the device definition, by its plain terms, encompasses IVDs manufactured by laboratories. This conclusion has more than “a merely plausible textual basis.” *Id.* at 2609. It is the most reasonable reading of the text, and the one that matches congressional intent as expressed through the statutory scheme overall, the legislative history, and subsequent statements from Congress.

Congress drafted the FD&C Act with broad reach, consistent with the remedial purpose of the legislation, and then exempted specific actors and activities as appropriate, but never exempted laboratories. In 1938, Congress included the term “diagnosis” in the FD&C Act specifically to empower FDA to address articles producing false diagnostic results, without any carveout for laboratories. FD&C Act (June 25, 1938), Pub. L. 75–717, 52 Stat. 1040 (defining

⁶⁹ One comment argued that this rulemaking will have practical consequences analogous to those in *Utility Air*--a significant increase in the number of applications, administrative costs, and the review period for applications--which shows that it presents a “major question.” FDA disagrees. As already discussed, FDA does not agree that the current effects of this rule are a reliable indicator of Congress’s intent in 1976. In addition, we do not agree that the practical effects here have the same weight as they did in *Utility Air*. See *Utility Air Regulatory Group v. EPA*, 573 U.S. 302, 321-22 (2014) (“EPA described the calamitous consequences of interpreting the Act in that way.”). And in this rulemaking, unlike *Utility Air*, FDA has discretion to develop enforcement policies to address practical concerns about implementation, underscoring the point that practical concerns should not be understood to reflect a lack of jurisdiction. *Id.* at 326 (rule was not “an exercise of EPA’s enforcement discretion” given the possibility of citizen suits).

⁷⁰ One comment also compared this rulemaking to the facts in *United States v. Franck’s Lab, Inc.*, 816 F. Supp. 2d 1209 (M.D. Fla. 2011), which concerned FDA’s authority over pharmacy compounding. However, that case was not a “major questions” case, and in any event, it was vacated by the Eleventh Circuit. *United States v. Franck’s Lab, Inc.*, 2012 U.S. App. LEXIS 27100 (11th Cir. 2012).

“drug” and “device” with reference to an intended use in “diagnosis,” among other things). In 1976, Congress reiterated that diagnostic articles should be regulated by FDA, now under the new, more robust device framework, and again made no distinction in the device definition between entities manufacturing those articles. See, e.g., H.R. Rep. 94–853 at 11 (February 29, 1976). As described in response to comment 53, the authorizing committees discussed concerns about diagnostic systems at length--and particularly the potential harms of faulty test results--but never mentioned that entities such as laboratories should fall outside the reach of the FD&C Act, even though laboratories were manufacturing tests at the time and FDA had recently announced, by regulation, that IVDs were devices regardless of their manufacturer. And in the over 30 years since FDA first stated its authority over LDTs specifically, Congress has not acted to limit the Agency’s jurisdiction. Instead, in 2014, Congress passed legislation expressly recognizing that “a clinical diagnostic laboratory test...offered and furnished only by a single laboratory” can be “cleared or approved by the Food and Drug Administration,” 42 U.S.C. 1395m-1(d)(5) & (d)(5)(B), and thus is within the definition of a device. Therefore, examining the text in context, the definition provides “clear congressional authorization” for this rulemaking.

E. Other Legal Comments

(Comment 93) Two comments raised First Amendment concerns. One comment asserted that LDTs are different from other devices in that the design and execution of LDTs, as well as the communication of test results, involve speech. In particular, the comment pointed to two CLIA regulations, 42 CFR 493.1445 and 493.1457, which provide that laboratory directors and clinical consultants must “[e]nsure that consultation is available to the laboratory’s clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions.” The comment asserted that these communications will be restricted if FDA has not authorized them through premarket review. The comment then argued that the premarket review requirement for LDTs cannot survive First Amendment analysis. Although the comment conceded that there is a government interest in ensuring that test results do not include

misleading information, the comment asserted that premarket review of LDTs would be too burdensome because such review would restrict laboratory directors and clinical consultants from sharing information about the meaning of test results. That outcome, the comment continued, would undermine the goal of providing healthcare practitioners with information relevant to treatment.

The other comment focused on the right of physicians to receive information as part of their professional speech. The comment suggested that professional speech is subject to special protections under *National Inst. of Family and Life Advocates v. Becerra*, 138 S. Ct. 2361 (2018) (NIFLA) and this special protection extends to physicians' right to receive information. Similar to the first comment, this comment asserted that an LDT is different from many other medical devices in that it is "an informational service" incorporating expert professional judgments. While the comment admitted that the FD&C Act properly places the burden on product sponsors to produce evidence that their products are safe and effective before they can be used, the comment asserted that "the Constitution flips the burden of proof" when regulating flows of medical information, so that FDA would bear the burden of establishing that an LDT is unsafe in order to regulate the LDT.

(Response 93) We disagree with these comments, both in terms of the premises and the analyses. As an initial matter, it is important to clarify the limited impact that the application of the device authorities to LDTs will have on professional communications. As the phaseout of the general enforcement discretion approach is implemented, laboratories that manufacture IVDs offered as LDTs will be generally expected to comply with several pre- and post-market submission and reporting requirements applicable to devices for humans. As most relevant to this discussion, the premarket review requirements are intended to ensure that a device has a reasonable assurance of safety and effectiveness (or other assurances as required under the FD&C Act) for its intended uses prior to being offered for use. For IVDs, appropriate assurances of safety and effectiveness mean, among other things, that a test is not providing false results,

which can stem from an analytical error or from a lack of clinical validity where a measured result is incorrectly associated with a particular clinical state. Accordingly, premarket review involves a scientific evaluation of the functioning of the device for accuracy and reliability. Where premarket requirements apply, a test may not be offered for use if those requirements have not been satisfied. But FDA does not generally consider professional advice regarding a patient's results as evidence of a new intended use, and nothing in this rule is intended to change this practice or otherwise limit the speech clinical professionals may employ in describing and interpreting the outputs of the devices that are lawful to employ. As discussed in more detail below, courts have upheld these premarket review requirements against First Amendment challenges.

Both comments suggested that LDTs are different from other devices because they convey individuals' health information--that is, test results. The comments asserted that this information constitutes speech. But LDTs are not unique in conveying individuals' health information. So too do many non-laboratory IVDs have informational outputs, as well as numerous other types of diagnostic devices, such as radiological imaging devices (such as mammography, x-ray, CT, ultrasound machines), electrocardiograms, blood pressure cuffs, pulse oximeters, cardiac monitors including fetal heart rate monitors, and thermometers. These devices all communicate information--in the form of words, numbers, images, and/or sounds. Yet FDA's statutory authority to regulate diagnostic devices is well established. *See* 21 U.S.C. 321(h) (defining "device" in part as an article "intended for use in the diagnosis of disease or other conditions"). And the constitutionality of Congress's grant of authority to regulate these devices, and to prohibit their sale or use where applicable premarket requirements are not satisfied, has not been questioned. There is nothing about LDTs, as compared with these other devices (or with non-LDT IVDs that produce diagnostic results), that suggests they uniquely implicate the First Amendment. They do not.

We are not aware of any instance in which a litigant has raised a First Amendment challenge to the application of the premarket review provisions of the FD&C Act for diagnostic devices based on the informational nature of their outputs. Any such challenge should fail on legal grounds. Even where LDTs or other diagnostic devices convey information about the health of patients, they do not convey ideas, creative expression, or editorial judgments--that is, they do not convey speech that implicates the First Amendment. Rather, they simply convey scientifically-generated test results purely as a function of the device. In this regard, they cannot be distinguished from a vast array of products whose regulation does not implicate the First Amendment: radar detectors, gas gauges, expiration lights for water filters, and so forth. Even though the very point of these products is to convey information, the Government may seek to ensure that they do so accurately and reliably--and may bar the sale of those that are not accurate and reliable--without triggering First Amendment scrutiny. Indeed, requirements of prior certification before commercial use of weighing and measuring devices--devices whose purpose is to convey information in ways analogous to diagnostic tests--are ubiquitous. *See, e.g., Nat'l Inst. of Standards & Technology, Weights and Measures Program Requirements: A Handbook for the Weights and Measures Administrator* 13-14 (2017) ("Before measuring instruments may be installed in stores or at business locations, most states require that the many types of measuring instruments have type evaluation certificates reporting that the models comply with the requirements of NIST Handbook 44," which provides "the technical and performance requirements for commercial measuring instruments used in the United States"). But we are unaware of a single court that has even applied First Amendment scrutiny to these requirements. The application of the FD&C Act's medical device regulation to LDTs is the same in all relevant respects.⁷¹

⁷¹ *See also Winter v. G.P. Putnam's Sons*, 938 F.2d 1033, 1035-36 (9th Cir. 1991) (citing numerous courts that have applied products liability law, without First Amendment scrutiny, to aeronautical charts that contain erroneous information, noting that: "Aeronautical charts are highly technical tools. They are graphic depictions of technical, mechanical data....The chart itself is like a physical 'product.'....[not] pure thought and expression.").

The comments also erred in their assessment of how the rule would affect professional speech. More specifically, the first comment was incorrect in suggesting that premarket review will preclude the laboratory directors and clinical consultants from consulting on the quality of the test results and their interpretation concerning specific patient conditions pursuant to the CLIA regulations. Premarket review for LDTs is intended to help assure that LDTs generate accurate and reliable test results. As noted, FDA does not generally consider professional advice regarding a patient's results as evidence of a new intended use, and nothing in this rule is intended to change this practice.⁷² FDA recognizes that laboratory directors and clinical consultants help with interpretation and consulting to the healthcare provider, and they can and do give recommendations that are not limited to the content of FDA-required labeling. This clinical consultation is unaffected by FDA's oversight of LDTs. Indeed, the CLIA provisions are not specific to LDTs and have coexisted with FDA regulation of other IVDs for some time. The commenter therefore was incorrect in construing the premarket review and related requirements discussed in this preamble as restricting laboratory directors and clinical consultants from sharing truthful and nonmisleading information about the meaning of a test result.

In addition, with respect to speech by laboratories more generally, contrary to the first comment's suggestion, FDA does not take the position that communications by medical product manufacturers are strictly limited to the content of FDA-required labeling. For example, FDA has issued final guidance regarding medical product manufacturers sharing data and information about the authorized uses of their products that are not contained in their products' FDA-required labeling; the final guidance provides recommendations on how to share the information in a truthful and non-misleading way (see Ref. 62). FDA has also issued draft guidance with recommendations on how medical product manufacturers can share truthful and non-misleading information about unapproved uses of medical products (see, e.g., Refs. 158 and 159).

⁷² In contrast, if a laboratory offers a test on its website for an unauthorized use, FDA would likely consider that offer to be evidence of a new intended use.

Essentially, then, the only content restriction is the requirement of premarket review itself--that laboratories cannot offer test results without first subjecting its device to premarket review to help assure that the device produces accurate and reliable results. A First Amendment challenge to the rule is therefore fundamentally a challenge to the FD&C Act's existing premarket requirements themselves, which prohibit the conduct of marketing devices absent satisfaction of those requirements. Even to the extent that the premarket requirements relate to speech in the form of labeling and marketing, they have long been upheld.

Courts have upheld these premarket review requirements in the context of First Amendment challenges on a variety of grounds. The premarket review requirements do not burden free expression because they are directed to conduct and not to speech. *United States v. Facticeau*, 89 F.4th 1, 29 (1st Cir. 2023), *petition for cert. filed*, ___ U.S.L.W. ___ (U.S. March 13, 2024) (No. 23-1016). A device is adulterated or misbranded "if, among other things, it is intended for a use [subject to premarket review] that has not been approved or cleared by FDA." January 2017 Memorandum at 40; *see generally* *id.* at 40-47 (Ref. 17). In this case, the relevant conduct includes making LDTs available for use and sale without premarket review when such review is required, which constitutes adulterating or misbranding the device while it is held for sale in violation of section 301(k) of the FD&C Act. "[I]t has never been deemed an abridgment of freedom of speech" to regulate conduct that involves language where the "effect on speech would be only incidental to its primary effect on conduct." *Expressions Hair Design v. Schneiderman*, 581 U.S. 37, 47 (2017) (cleaned up). Accordingly, regulation of the conduct of making a device available without premarket review has only "incidental effects" on speech and "do[es] not implicate the First Amendment." *Facticeau*, 89 F.4th 1 at 29 *petition for cert. filed*, ___ U.S.L.W. ___ (U.S. March 13, 2024) (No. 23-1016) (cleaned up). *See also* *Flytenow, Inc. v. FAA*, 808 F.3d 882, 894 (D.C. Cir. 2015) (any "incidental burden" that regulatory requirements impose on speech "does not violate the First Amendment" where the requirements "further an important government interest unrelated to the suppression of free expression," such as promoting safety).

As explained above, premarket review helps assure medical products are safe and effective-- which is a substantial government interest unrelated to the suppression of free expression.

And it is “constitutionally permissible” to rely on speech to “infer intent,” including where that intent establishes that the product is within a category that is subject to and violative of FDA premarket review requirements. *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004). For example, charcoal products intended for emergency treatment of poisoning by ingestion are drugs regulated by FDA, but charcoal sold as fuel is not within FDA’s jurisdiction. The product’s intended use, which may be determined from the product’s labeling, establishes whether the product is within FDA’s jurisdiction (see Ref. 17). The First Circuit recently observed that “courts to consider the issue have uniformly concluded that using speech merely as evidence of a misbranding offense under the [FD&C Act] does not raise First Amendment concerns.” *United States v. Facticeau*, 89 F.4th 1 at 25, *petition for cert. filed*, ___ U.S.L.W. ___ (U.S. March 13, 2024) (No. 23-1016). *See, e.g., Nicopure Labs*, 944 F.3d 267 at 282 (“FDA’s reliance on a seller’s claims about a product as evidence of that product’s intended use, in order that the FDA may correctly classify the product and restrict it if misclassified, does not burden the seller’s speech”); *United States v. LeBeau*, 2016 U.S. Dist. LEXIS 13612, *27 (E.D. Wisc. February 3, 2016) (“A product’s labeling can be used to infer the seller’s intended use and whether the product is an unapproved drug under the FDCA.”), *aff’d*, 2016 U.S. App. LEXIS 12375 (7th Cir. 2016); *United States v. Cole*, 84 F. Supp. 3d 1159, 1166 (D. Or. 2015); *United States v. Livdahl*, 459 F. Supp. 2d 1255 (S.D. Fla. 2005); *United States v. Lane Labs-USA, Inc.*, 324 F. Supp. 2d 547 (D.N.J. 2004); *U.S. v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692 at 703 (D. Md. 2001). *See also Flytenow, Inc. v. FAA*, 808 F.3d at 894 (the “evidentiary use of speech” is “well settled”).⁷³

⁷³ Although the Second Circuit stated in *United States v. Caronia*, 703 F.3d 149, 169 (2d Cir. 2012) that “the government cannot prosecute pharmaceutical manufacturers and their representatives under the [FD&C Act] for speech promoting the lawful, off-label use of an FDA-approved drug,” the Second Circuit later confirmed that “*Caronia* left open the government’s ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for a use that is not included on the drug’s FDA approved label.” *United States ex rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613 n.2 (2d Cir. 2016). The First Circuit likewise found that *Caronia* provides

Nor does FDA’s determination to exercise enforcement discretion with respect to premarket review in certain specific contexts (see discussion in section V.B) restrict or burden speech. As the First Circuit recently explained in rejecting a First Amendment challenge to an FDA final guidance describing an enforcement discretion policy, the enforcement policy does not “burden[] what [medical product] manufacturers may say,” but instead “expands, rather than contracts, the domain of speech that the government shields from being used as evidence” of intended use. *Facteau*, 89 F.4th at 28, *petition for cert. filed*, __ U.S.L.W. __ (U.S. March 13, 2024) (No. 23-1016). The court held that “a policy that limits the consideration of [certain] speech as evidence of intended use does not raise First Amendment concerns.” *Id.* at 25. The D.C. Circuit similarly held, regarding an earlier iteration of the enforcement policy, that a policy that provides a “safe harbor” from the use of certain speech as evidence of intended use did not establish “independent authority to regulate manufacturer speech” and therefore was not subject to First Amendment scrutiny. *Washington Legal Found. v. Henney*, 202 F.3d 331, 336 (D.C. Cir. 2000).

Moreover, to be protected under the First Amendment, commercial speech must “concern lawful activity.” *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 566 (1980). Where Congress requires FDA premarket review of a product, making the LDTs available for use or sale without such review “renders the sale-as-labeled unlawful.” *Nicopure Labs. v. FDA*, 944 F.3d 267, 284 (D.C. Cir. 2019). The speech proposing an illegal sale of such a product is “related to illegal activity” and therefore is “not subject to constitutional protection.” *Id.*; *accord United States v. LeBeau*, 654 Fed. App’x 826, 831 (7th Cir. 2016) (“Because [defendant]’s statements promoted the unlawful sale of an unapproved drug, they were not entitled to protection.”); *United States v. Caputo*, 517 F.3d 935, 940-41 (7th Cir. 2008) (the unapproved device “could not lawfully be sold at all” and therefore “[t]here was no lawful

“no basis to depart from the rule... that the evidentiary use of speech does not violate the First Amendment.” *Facteau*, 89 F.4th at 24, *petition for cert. filed*, __ U.S.L.W. __ (U.S. March 13, 2024) (No. 23-1016).

activity for speech to promote”); *United States v. Cole*, 84 F. Supp. 3d 1159, 1166-67 (D. Or. 2015) (“[d]efendants’ speech concerns an illegal activity--the introduction into interstate commerce of unapproved new drugs[.]...the First Amendment is not violated.”).

And commercial speech is protected under the First Amendment only to the extent that it is “not...misleading.” *Central Hudson*, 447 U.S. 557 at 566. The labeling and advertising for unapproved medical products may be considered misleading where the labeling or advertising “claim [the product] to be safe and effective without any scientific support.” *United States v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692, 703. In such instances, the labeling and advertising is “entitled to no First Amendment protections.” *Id.*

Even if the premarket review and related requirements for devices were subject to First Amendment scrutiny, they would easily pass muster under *Central Hudson* and even more exacting levels of scrutiny. Under the *Central Hudson* framework, if the speech is truthful, not inherently or actually misleading, and relates to lawful activity, the government may impose restrictions that advance a “substantial” government interest and are no “more extensive than is necessary to serve that interest.” *Central Hudson*, 447 U.S. 557 at 566. As FDA has explained elsewhere, premarket review and related requirements for medical products advance several substantial government interests including motivating the development of robust scientific data on safety and efficacy; maintaining the premarket review process for safety and efficacy to prevent harm, protect against fraud, misrepresentation, and bias, and to prevent the diversion of healthcare resources toward ineffective treatments; and ensuring required labeling is accurate and informative. *See* January 2017 Memorandum at 3; *see also id.* at 4-11 (Ref. 17); *Nicopure Labs*, 944 F.3d 267 at 285 (premarket and labeling requirements “directly advance[] the government’s interest in accuracy and public health”). These interests apply to LDTs: as explained above, premarket review and related requirements help assure the safety and effectiveness of IVDs offered as LDTs.

These premarket review and related requirements are appropriately tailored to achieve these goals. To the extent that premarket review requirements relate to speech at all, they implicate speech only by firms responsible for the product's development and/or distribution--the parties best able to conduct the research and gather information necessary for premarket review and otherwise take steps necessary to assure that the medical product is safe and effective (see Ref. 17 at 24-25). In this way, these requirements are similar to other Federal regulatory programs that are directed to particular regulated industry and the products those companies produce. Moreover, these requirements do not operate to ban speech but rather to establish a process for evaluating medical products that fosters truthful, non-misleading, and appropriately substantiated speech. *See Nicopure Labs*, 944 F.3d 267 at 289 (products subject to premarket review are “not excluded from the marketplace of information, only evaluated first to prevent them from misleading consumers”); Ref. 160 (“Commercial speech serves an ‘informational function’ and can be regulated to ensure that the public has access to accurate information. The FDA serves exactly this end. The agency aims not to censor company speech, but to foster the development of accurate and reliable information, and channel that information into settings where it can be rigorously evaluated.”).

The Agency has also considered a variety of alternative approaches and has determined that they would not optimally advance the government interests described above. One alternative would be to continue to exercise enforcement discretion in perpetuity regarding premarket review requirements for IVDs offered as LDTs and instead rely on postmarket remedies, such as enforcement actions for LDTs shown to be unsafe. However, FDA has carefully tailored this final rule to balance competing interests important to the protection of the public health and determined to exercise enforcement discretion with respect to premarket review in certain specific contexts (see discussion in section V.B); FDA has determined that, in other contexts, exclusive reliance on post-market remedies would not be in the best interest of public health

because it does not provide a reasonable assurance of safety and effectiveness prior to the introduction of an IVD to the market.

One comment suggested, as an alternative approach to premarket review, that LDT regulation should “replicate CLIA’s reliance on private ordering solutions (e.g., private accreditation) and rely on postmarketing assessment (rather than premarket review) of LDT safety and effectiveness.” Another alternative would be to enforce premarket review requirements only for the highest risk LDTs. Yet another alternative would be for FDA to continue to exercise enforcement discretion for IVDs offered as LDTs but have unauthorized LDTs disclose that they are not FDA-reviewed. All of these potential alternatives, like FDA’s continuing to exercise enforcement discretion in perpetuity, would fall short in achieving FDA’s public health objectives: by forgoing most or all premarket review except in the limited circumstances covered by the enforcement discretion policies described in section V.B of this preamble (or other enforcement discretion policies that FDA may adopt), these approaches would not sufficiently address the safety and effectiveness concerns that have led to the issuance of this rule.

More specifically, the steps suggested by the comment--replicating CLIA’s reliance on private ordering solutions and relying on postmarketing assessments--would be inadequate substitutes for premarket review. Among other things, CLIA inspections are conducted biennially, so that, if a laboratory has not developed a safe and effective test, it could be giving false or invalid results to healthcare providers or patients for up to 2 years before the laboratory’s CLIA inspection. Also, CLIA inspectors typically pick a sample of tests for detailed review. Therefore, an LDT from a laboratory test manufacturer that has added multiple new tests since its last inspection may not have any review of the underlying documentation for that test. For additional discussion of why CLIA does not provide sufficient assurances of safety and effectiveness for IVDs offered as LDTs, see our responses to comments in section VI.C.2 of this preamble.

Now we turn to the remaining arguments made in the comments. As noted, one comment suggested that the rule would impermissibly interfere with physicians' right to receive information as part of their professional speech. As discussed above, however, this comment failed to acknowledge that premarket review relates to a scientific evaluation of the accuracy and reliability of the test results, which is the function of the device; FDA does not intend to consider professional advice regarding a patient's results as evidence of a new intended use. In addition, framing the issue from the perspective of the healthcare practitioner receiving information, as opposed to the perspective of the speaker, does not change the First Amendment analysis. For example, the origin of the commercial speech doctrine was based largely on the interests of consumers in receiving information. *See Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council*, 425 U.S. 748, 757 (1976). Accordingly, focusing on the interests of the listener, as opposed to the interests of the speaker, does not render the *Central Hudson* analysis inapplicable in evaluating the constitutionality of premarket review.

It also makes no difference whether the recipient of the information is a healthcare practitioner or a patient. Congress enacted the FD&C Act to cover medical products directed to both healthcare practitioners and patients. For example, FDA regulates the labeling of medical products to help assure that they are used safely and effectively, whether the labeling is directed to healthcare practitioners or patients. And the government interest in providing a reasonable assurance of safety and effectiveness of devices applies no matter who is the audience for the information.

Contrary to one comment's suggestion, the Supreme Court's opinion in *NIFLA* is inapposite. On the topic of professional speech, that decision merely held that "neither California nor the Ninth Circuit has identified a persuasive reason for treating professional speech as a unique category that is exempt from ordinary First Amendment principles" but the Court did not "foreclose the possibility that some such reason exists." *NIFLA*, 138 S. Ct. 2361 at 2375. In any

event, our analysis does not rely on treating professional speech as a unique category that is exempt from ordinary First Amendment principles.

We also disagree with the comments' assertions that strict scrutiny should apply because the speech regarding test results is not itself commercial. As discussed above, these devices produce scientifically-generated informational outputs as their function; they do not convey the type of speech that might justify heightened scrutiny. Moreover, courts do not apply the concept of commercial speech so narrowly: information disclosed "in connection with a proposed commercial transaction" constitutes commercial speech, even where the relevant speech itself does not propose a commercial transaction. *See N.Y. State Rest. Ass'n v. N.Y. City Bd. of Health*, 556 F.3d 114, 131 (2d Cir. 2009) (a requirement to post calorie content information on menus "is clearly commercial speech"). More specifically, courts have held that FDA's premarket review requirements are subject to review under the commercial speech doctrine rather than strict scrutiny, even where the manufacturer's speech involves matters of science. *See Discount Tobacco v. United States*, 674 F.3d 509, 532-33 (6th Cir. 2012) (*Central Hudson* was the appropriate test for premarket review of tobacco harm reduction claims where the claims were "consumer-directed" and "regarding a manufacturer's specific products"); *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 62-65 (D.D.C. 1998) (finding manufacturers' dissemination of scientific information about their products to health practitioners to be commercial speech), vacated in part on other grounds, 202 F.3d 331 (D.C. Cir. 2000). Nevertheless, even if this rule were subject to First Amendment scrutiny (which, as explained above, it is not) and even if strict scrutiny were then applied, that test would be satisfied here because the government has a compelling interest in protecting the public health, and premarket review is narrowly tailored to achieve that result, for the reasons explained above.

Finally, we are not aware of any authority to support the flipped-burden-of-proof theory regarding premarket review. Congress established the premarket review requirements under the FD&C Act, which places the burden on the manufacturer to establish the safety and effectiveness

of medical products. To the extent a stakeholder challenges those requirements under the First Amendment, it is the government's burden to establish that the requirements are constitutionally permissible. That is, the government bears the burden on the *Central Hudson* analysis or other applicable First Amendment doctrine of making the required showing, e.g., that the premarket review requirement directly advances a substantial government interest. But there is no First Amendment principle that would result in a court or an agency rewriting the premarket review provisions of the FD&C Act to require FDA to prove that an individual LDT is unsafe.

In sum, FDA's premarket review and related requirements for medical devices do not violate the First Amendment, and the action FDA is taking today to clarify their application to LDTs does not raise any constitutional concerns.

(Comment 94) One comment suggested that the rule might raise concerns under Equal Protection principles on the ground that the rule unduly favors large entities over smaller ones without a rational basis for the distinction. The comment similarly suggested the rule may have antitrust implications by disproportionately affecting smaller laboratories to the benefit of larger entities because the costs of entry or operation will be too high for the small laboratories to compete.

(Response 94) The rule does not raise either Equal Protection or antitrust concerns. Under Equal Protection jurisprudence, the government has "considerable leeway" to issue rules that "may appear to affect similarly situated people differently." *Clements v. Fashing*, 457 U.S. 957, 962-963 (1982). The case law refers to such an effect as a "classification." Where the classification involves a suspect class, such as race or nationality, or infringes on a fundamental right, the law will be subject to heightened scrutiny. *Massachusetts Bd. of Retirement v. Murgia*, 427 U.S. 307, 312 (1976). In the absence of those circumstances, a law containing a classification is "accorded a strong presumption of validity," *Heller v. Doe*, 509 U.S. 312, 319 (1993), and will be upheld if it "bears some fair relationship to a legitimate public purpose." *Plyler v. Doe*, 457 U.S. 202, 216 (1982).

We disagree with the comment's suggestion that this rule involves a classification.

Neither the underlying provisions of the FD&C Act, nor the gradual phaseout of FDA's general enforcement discretion approach, treats smaller entities differently from larger ones. Thus, Equal Protection principles have no application here.

But even assuming that the rule involved a classification in the form of a different effect on smaller entities, the rule would be subject to rational basis review. The comment did not claim that this rule involves any suspect classification or fundamental right. Although the comment stated that certain diseases are more prevalent in certain "ethnic groups," and the rule must be implemented in a non-discriminatory manner to the extent it may affect IVDs offered as LDTs that are intended for those diseases, the comment does not explain how these facts would support a suspect classification theory. Even if the rule were to have a disproportionate impact, a disproportionate impact, by itself, does not trigger strict scrutiny under Equal Protection principles. *Washington v. Davis*, 426 U.S. 229, 242 (1976).

Accordingly, even if the rule involved a classification (which it does not), the rule would be subject to rational basis review, which the rule would easily satisfy. FDA rationally concluded that the phaseout policy will help to ensure the safety and effectiveness of IVDs offered as LDTs and more accurate diagnoses, which will lead to better care and advance public health overall. The rule therefore is rationally related to a legitimate purpose.

FDA also disagrees that the rule raises antitrust concerns. Antitrust law is directed toward preserving free and unfettered competition by curtailing anti-competitive conduct by private entities, such as precluding private arrangements among companies that unreasonably restrain competition. *See, e.g., Northern Pac. Ry. Co. v. United States*, 356 U.S. 1, 4-5 (1958). Antitrust law does not concern and does not curtail the Federal government's oversight in the interest of protecting and promoting the public health.

(Comment 95) One comment asserted that the LDT rule would constitute a "taking" under the Fifth Amendment to the U.S. Constitution because it would disadvantage smaller,

more specialized laboratories to the benefit of larger laboratories and AMCs. The comment contended that this would be a regulatory taking in that it would significantly diminish the value of property without a valid public purpose.

(Response 95) We disagree that the rule would constitute a taking. The Fifth Amendment to the U.S. Constitution prohibits the Government from taking private property for public use without just compensation. The Supreme Court has held that the Government effects a “per se” taking when it physically appropriates property, which is the “clearest sort of taking.” *Cedar Point Nursery v. Hassid*, 141 S. Ct. 2063, 2071 (2021). The Court has also recognized that there may be a regulatory taking where regulations that “restrict an owner’s ability to use his own property” go “too far.” *Id.* at 2071-72. In such cases, a taking may be found based “on a complex of factors, including: (1) the economic impact of the regulation on the claimant; (2) the extent to which the regulation has interfered with distinct investment-backed expectations; and (3) the character of the governmental action.” *Murr v. Wisconsin*, 582 U.S. 383, 393 (2017) (cleaned up) (referred to as the “Penn Central factors” after *Penn Central Transp. Co. v. New York City*, 438 U.S. 104, 124 (1978)). The force of any one of these three Penn Central factors may be “so overwhelming...that it disposes of the taking question.” *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1005.

As the phaseout of the general enforcement discretion approach is implemented, laboratories that manufacture IVDs offered as LDTs generally will be expected to comply with several pre- and post-market submission and reporting requirements applicable to devices for humans, including premarket notification/PMA requirements (as applicable), registration and listing, labeling requirements, reporting requirements regarding adverse events and corrections and removals, QS requirements, and certain IDE regulations. To our knowledge, the FD&C Act’s premarket review and related requirements have never been held to effectuate a taking of property. It has long been established that the government may regulate products in the interests of public health and safety and such regulation “cannot, in any just sense, be deemed a taking.”

Mugler v. Kansas, 123 U.S. 623, 668 (1887). The takings doctrine is based on the concept that, when the government seizes property for the public benefit, such as land for a road or a dam, the public should compensate the owner. But that is a different scenario from where the government limits the use of property to protect public health and safety. *See id.* at 669. As the Supreme Court has elaborated, “[l]ong ago it was recognized that all property in this country is held under the implied obligation that the owner’s use of it shall not be injurious to the community, and the Takings Clause did not transform that principle to one that requires compensation whenever the State asserts its power to enforce it.” *Keystone Bituminous Coal Ass’n v. DeBenedictis*, 480 U.S. 470, 491-92 (1987) (cleaned up). As a result, restrictions on “uses of personal property” that are “directed at the protection of public health and safety” are “the type of regulation in which the private interest has traditionally been most confined and governments are given the greatest leeway to act without the need to compensate those affected by their actions.” *Rose Acre Farms, Inc. v. United States*, 559 F.3d 1260, 1281 (Fed. Cir. 2009).

The phaseout of the general enforcement discretion approach for LDTs is intended to protect public health and safety and to prevent injuries to the community. FDA is taking this action to help ensure the safety and effectiveness of IVDs offered as LDTs and to achieve more accurate diagnoses, which will lead to better care and advance the public health overall. Accordingly, the character of the government’s action here--to advance the public health--weighs heavily, if not conclusively, against finding that the phaseout effects a taking.

The other Penn Central factors also weigh in favor of finding no taking here. With regard to economic impact, the comment asserted that the value of the property of small laboratory manufacturers will be diminished. However, many changes in government laws, regulations, and policies have economic consequences, and the Supreme Court has long recognized that “[g]overnment hardly could go on if to some extent values incident to property could not be diminished without paying for every such change in the general law.” *Pennsylvania Coal Co. v. Mahon*, 260 U.S. 393, 413 (1922). The Supreme Court has explained that “mere diminution in

the value of property, however serious, is insufficient to demonstrate a taking.” *Concrete Pipe & Prods. v. Constr. Laborers Pension Trust*, 508 U.S. 602, 645 (1993). Similarly, a “loss of profit” does not establish a taking. *74 Pinehurst LLC v. New York*, 59 F.4th 557, 566 (2d Cir. 2023). And courts have rejected regulatory takings claims even where the government’s action “impose considerable costs on private actors in the regulated industry.” *Mobile Relay Assocs. v. FCC*, 457 F.3d 1, 12 (D.C. Cir. 2006). Instead, in evaluating the economic impact of a regulation, courts have explained that the “touchstone” is “proportionality”: “the size of a liability only weighs in favor of finding a taking insofar as it is out of proportion to the legitimate obligations society may impose on individual entities.” *B&G Constr. Co. v. Dir., OWCP*, 662 F.3d 233, 260 (3d Cir. 2011) (cleaned up).

In enacting the FD&C Act, Congress determined that manufacturers of medical products should bear the costs of ensuring that their products are appropriately safe and effective, and these costs are proportional to the resulting benefits of FDA oversight to the public health. Furthermore, as discussed elsewhere in this preamble, FDA has taken several steps to address the economic impact of the final phaseout policy--for example, by including certain enforcement discretion policies in the final phaseout policy (see section V.B of this preamble). Accordingly, the phaseout policy does not place disproportionate costs on laboratory manufacturers.

With respect to the last Penn Central factor, a “reasonable investment-backed expectation must be more than a unilateral expectation or an abstract need.” *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986 at 1005 (cleaned up). Courts have held that those who do business in highly regulated fields are on notice that changes are possible. *Connolly v. Pension Ben. Guar. Corp.*, 475 U.S. 211, 226-27 (1986) (“Those who do business in the regulated field cannot object if the legislative scheme is buttressed by subsequent amendments to achieve the legislative end”) (cleaned up).

Laboratory manufacturers have been on notice for some time that their tests could be subject to increased oversight. As a legal matter, FDA has long taken the position that LDTs are

devices subject to regulation under the FD&C Act, over which it was exercising enforcement discretion. Moreover, laboratory manufacturers have been on notice that their tests could be subject to increased oversight at various times--e.g., after issuance of the preamble to the ASR rule nearly 30 years ago, stating that “FDA believes that clinical laboratories that develop [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act” (62 FR at 62249), and after two draft guidance documents were issued by FDA on October 3, 2014, entitled “Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)” (79 FR 59776) and “FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)” (79 FR 59779) (Refs. 38 and 112). Accordingly, laboratory manufacturers did not have reasonable investment-backed expectations that they would not ever be subject to FDA oversight.

Accordingly, application of the Penn Central factors confirms that FDA’s phaseout of the general enforcement discretion approach for LDTs will not effect a taking.

(Comment 96) Various comments requested, or stated that FDA should have granted,⁷⁴ an extension of the 60-day comment period. Most of these comments requested a 60-day or longer extension. The comments argued for an extension given the following: (1) the complex and multifaceted nature of the proposed rule, which required review by experts in various fields; (2) the significant implications that the final rule will have on stakeholders; (3) the numerous legal issues raised by the rule; (4) differences in FDA’s proposal compared to its previous proposals (e.g., with respect to tests currently on the market and the timeline for premarket review expectations); (5) a longer comment period would be in line with Agency precedent (e.g., the comment period for the 2014 draft LDT guidance documents was 120 days, and other FDA rulemakings “with more modest impact” had longer than 60-day comment periods); (6) the

⁷⁴ FDA received 14 requests for extensions soon after publication of the NPRM. For those requests, FDA responded directly to the requesters (and submitted a sample of such a response to the docket, see e.g. Ref. 161) and posted an update to its website stating that “[a]fter considering the [request/requests] and other factors, including the extensive background of public comment on this topic and the public health benefits of proceeding expeditiously, the FDA has determined to proceed with the standard 60-day comment period” (Ref. 113).

length of time that FDA has been working on the proposed rule (at least 7 months, according to one comment); and/or (7) the comment period spanned the Thanksgiving holiday season.

Various comments described what they would do with additional time, which included surveying small businesses and investors to better understand the implications of the costs of the rule; estimating added costs to the U.S. healthcare system from the loss of competition resulting from the rule; and assessing the harm to patients resulting from small entities exiting the market and/or reducing operations. Several comments stated that FDA's denial of requests for extensions raised concerns about the thoroughness of stakeholder engagement and noted that the denials were based on FDA's "manufactured sense of urgency."

(Response 96) After reviewing the public comments and the requests for additional time for comment, FDA does not believe that extending or reopening the comment period is necessary for the public to receive a meaningful opportunity to comment on the NPRM. Consequently, and in light of the public health benefits of proceeding expeditiously, FDA is again declining to extend the comment period.

Under the APA, agencies are required to provide interested persons an opportunity to participate in the rulemaking through submission of comments. 5 U.S.C. 553(c). Although the APA does not delineate a minimum number of days that a comment period must run, courts have said that the length of a comment period must provide a meaningful opportunity to comment. See *Rural Cellular Ass'n v. FCC*, 588 F.3d 1095, 1101 (D.C. Cir. 2009). And while some courts have found comment periods of less than 30 days to be appropriate, various courts have observed that 30 days is generally the shortest time period for interested persons to meaningfully review a proposed rule and provide informed comment. See, e.g., *Nat'l Lifeline Ass'n v. FCC*, 921 F.3d 1102, 1117 (D.C. Cir. 2019). FDA's own regulations require that the Agency generally provide 60 days for comment on proposed regulations, see 21 CFR 10.40(b)(2), and EO 12866 generally recommends a comment period of at least 60 days for most rulemaking, see EO 12866, sec. 6(a), 58 FR 51735, October 4, 1993.

The Supreme Court has stated that the APA “sets forth the full extent of judicial authority to review executive agency action for procedural correctness.” *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 513 (2009). Moreover, the Court has emphasized that beyond the APA’s minimum requirements, courts lack authority “to impose upon [an] agency its own notion of which procedures are ‘best’ or most likely to further some vague, undefined public good.” *Vermont Yankee Nuclear Power Corp. v. NRDC*, 435 U.S. 519, 549 (1973). Under this rubric, many courts have refused to find an APA violation where an agency provides a 60-day (or even shorter) comment period and otherwise provides a meaningful opportunity to comment. *See Little Sisters of the Poor Saints Peter & Paul Home v. Pennsylvania*, 140 S. Ct. 2367, 2386 (2020) (“The Departments complied with each of these statutory procedures. They ‘request[ed] and encourag[ed] public comments on all matters addressed’ in the rules....They also gave interested parties 60 days to submit comments.”) (internal citations omitted); see also *Chamber of Com. of United States v. United States Sec. & Exch. Comm’n*, 85 F.4th 760, 779–80 (5th Cir. 2023) (“We cannot conclude that the initial [45-day] comment period was so short as to deprive petitioners of a meaningful opportunity to comment on the proposed rulemaking. Petitioners may have hoped for more time, but it is not for us to decide whether an agency has chosen a maximally net beneficial comment period.”).

FDA has determined that the 60-day comment period for the NPRM allowed sufficient time for a meaningful opportunity to comment. There was ample time for the submission of more than 6,500 comments. A variety of entities submitted comments, including medical device associations, industry, medical and healthcare professional associations, other advocacy organizations, government agencies, and individuals, and they offered a broad array of perspectives on FDA’s proposal. In addition, FDA has determined that an extension would not be appropriate in light of the public health benefits of proceeding expeditiously in finalizing this rulemaking.

We note that many of the complex policy and legal issues have been discussed by FDA and stakeholders for over a decade.⁷⁵ In addition, after publication of the NPRM, FDA worked to ensure that stakeholders fully understood the proposal, including by hosting a webinar (see Ref. 162). The webinar addressed, among other things, the various differences in FDA's proposal compared to its previous proposals.

We are not persuaded by the other arguments made in the comments. For example, we do not believe it would be appropriate to extend the comment period for this NPRM to align it with the comment period of other FDA proposed rules or the 2014 LDT draft guidance documents. The appropriate length for a comment period is not a one-size-fits-all analysis but rather depends on many relevant factors, which were all considered in choosing a 60-day comment period for this NPRM and considering extension requests. In addition, we disagree that the length of time that FDA spent developing, drafting, and publishing the NPRM suggests that a meaningful opportunity to comment was not provided to interested persons or that an extension is appropriate based on that timing. Finally, as noted above, one comment argued for an extension because the comment period was over Thanksgiving, and also because various small laboratories would be preparing during the 60-day comment period for a January conference. Although the 60-day comment period covered Thanksgiving, it ended on December 4, 2023, and a 30- or 60-day extension would have extended the comment period through the December/January holiday

⁷⁵ As discussed in the NPRM (88 FR 68006 at 68016) and elsewhere in this preamble, the Agency held a 2-day public meeting and opened a docket for public comment in 2010 regarding FDA's plans to develop a broad approach to the oversight of LDTs (75 FR 34463, June 17, 2010). Input received through those proceedings informed two draft guidance documents issued by FDA on October 3, 2014, entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" (79 FR 59776) and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)" (79 FR 59779). FDA solicited public feedback on the draft guidance documents and held a public workshop on January 8 and 9, 2015 (79 FR 69860, November 24, 2014). From October 2014 through 2016, FDA analyzed more than 300 sets of comments on the draft guidance documents, as well as discussion from the public workshop, and engaged extensively with stakeholders in meetings and conferences. A number of interested parties provided feedback, including laboratories, healthcare providers, patients, conventional IVD manufacturers, government agencies, and members of Congress. The feedback ranged generally from strong opposition to strong support for FDA's proposed increased oversight of LDTs and addressed a wide range of topics, including FDA's authority to regulate LDTs, the risks posed by LDTs without increased FDA enforcement, the effect of a new enforcement approach on test access and innovation, the potential interplay between FDA regulation and CLIA, and the implications of increased FDA oversight for competition in the IVD market. FDA also has received and responded to multiple citizen petitions raising some of the same policy and legal issues raised in this rulemaking. *See* Refs. 114-115.

season. Moreover, although certain small laboratories impacted by this rulemaking may have participated in a January conference, we do not believe that an extension to accommodate such a commitment would have been appropriate in light of the public health benefits of proceeding expeditiously in finalizing this rulemaking.

(Comment 97) One comment stated that a 180-day extension of the comment period was appropriate (and preferred a 9 to 12-month extension), noting that such a request aligns with the *Federal Register's* Guide to the Rulemaking Process.

(Response 97) For the reasons set forth in response to comment 96, after reviewing the public comments and the requests for additional time for comment, FDA does not believe that extending the comment period is necessary for the public to receive a meaningful opportunity to comment on the NPRM. Consequently, and in light of the public health benefits of proceeding expeditiously, FDA is again declining to extend the comment period.

Notably, in its Guide to the Rulemaking Process, the *Federal Register* acknowledges that comment periods on proposed rules typically range from 30 to 60 days: “[i]n general, agencies will specify a comment period ranging from 30 to 60 days in the ‘Dates’ section of the Federal Register document, but the time period can vary” (Ref. 163). Although the *Federal Register* states that for complex rulings, agencies may provide for longer periods, such as 180 days or more, see *id.*, the *Federal Register* is clear that this is not a requirement.

(Comment 98) Several comments emphasized that a 60-day comment period was insufficient specifically for practitioners, who are directly impacted by the rule. These comments noted that practitioners are busy taking care of patients, some were uncertain regarding the details of the proposed rule, and many were not aware of the proposed rule when it issued.

(Response 98) For the reasons discussed in response to comment 96, FDA disagrees that the 60-day comment period was insufficient. Moreover, we note that to help ensure stakeholders understood the proposal, FDA held a webinar on October 31, 2023, providing information on and answering questions about the NPRM (see Ref. 162). In addition, although certain individual

practitioners may not have been aware of the proposal after it was issued, FDA received numerous lengthy and substantive comments from practitioners, trade groups, and other organizations representing practitioners, and those comments have helped to shape the final phaseout policy.

(Comment 99) One comment urged FDA to hold a public meeting (not less than 60 days before the comment deadline) to educate laboratories on the specifics of the “regulatory requirements FDA plans to impose,” among other things.

(Response 99) To help stakeholders understand and comment on the NPRM, FDA held a webinar on October 31, 2023, to provide stakeholders with information on and answer questions about the NPRM (see Ref. 162). The presentation, printable slides, and transcript from the Webinar have been available on FDA’s website since that date (see Ref. 72).

(Comment 100) One comment stated that the initial categorization of the proposed rule as not “Section 3(f)(1) significant” was inconsistent with EO 12866 and the Office of Information and Regulatory Affairs’ (OIRA’s) April 6, 2023 memorandum regarding implementation of that EO because the proposed rule impacts the three listed categories of significant regulatory actions and exceeds the threshold for economic significance. The comment noted that although the proposed rule was later re-assigned a categorization of “Section 3(f)(1) significant,” the original categorization demonstrates “a lack of consideration of all relevant factors by the FDA” and “portrays a lack of partnership in helping to identify and establish a regulatory framework that could work for the industry being regulated.”

(Response 100) The proposed rule was originally categorized as “Other significant” in the Spring 2023 Unified Agenda--i.e., as significant under a provision of EO 12866 other than section 3(f)(1)--and then categorized as “Section 3(f)(1) significant” in all subsequent Unified Agendas. For the Spring 2023 Unified Agenda, the exact proposal was still under development and it was not clear whether the proposed rule would be “Section 3(f)(1) significant.” As such, FDA categorized it as “Other significant.” As discussed in section VIII, OIRA has determined

that the final rule is a significant regulatory action under EO 12866 section 3(f)(1). In any event, the comment does not explain, and it is otherwise unclear to FDA, how this initial categorization demonstrates a lack of consideration by FDA of “relevant factors” or a “lack of partnership” with industry to establish an appropriate policy.

(Comment 101) One comment stated that FDA failed to conduct the required federalism analysis under EO 13132 and the Agency erroneously stated in the NPRM that “this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government.”⁷⁶ The comment stated that because the proposed rule has such effects, and would preempt state law under section 521 of the FD&C Act (21 U.S.C. 360k), FDA must comply with all of the requirements of sections 6(c)⁷⁷ and 8(a)⁷⁸ of EO 13132. Another comment stated that the conclusions in the proposed rule regarding federalism “do not reflect the impact on practice of medicine” given that the proposed rule conflicts with certain state medical practice acts as well as NYS CLEP that currently permits the review, approval, and use of LDTs.

(Response 101) Although EO 13132 contains principles that apply broadly to “policies that have federalism implications,” which means “regulations, legislative comments or proposed legislation, and other policy statements or actions that have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government,” a federalism summary impact statement is required for a “regulation” that has federalism implications and that meets

⁷⁶ Another comment agreed with this comment to the extent FDA was asserting authority to regulate States and State-owned entities (*see* comment 106).

⁷⁷ Section 6(a) of EO 13132 states that “[t]o the extent practicable and permitted by law, no agency shall promulgate any regulation that has federalism implications and that preempts State law, unless the agency, prior to the formal promulgation of the regulation” meets certain prescribed requirements.

⁷⁸ Section 8(a) of EO 13132 states that “[i]n transmitting any draft final regulation that has federalism implications to the Office of Management and Budget pursuant to Executive Order 12866 of September 30, 1993, each agency shall include a certification from the official designated to ensure compliance with this order stating that the requirements of this order have been met in a meaningful and timely manner.”

certain additional criteria. Because the requirement for a federalism summary impact statement applies specifically to “regulation” and not to policy, the requirement for a federalism summary impact statement applies to the proposed amendment to § 809.3 and not to the proposed phaseout policy. And because the proposed amendment to § 809.3 would not establish any new requirements, it would not have any federalism implications under EO 13132 (see section XI).

Even if the requirement for a federalism summary impact statement were to apply to the phaseout policy, the policy does not have federalism implications because it is not establishing any new requirements. Rather, the phaseout policy is about increasing oversight of existing requirements under the FD&C Act and FDA regulations. All laboratory manufacturers, including State-owned laboratories, have been legally subject to these requirements even though the Agency generally has not enforced them. As such, the enforcement policy is not changing their legal obligations.

Moreover, we note that EO 12866, section 11 makes clear that the order “is intended only to improve the internal management of the executive branch, and is not intended to create any right or benefit, substantive or procedural, enforceable at law by a party against the United States, its agencies, its officers, or any person.”

For additional discussion regarding NYS CLEP, see sections V.B.2 and VI.F.5 of this preamble.

(Comment 102) Several comments stated that FDA has violated the MDA General Rule because the proposed rule is unduly burdensome and lacks flexibility.

(Response 102) The “general rule” provision for records and reports in the MDA states that: “Every person who is a manufacturer, importer, or distributor of a device intended for human use shall establish and maintain such records, make such reports, and provide such information, as the Secretary may by regulation reasonably require to assure that such device is not adulterated or misbranded and to otherwise assure its safety and effectiveness,” and that “Regulations prescribed under the preceding sentence--(1) shall not impose requirements unduly

burdensome to a device manufacturer, importer, or distributor taking into account his cost of complying with such requirements and the need for the protection of the public health and the implementation of this Act....” Section 2 of the MDA, Pub. L. 94-295 (1976), codified at section 519 of the FD&C Act. Section 519 has since been amended and this provision now appears at section 519(a) and (a)(4).

As an initial matter, the “general rule” provision referenced in the comment is not applicable to this rulemaking. FDA is not prescribing new regulations under section 519 of the FD&C Act regarding records and reports, but rather is amending § 809.3 and phasing out the general enforcement discretion approach for IVDs offered as LDTs.

In any event, FDA disagrees with the assertion that the proposed rule is overly burdensome and lacks flexibility such as might violate this provision. For additional discussion of FDA’s adherence to least burdensome principles, see the response to comment 12.

(Comment 103) Several comments stated that FDA violated the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4) (UMRA) because it did not assess all regulatory options and select the least burdensome avenue in its proposal. Some of these comments asserted that the proposal shows no evidence of consideration of viable alternatives.

(Response 103) Under the UMRA, before issuing any rule for which a written statement is required under section 202 of the UMRA, agencies must “identify and consider a reasonable number of regulatory alternatives and from those alternatives select the least costly, most cost-effective or least burdensome alternative that achieves the objectives of the rule.” *See* 2 U.S.C. 1535. Under section 202 of the UMRA, unless otherwise prohibited by law, a written statement containing certain prescribed information must be prepared before an agency issues any general notice of proposed rulemaking that “is likely to result in promulgation of any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any 1 year.”

As an initial matter, the UMRA requirement referenced in the comment is not applicable to this rulemaking. This rulemaking is not likely to result in a final rule that includes any Federal mandate, as that term is defined in the UMRA (see 2 U.S.C. 658(6)), and so a written statement is not required under section 202 and the requirements at 2 U.S.C. 1535 do not apply.

Even if the requirements applied, however, FDA disagrees with the assertion that it did not assess all regulatory options and select the least burdensome avenue in its proposal such as might violate the UMRA. FDA identified and considered a reasonable number of regulatory alternatives and selected the most cost-effective or least burdensome alternative that achieves the objective of this rule, as required by the UMRA. Specifically, FDA considered five different regulatory alternatives, comparing the total costs, benefits, and transfers with one option that would be more stringent and three options that would be less stringent than the proposal. *See* section II.J of the PRIA (Ref. 60). FDA also sought comments on various additional policies and has considered those comments and made changes to the proposal based on some of the comments submitted.

(Comment 104) One comment stated that the NPRM fails to comply with a new provision of the APA, codified at 5 U.S.C. 553(b)(4), which requires that an NPRM include a website with a 100-word or less, plain language summary of the NPRM that is posted on regulations.gov.⁷⁹ The comment asserted that this failure undermines the ability of stakeholders--particularly smaller laboratories and their employees--to understand FDA's proposal and participate meaningfully in the public comment process. As such, the comment stated that FDA must publish a concise summary of its proposal, reissue the NPRM with the mandatory internet address included, and restart this proceeding with a new public comment period.

⁷⁹ On July 23, 2023, the "Providing Accountability Through Transparency Act of 2023," Pub. L. No. 118-9, amended section 553(b) of the APA, adding the requirement that an NPRM include "the Internet address of a summary of not more than 100 words in length of the proposed rule, in plain language, that shall be posted on the Internet website under section 206(d) of the E-Government Act of 2002 (44 U.S.C. 3501 note) (commonly known as regulations.gov)." Section 553(b)(4) of the APA.

(Response 104) We disagree. FDA substantially complied with this new APA requirement by including an 89-word, plain-language summary of the NPRM on its website (see Ref. 115), which is included as Ref. 56 of the NPRM, posted on [regulations.gov](https://www.regulations.gov).^{80,81} That suffices, but even if it did not, any insufficiency would not have undermined the ability of stakeholders to understand FDA’s proposal and participate meaningfully in the public comment process. During the comment period, a summary of the NPRM was included on FDA’s LDT webpage (see Ref. 134), a summary of the NPRM was included at the beginning of the NPRM, FDA’s press release for the NPRM provided high-level information regarding the content of the NPRM (see Ref. 164), and FDA held a webinar after issuance of the NPRM to provide stakeholders with information on and answer questions about the NPRM (see Ref. 162). In light of all of this, we disagree that stakeholders, particularly smaller laboratories and their employees, were deprived of a meaningful public comment process. In fact, the sheer number of comments submitted on the NPRM, including by small laboratories and their employees, contradicts such an assertion. Nor did any commenter identify any way in which the comments they submitted would have differed in any way had FDA published a 100-word summary on <https://www.regulations.gov>. For these reasons, FDA declines to reissue the comment period.

(Comment 105) Several comments stated that State-owned and academic institutions should not fall under the jurisdiction of FDA. One of these comments stated that FDA’s regulation of State governmental entities is constrained by the text of the FD&C Act, which the comment stated does not treat states as “persons” subject to various significant medical device provisions of the FD&C Act (e.g., registration requirements under section 510(c), premarket

⁸⁰ Under the “Increased FDA Oversight to Help Ensure Safety and Effectiveness of LDTs” heading, which was posted the same day of publication of the NPRM, FDA included the following summary of the NPRM: “On September 29, 2023, the FDA announced a proposed rule aimed at helping to ensure the safety and effectiveness of these tests. The proposed rule seeks to amend the FDA’s regulations to make explicit that IVDs are devices under the Federal Food, Drug, and Cosmetic Act, including when the manufacturer of the IVD is a laboratory. Along with this amendment, the FDA is proposing a policy under which the FDA intends to provide greater oversight of LDTs through a phaseout of its general enforcement discretion approach for most LDTs.” (Ref. 113).

⁸¹ On March 11, 2024, a summary was added to the “Docket Details” of the LDT NPRM. See <https://www.regulations.gov>.

notification requirements under section 510(k), premarket approval requirements under section 515(c), and adverse event reporting requirements in part 803). The comment stated that these provisions regulate “persons,” not sovereign states, and that the Supreme Court’s “longstanding presumption” against treating U.S. states as “persons” can be “disregarded only upon some affirmative showing of statutory intent to the contrary.”⁸² The comment stated that the FD&C Act provides no affirmative showing of congressional intent for FDA to regulate laboratories owned by State agencies and State universities.

(Response 105) FDA disagrees. The comment does not include several key points that, when taken together, indicate that a state is properly understood as a “person” under the FD&C Act.

The comment relies on the Supreme Court’s decision in *Vt. Agency for Nat. Res. v. U.S. ex rel. Stevens* to support the assertion that the term “person” does not encompass States. After its decision in *Stevens*, however, the Court made clear that “qualification of a sovereign as a ‘person’ ...depends not upon a bare analysis of the word ‘person,’ but on the legislative environment in which the word appears.” *Inyo County v. Paiute-Shoshone Indians of the Bishop Cmty. of the Bishop Colony*, 538 U.S. 701, 711 (2003) (citations and internal quotations omitted); see also *Pfizer, Inc. v. Gov’t of India*, 434 U.S. 308, 313 (1978) (“In light of the law’s expansive remedial purpose, the Court has not taken a technical or semantic approach in determining who is a ‘person’ entitled to sue for treble damages. Instead, it has said that ‘[t]he purpose, the subject matter, the context, the legislative history, and the executive interpretation of the statute are aids to construction which may indicate’ the proper scope of the law.”) (quoting *United States v. Cooper Corp.*, 312 U.S. 600, 605 (1941)).

There are two key features of the “legislative environment” of the FD&C Act that, taken together, make clear that the statute’s reference to “person” encompasses States--a position long reflected in FDA’s regulations. See § 814.3(h) (issued in 1986) (defining “[p]erson” to include,

⁸² See *Vermont Agency of Natural Resources v. US ex rel Stevens*, 529 U.S. 765, 766 (2000).

among other things, “any...scientific or academic establishment, Government agency, or organizational unit thereof, or any other legal entity”). First, the definition of “person” in the FD&C Act uses the term “includes.” 21 U.S.C. 321(e) (“[t]he term ‘person’ includes individual, partnership, corporation, and association”). It is a longstanding rule of statutory construction that, “[i]n definitive provisions of statutes and other writings, ‘include’ is frequently, if not generally, used as a word of extension or enlargement rather than as one of limitation or enumeration.” *Am. Sur. Co. of New York v. Marotta*, 287 U.S. 513, 517 (1933). Accordingly, in choosing to define “person” in the FD&C Act as “includ[ing]” individuals, partnerships, corporations, and associations, Congress indicated the term could be construed broadly to include entities in addition to the enumerated ones. This is particularly clear in light of the other definitions in section 201 of the FD&C Act, most of which use the term “means” (i.e., “The term X means...”). If Congress had intended a limited meaning, it would have used the much more restrictive sentence structure that appears in all of the surrounding definitions and said: “The term person *means* individuals, partnerships, corporations, and associations” (emphasis added). Indeed, in *Vermont Agency of Natural Resources*, the Supreme Court acknowledged that very distinction in Stevens--definitions of person that used the term “means,” as in the example in that case, point to a different result from those that use the term “includes.” 529 U.S. 765, 786 n.17 (2000) (citing *California v. United States*, 320 U.S. 577, 585–86 (1944)).⁸³

Second--and crucially--Congress demonstrated its understanding that the FD&C Act’s reference to “person” includes government entities when it enacted provisions involving the payment of fees in connection with the submission of certain premarket review submissions to FDA. The FD&C Act requires that “[e]ach person” who submits several different types of premarket review submissions shall be subject to a fee. *See* 21 U.S.C. 379h(a)(1)(A), 379j(a)(2)(A), 379j-42(a)(1)(A), 379j-52(a)(1)(A). The FD&C Act then exempts “State and

⁸³ Similarly, in *Return Mail, Inc. v. USPS*, the Court invoked the presumption that a person does not include governmental entities where the statute did not define “person.” 139 S. Ct. 1853, 1861 (2019).

Federal” government entities from the payment of fees for submissions relating to products that will not be distributed commercially. *See* 21 U.S.C. 379g(1), 379j(a)(2)(B), 379j-41(1)(b)(ii), 379j-51(4)(b)(iv). These exemptions would be superfluous if the term “person” already excluded governmental entities. In addition, under the terms of the statute, governmental entities are subject to fees for submissions related to products to be distributed commercially. *See, e.g.,* 21 U.S.C. 379j(a)(2)(B)(iii). These provisions, too, demonstrate that Congress intended their devices to be subject to premarket review under the FD&C Act.

(Comment 106) One comment cited a June 2020 memorandum from Robert Charrow (then-HHS General Counsel) to Stephen Hahn, MD (then-Commissioner of Food and Drugs) that said that the FDA likely had limited to no authority to regulate states and state-owned entities. The comment noted that FDA omitted any discussion of this potential, significant legal limitation in the proposed rule and regulatory impact analysis and did not comment on whether the current HHS General Counsel or FDA accepted or rejected the prior legal analysis. The comment noted that this limitation would have a profound impact on State-owned AMCs and other State-owned laboratory entities and stated that the issue should be subject to more significant administrative or judicial consideration prior to advancing any proposed rule.

(Response 106) FDA referenced the memorandum from the HHS Office of the General Counsel in the proposed rule, noting that it informed HHS’ August 2020 posting of a statement on its website entitled “Rescission of Guidances and Other Informal Issuances.” 88 FR 68006 at 68016. FDA stated that in November 2021, based on new advice from the HHS Office of the General Counsel, HHS leadership determined that the August 2020 statement no longer represented the Department’s policy or legal views. *Id.* As stated in the response to comment 105, FDA does not agree that it has limited to no authority to regulate States and State-owned entities, and we do not agree that additional consideration of this issue is necessary or appropriate prior to advancing this rulemaking.

(Comment 107) One comment stated that FDA has significant conflicts of interest associated with the rulemaking because the final rule will significantly increase the Agency's acquisition of fees and likely also its Federal appropriations, as increased oversight will require additional funding. The comment noted that FDA's relationships with manufacturers are also a conflict of interest as the final rule will primarily benefit test manufacturers from who FDA currently receives significant user fees. Finally, the comment noted that a rule that increases test manufacturers' market share in laboratory testing and which may result in increased submissions to the FDA from such manufacturers provides additional financial incentives to FDA.

(Response 107) We disagree. FDA frequently issues rules, like this final rule, that have significant implications on the number of applications and submissions (many of which have associated user fees) that it receives. The fact that a rule may result in increased submissions/applications (with associated user fees) does not mean that there are conflicts of interest at issue.

To the extent the comment is suggesting that the motivation behind the rulemaking is some type of financial gain, we also disagree. As FDA has noted in the NPRM and elsewhere in this preamble, we are issuing this rule to help ensure the safety and effectiveness of IVDs offered as LDTs and to achieve more accurate diagnoses, which will lead to better care and advance public health overall (88 FR 68006 at 68012). Although the final rule is expected to increase the number of applications and submissions FDA receives, the collection of those fees is not the driver behind this rulemaking. Finally, FDA does not control the amount of funds appropriated by Congress, so it is unclear how this rulemaking could be argued to be motivated by FDA's desire for an increase in appropriated funds.

(Comment 108) One comment stated that FDA provides no legal basis or justification for excluding certain tests from its definition of an LDT (i.e., an IVD that is intended for clinical use and that is designed, manufactured, and used within a single laboratory that is certified under CLIA and meets the regulatory requirements under CLIA to perform high complexity testing).

The comment also stated that FDA excludes certain tests from its definition that are specifically recognized under CLIA regulations. Another comment expressed concern about the definition, and specifically the lack of clarity regarding the meaning of “clinical use” and the process for assessing “intent” when applied to genomics.

(Response 108) As noted in the NPRM and in this preamble, FDA has generally considered an LDT to be an IVD that is intended for clinical use and that is designed, manufactured, and used within a single laboratory that is certified under CLIA and meets the regulatory requirements under CLIA to perform high complexity testing (88 FR 68006 at 68009). Although FDA’s general enforcement discretion approach has been focused on LDTs, FDA’s phaseout policy has a broader scope. Specifically, FDA is applying the phaseout policy to IVDs that are manufactured and offered as LDTs by laboratories that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing, and used within such laboratories, even if those IVDs do not fall within FDA’s traditional understanding of an LDT because they are not designed, manufactured, and used within a single laboratory. Whether a test falls within FDA’s traditional understanding of an LDT therefore is inapposite for purposes of the phaseout policy. Moreover, for the enforcement discretion policies included in this rule that apply to certain types of “LDTs,” FDA has included its rationale for those policies and their scopes in section V.B.

(Comment 109) One comment stated that the final rule should explicitly state the legal authority supporting the regulation and should highlight the urgency of “addressing LDT regulation given that it currently falls within a regulatory gap.”

(Response 109) FDA has included a discussion of the legal authority for the rule (see sections I.C and IV of this preamble) as well as a discussion of the need for the rule (section III.B of this preamble).

(Comment 110) One comment stated that this rule cannot become a binding regulation until it is subjected to the centralized regulatory review process, which consists of a benefit-cost analysis and Office of Management and Budget (OMB) review.

(Response 110) To the extent the comment is implying that this rulemaking did not include centralized regulatory review, it is incorrect. FDA has gone through that process. As part of that process, it has prepared preliminary and final regulatory impact analyses under EOs 12866, 13563, and 14094, as well as the Regulatory Flexibility Act and the Unfunded Mandates Reform Act. OIRA has reviewed those analyses and this rule.

Although this rule has been issued in accordance with the centralized regulatory review process described in EO 12866 and its amendments, FDA disagrees with the assertion that a rule would not be “binding” were it not subjected to all aspects of centralized regulatory review as specified by EO 12866. Legal requirements for rulemaking are set forth in the APA and related statutes, organic statutes such as the FD&C Act, and applicable regulations. Additionally, Section 10 of EO 12866 provides: “This Executive order is intended only to improve the internal management of the Federal Government and does not create any right or benefit, substantive or procedural, enforceable at law...” *See also Alliance for Natural Health U.S. v. Sebelius*, 775 F. Supp. 2d 114, 135 n.10 (D.D.C. 2011) (citing Section 10 in rejecting challenge to FDA regulation for alleged violation of EO 12866); EO 13563 section 7(f) (noting that the EO does not create any right or benefit enforceable at law or in equity); EO 14094 section 4(c) (same). EO 12866 thus does not establish legally enforceable requirements for rulemaking.

(Comment 111) One comment argued that, to phase out the general enforcement discretion approach for IVDs offered as LDTs, FDA would have to provide data “to cross a predetermined threshold for action,” and the data should be presented “along with the minutes of meetings around it.”

(Response 111) There is no requirement--in the APA, FD&C Act, or otherwise--establishing a “predetermined threshold” for changing an enforcement discretion approach. As

FDA explained in section III.B of this preamble as well as the NPRM, the LDT landscape has evolved significantly since the enactment of the MDA (88 FR 68006 at 68009), and several factors justify this rule, including, but not limited to, the increased complexity of IVDs offered as LDTs and their growing share of the testing market. The documents supporting FDA's findings, including sources such as peer-reviewed literature and FDA memoranda, were published in the docket for this rulemaking.

(Comment 112) One comment expressed concern with FDA characterizing the proposed rule, if finalized, as not establishing any requirements. The comment stated that “applying a panoply of regulations to an entirely new class that had not hitherto been regulated is, from the perspective of laboratories, imposing entirely new requirements.”

(Response 112) To the extent the commenter is suggesting that FDA is required to go through notice-and-comment rulemaking to phase out the general enforcement discretion approach for applicable requirements, we disagree. The phaseout policy does not impose any binding requirements on the Agency or LDT manufacturers, but rather describes how FDA intends to phase out the general enforcement discretion approach for existing requirements under the FD&C Act that apply to LDTs as devices. The phaseout policy described in the NPRM, and this preamble, is a general statement of policy and therefore, it is exempt from the rulemaking procedures of the APA. 5 U.S.C. 553(b)(3)(A). Moreover, the phaseout policy is an enforcement policy, and the FD&C Act's enforcement provisions commit broad discretion to FDA to decide how and when they should be exercised. *See Heckler v. Chaney*, 470 U.S. 821, 835 (1985). In any event, such an argument is misplaced given that FDA is in fact engaging in notice-and-comment rulemaking here.

To the extent the comment is instead suggesting that FDA's characterization means that the Agency is underestimating the costs of the phaseout, we also disagree. The economic analyses in the proposed and final rules do not assume zero costs to laboratories because FDA is

not changing any legal requirements. Rather, these analyses account for all of the costs associated with changes in FDA's enforcement approach.

(Comment 113) One comment stated that two sources--an overview of Federal law related to IVDs and clinical laboratories appearing in *Clinical Chemistry*, and a white paper written on behalf of ACLA--provide a good alternative to FDA's position.

(Response 113) It is not clear if this comment was saying that these sources provide an alternative policy FDA should consider, or if the comment was saying that these papers undermine FDA's legal position. In any event, to the extent those sources make significant arguments that have been advanced by other comments submitted to the docket for this rulemaking, those arguments have been addressed. In particular, the express purpose of the referenced journal article is "to provide a legislative and regulatory history of IVDs to foster a foundational basis for future LDT discussions," and FDA addresses comments it received regarding the history of its statements on LDTs elsewhere in this preamble. The argument that LDTs are not devices and are therefore outside FDA's jurisdiction, which is advanced in the white paper written on behalf of ACLA, has likewise been addressed elsewhere in this preamble.

F. Phaseout Policy

1. General Comments on the Phaseout Policy

(Comment 114) Some comments stated that FDA's approach to phasing out the general enforcement discretion approach for LDTs is too broad and does not appropriately account for differences in the types of IVDs offered as LDTs. Some comments stated that FDA should utilize a risk-based approach in its oversight of IVDs offered as LDTs.

(Response 114) FDA does not agree with these comments. FDA has crafted a tailored phaseout policy intended to better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance. Notably, the phaseout policy includes several new, targeted enforcement discretion policies, based in part on comments submitted on the

NPRM regarding whether and how FDA should phase out the general enforcement discretion approach for more than a dozen specific types of tests (see section VI.L). FDA's reasons for adopting these policies are discussed further in section V.B. For other categories of IVDs, for the reasons discussed throughout this preamble, including responses to comments in sections L and F, FDA is not adopting enforcement discretion policies.

(Comment 115) Some comments suggested that FDA's phaseout of the general enforcement discretion approach should only apply to "commercial" manufacturers and for-profit laboratories, and that FDA should establish a separate framework for oversight of LDTs that are offered in laboratories that work closely with treating physicians and are directly integrated into patient care. One comment suggested that FDA continue its enforcement discretion approach for tests that are designed and overseen by physicians and laboratories for the care of their patients in consultation with their clinical providers.

(Response 115) FDA disagrees that the Agency should phase out the general enforcement discretion approach only for conventional manufacturers and for-profit laboratories. The need for greater FDA oversight to better assure the safety and effectiveness of IVDs offered as LDTs applies to IVDs offered as LDTs by non-profit laboratories as well as other types of laboratories.

Regarding the comments about LDTs manufactured by laboratories that work closely with treating physicians or that are directly integrated into patient care, we note that FDA is adopting an enforcement discretion policy for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. As discussed in section V.B.3, FDA has determined that an enforcement discretion policy for premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for such LDTs is appropriate given the likelihood that laboratories would stop manufacturing unmet need LDTs under the proposed phaseout policy (given the limited market for such LDTs and perceived costs of compliance with

premarket review and QS requirements), the risk mitigations present in these circumstances, and the lack of available FDA-authorized IVDs to meet the patient's need.

(Comment 116) Several comments suggested alternatives to the phaseout policy, including combining a quality framework like ISO 9001 with a risk-based self-regulation model; utilizing a targeted program focusing on areas of concern by providing tools to qualify both LDTs and other IVDs for specific indications; updating the CLIA regulations or otherwise tightening the regulation of laboratories and standardizing best practices; “leveraging” existing quality assurance programs and programmatic guardrails for lower risk tests; “exempting” tests that have been reviewed and approved by NYS CLEP and providing for other “categorical exemptions”; exercising enforcement discretion for LDTs developed and offered locally in small volumes; creating a framework for LDT manufacturers to make their validation studies public (which FDA could then utilize for risk-based enforcement); incorporating principles from the proposed VALID Act; establishing national accuracy laboratories or partnering with existing organizations to serve as independent entities dedicated to evaluating and verifying the performance of diagnostic tests; or establishing regional market zones for LDTs (by state or locality) to facilitate conversations between laboratories and clinicians.

(Response 116) Many of the suggestions provided in these comments are outside of FDA's authority to implement. For example, FDA does not have the statutory authority to implement specific provisions of the VALID Act bill (e.g., technology certification), as the bill was never enacted. Similarly, regarding the comments about CLIA, FDA is not the agency in charge of administering that statute. Other suggestions may fall outside of FDA's authority and also lack sufficient clarity, such as suggestions that FDA establish national accuracy laboratories or regional market zones for LDTs. With respect to making validation studies public, adopting a risk-based self-regulation model, or utilizing a targeted program focusing on areas of concern by providing tools to qualify LDTs and other IVDs for specific indications, FDA disagrees that these measures reduce the public health need for additional FDA oversight of IVDs offered as

LDTs. These measures would not include critical aspects of FDA’s oversight (such as requirements for premarket review, QS, registration and listing or centralized adverse event reporting), would not provide for oversight by independent experts, and would not address the risks associated with IVDs for indications that do not fall within specific “areas of concern.”

Likewise, with respect to standardizing best practices or “leveraging” existing quality assurance programs and programmatic guardrails for lower risk tests, FDA disagrees that such mechanisms mitigate the need to phase out the general enforcement discretion approach for LDTs, as explained in sections VI.C.1 and VI.C.3. FDA also disagrees that an enforcement discretion policy for LDTs that are developed and offered locally in small volumes would be appropriate, as FDA has concerns that there would not be sufficient risk mitigations in such circumstances.

With respect to the comment about LDTs that have been reviewed and approved by NYS CLEP, we agree that an enforcement discretion policy for LDTs approved by NYS CLEP is appropriate, as explained in section V.B.2.

(Comment 117) FDA received a comment from DoD stating that FDA should continue the general enforcement discretion approach for LDTs used within DoD. Specifically, DoD explained that its “use of LDTs is based on unique, military-relevant scenarios not encountered within the civilian or commercial sectors, therefore, there is no commercial market or incentive for private development of such tests. For example, DoD, on behalf of the United States, is a party to international agreements that require deployed service members to test negative for certain infectious diseases prior to deployment... In addition, with DoD personnel and US citizens deployed worldwide, to sometimes austere environments, isolated cases of rare infectious diseases require LDT testing without the benefit of a declared emergency and access to the FDA EUA pathway.” DoD further explained that “Department of Defense Instruction (DoDI) 6640.02, establishes the Center for Clinical Laboratory Medicine (CCLM),” and that

“DoD would work with FDA to establish standards within the DoD unique internal program to achieve stated objectives that provide for clinical validity of LDTs.”

(Response 117) For the reasons discussed further in section V.B.1, FDA intends to exercise enforcement discretion and generally not enforce applicable requirements for LDTs manufactured and performed within DoD.

(Comment 118) FDA received several comments stating that FDA should continue the general enforcement discretion approach for LDTs manufactured and performed within VHA. Two comments suggested that FDA should not continue the general enforcement discretion approach for LDTs manufactured and performed within VHA because VHA’s program is not in alignment with FDA regulation (though one of these comments supported “leveraging” outside programs “in principle”). One comment asked whether continuation of the general enforcement discretion approach for LDTs manufactured and performed within VHA would extend beyond the administrative boundaries for which VHA’s program is currently limited.

(Response 118) FDA agrees with those comments that stated that FDA should have an enforcement discretion policy for LDTs manufactured and performed within VHA. For the reasons discussed in more detail in section V.B.1, FDA intends to exercise enforcement discretion and generally not enforce applicable requirements for LDTs manufactured and performed within VHA. With respect to concerns that VHA’s program is not currently in alignment with FDA regulation, FDA notes that VHA is taking steps in consultation with FDA to track all LDTs in its system and to ensure both the analytical and clinical validity of its LDTs, the quality manufacturing of its LDTs, and the central reporting of adverse events. As noted in section V.B.1, this enforcement discretion policy applies only to LDTs used for patients that are being tested and treated within the VHA program.

(Comment 119) One comment requested that FDA provide more clarity “for LDTs where the testing laboratory does [not] manufacture any parts of the tests.”

(Response 119) As discussed in the responses to comments in section VI.D.2, a test system is a device regardless of who manufactures it or its components, and is subject to applicable requirements in the FD&C Act and implementing regulations.

2. Continued Enforcement Discretion for Currently Marketed IVDs Offered as LDTs

(Comment 120) We received many comments urging FDA to maintain the general enforcement discretion approach with respect to applicable requirements (or a subset thereof) for currently marketed IVDs offered as LDTs. Many of these comments stated that continuing the general enforcement discretion approach for such IVDs is critical to prevent patients from losing access to certain valuable tests. Several of these comments also suggested that “the for-profit sector” would not step in to fill the gaps left by market withdrawal of IVDs for which there are “small markets.” Other comments stated that it is important to continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs to sustain successful patient outcomes. Some of these comments asserted that certain IVDs offered as LDTs have become the standard of care, and some stated that losing access to certain currently marketed IVDs offered as LDTs could require the use of inferior tests. Other comments argued that currently marketed IVDs offered as LDTs that are already integrated into clinical practice pose a minimal safety risk, as many have been used effectively for years without causing harm, and/or already satisfy accreditation criteria from recognized accreditation bodies. A few comments noted that some currently marketed IVDs offered as LDTs address unmet needs for which authorized tests do not exist, or for which authorized tests do not reflect the latest advances in science, suggesting that FDA ought to continue the general enforcement discretion approach to currently marketed IVDs offered as LDTs to avoid disrupting access to these IVDs.

Some comments asserted that not continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs would negatively impact specific populations, such as children, individuals with rare diseases, individuals requiring transplantation, and oncology patients. Comments stated that certain IVDs offered as LDTs for use in children are the gold

standard, and that essential, time-sensitive testing conducted by pediatric laboratories is performed most effectively if done rapidly in house.

Comments also stated that laboratories have substantial reliance interests in currently marketed IVDs offered as LDTs, having made business decisions against the backdrop of FDA's decades-long general enforcement discretion approach. These comments asserted that discontinuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs would not recognize these reliance interests. Other comments stated that patients have reliance interests in IVDs offered as LDTs that would be "suddenly rendered uneconomical," and that these reliance interests would not be recognized if FDA did not continue the general enforcement discretion approach for these IVDs.

In addition, many comments stated that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs to reduce the demands on FDA resources. Some comments described concerns based on experiences with EUA requests during the COVID-19 pandemic. Other comments highlighted the estimated number of premarket submissions in FDA's PRIA. The comments generally argued that continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs would help to ensure that FDA has sufficient resources to conduct timely reviews of other submissions and would avoid bottlenecks such as those that have been observed in other jurisdictions. Many comments also stated that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs to reduce the burden on laboratories. These comments generally emphasized the many submissions that laboratories might reasonably need to prepare within the applicable timeframe and stated that user fee payments would be too high. One comment added that although it is "critical" that FDA not enforce against IVDs offered as LDTs for lacking premarket authorization while a submission for that IVD is reviewed, such an approach does not mitigate the need to continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs, as it does not address the burden of preparing and

reviewing submissions. Several comments argued that continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs would help to reduce the need for laboratories to divert resources from innovation to support the compliance of currently marketed IVDs.

Other comments supported continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs because, according to these comments, validation studies may otherwise need to be repeated that would be impossible or unethical to repeat; financial costs to patients and legal costs to providers would otherwise increase; and because FDA previously expressed support for continuing the general enforcement discretion approach with respect to certain requirements for currently marketed LDTs (see Ref. 57).

(Response 120) As discussed in section V.B.3, FDA generally intends to exercise enforcement discretion with respect to premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3. The scope of and basis for this policy are set forth in section V.B.3.

Although FDA is adopting this policy, it does not necessarily agree with all of the statements made in comments supporting an enforcement discretion policy for currently marketed IVDs offered as LDTs. For example, we do not agree that currently marketed IVDs offered as LDTs that are already integrated into clinical practice pose a minimal safety risk, or that meeting accreditation criteria from recognized accreditation bodies eliminates the need for FDA oversight for the reasons discussed in response to comments under section VI.C.3. Rather, FDA is including this enforcement discretion policy in consideration of other factors, as discussed in section V.B.3.

(Comment 121) In contrast, FDA received several comments that did not support continuing the general enforcement discretion approach for currently marketed IVDs offered as

LDTs, or favored significantly limiting the number of IVDs that would fall under the continued enforcement discretion approach. Comments expressed concern that continuing the general enforcement discretion approach would be inappropriate given the evidence of “low-performing” IVDs offered as LDTs currently on the market. Other comments expressed concern that continuing the general enforcement discretion approach for these IVDs may cause certain IVDs to appear to be FDA-authorized even when they have not been authorized, and that laboratories might extensively modify their IVDs and avoid compliance with applicable requirements for these modified IVDs. One comment opposed continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs “particularly for commercial testing”; other comments asserted that continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs would inappropriately focus on where or by whom an IVD was developed, rather than the risk of the IVD, and stated that it would be more “effective” to narrowly tailor any continued enforcement discretion approach to LDTs that are not associated with safety or effectiveness concerns.

Finally, a few comments did not completely oppose or support an enforcement discretion policy for currently marketed IVDs offered as LDTs. For example, some comments stated that continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs would not be sufficient to address other problems with the phaseout policy, including laboratories’ inability to make “necessary” updates to their IVDs or respond to changing public health needs. Other comments suggested that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs only if FDA does not establish other more specific policies.

(Response 121) FDA has also carefully considered the comments recommending against the inclusion of a policy for currently marketed IVDs offered as LDTs. FDA agrees that there is evidence in the record demonstrating that there are problematic IVDs offered as LDTs that are currently marketed. However, FDA remains concerned about the potential harms from loss of

access to beneficial IVDs offered as LDTs on which patients are currently relying. Therefore, FDA has determined that it best serves the public health to adopt a more targeted expectation of compliance for currently marketed IVDs offered as LDTs. As noted in section V.B.3, FDA anticipates that adverse event reporting, information contained in labeling, and other sources of information (including public reports and any relevant information from the healthcare community) will help the Agency identify problematic currently marketed IVDs offered as LDTs for which enforcement or other action is warranted. FDA intends to take such action as appropriate. In this way, FDA's policy is consistent with one comment's recommendation to "narrowly tailor" the approach, taking into account "safety or effectiveness concerns" with currently marketed IVDs offered as LDTs.

One comment argued against an enforcement discretion policy for currently marketed IVDs offered as LDTs because such a policy may cause these IVDs to appear to be FDA-authorized even when they have not been authorized. FDA disagrees. Devices marketed under an enforcement discretion policy are not lawfully on the market, and should not be understood to share the same legal status as lawfully marketed devices. Statements in labeling that an unauthorized IVD is authorized by FDA, or suggestions along those lines, would misbrand the IVD under section 502(a) of the FD&C Act. We believe that enforcing this and other labeling requirements would help to address the concern raised in the comment.

Another comment stated that a policy for currently marketed IVDs offered as LDTs could be problematic because laboratories might extensively modify their IVDs and avoid compliance with applicable requirements for these modified IVDs. As described in section V.B.3, the enforcement discretion policy for currently marketed IVDs offered as LDTs is limited to instances in which the IVD is unmodified, or the IVD is modified only in certain limited ways. If an IVD is modified in more significant ways, FDA intends to phase out the general enforcement discretion approach with respect to all requirements for that IVD. We believe this policy addresses the concern raised in the comment.

FDA also acknowledges that under this policy, its compliance expectations for currently marketed IVDs will differ depending on whether the IVD is offered by a laboratory or a conventional manufacturer. However, in light of the reliance interests engendered by FDA's longstanding enforcement discretion approach for LDTs, as described in the comments, we have determined that this differential treatment is warranted. Over time, FDA anticipates that IVDs will evolve and eventually come into compliance with FDA requirements, such that IVDs manufactured by laboratories will generally fall under the same enforcement approach as other IVDs. In the FRIA, we estimate that 50 percent of currently marketed IVDs offered as LDTs will be submitted to FDA for premarket review (e.g., due to significant modifications as described in section V.B.3) over the course of 20 years.

To the extent that some comments indicated that this policy is appropriate to address unmet needs, FDA notes that discussion regarding tests for unmet needs can be found in section VI.L.5 of this preamble. Also, discussion regarding potential impacts on specific patient populations can be found in section VI.K.

(Comment 122) Some comments stated that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs only with respect to premarket review requirements. Other comments stated that the enforcement discretion policy for currently marketed IVDs offered as LDTs should be for premarket review requirements and all QS requirements, though one comment recommended that the policy apply for premarket review requirements and QS requirements related only to design controls. Most comments that supported continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs were focused on premarket review and QS requirements, and not all requirements. However, a few comments suggested that the general enforcement discretion approach continue for all applicable requirements. Several comments stated that MDR requirements and registration and listing requirements should be enforced, as these requirements would provide important information about the testing landscape. One comment suggested that

while registration and listing requirements should still be enforced, currently marketed IVDs offered as LDTs from hospital and health system laboratories should not be “subject to overly burdensome requirements” for registration and listing; for example, FDA should limit the amount of listing information expected for those IVDs. Another comment expressed concern that enforcing registration requirements for laboratories manufacturing currently marketed IVDs offered as LDTs could “be prohibitive” for some laboratories. One comment stated that laboratories that have a system for reporting errors, and that are integrated into a health system, generally should not be expected to comply with adverse event reporting requirements (it is not clear if this comment was intended to be specific to currently marketed IVDs offered as LDTs, but the organization of the comment suggests that it was).

(Response 122) FDA agrees that it should phase out the general enforcement discretion approach for all applicable requirements other than premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3. This policy reflects a careful balancing of relevant considerations, as discussed in section V.B.3 and in response to comment 120.

We note that the costs of compliance with premarket review and QS requirements are a significant portion of the overall anticipated costs to laboratories of complying with applicable FDA requirements (see section II.F.5 of the FRIA (Ref. 10)). Of the total estimated discounted costs to industry of \$1.17 billion, the average estimated costs of compliance with stages 1 and 2 are approximately \$9,522 per test (\$74,783 per laboratory) and the average estimated costs of compliance with premarket review and QS requirements are approximately \$3.02 million per test (\$1.26 million per laboratory). As a result, FDA has concluded that focusing the policy on these requirements should address the concerns about widespread market exit. As noted above, FDA expects compliance with requirements under part 820, subpart M (Records), including

compliance with QS requirements regarding complaint files. This will facilitate compliance with MDR requirements, because complaints will then be reviewed to determine whether they are MDR reportable. FDA intends to review complaint files during an inspection to assess compliance with relevant QS and MDR requirements.

FDA intends to phase out the general enforcement discretion approach for requirements other than premarket review and most QS requirements in order to gather information about, and take appropriate action with respect to, currently marketed IVDs offered as LDTs. FDA has determined that the public-health value of compliance with these requirements outweighs any concerns raised in the comments. In particular, based on the information in the FRIA, we do not believe compliance with these other requirements will cause laboratories to stop offering IVDs on which patients currently rely. In addition, FDA disagrees that laboratories that have a system for reporting errors and are integrated into a health system should not be expected to submit MDRs to FDA for currently marketed IVDs offered as LDTs (or for other IVDs). Centralized reporting of adverse events enables FDA to track trends across devices of the same type, identify when issues arise, and work with stakeholders to address those issues. For example, as discussed in section III.B, FDA was able to identify a biotin interference issue through analysis of MDRs indicating inaccurate test results. Biotin is commonly used in immunoassays as part of the test technology. Therefore, when high dose biotin supplements (advertised for hair and nail growth) became more popular, FDA began seeing inaccurate test results associated with these immunoassays. FDA's investigation revealed that this biotin interference affected dozens of tests across multiple manufacturers. This led to a multiyear interactive effort to have manufacturers address the issue through assay re-design. Notably, it is likely many RUO immunoassay kits still use biotin that would be affected in the same manner by these supplements, and it is likely that those manufacturers have not addressed this issue. These RUO kits currently may be offered as LDTs by laboratories. Enforcement of adverse event reporting and registration and listing requirements for these currently marketed IVDs offered as LDTs will help FDA identify where

this problem may still be occurring, and where other problems are occurring, so that these problems can be addressed.

For additional discussion of FDA's phaseout of the general enforcement discretion approach with respect to registration and listing requirements and adverse event reporting requirements, see sections VI.F.7 and VI.F.8 of this preamble.

(Comment 123) Some comments recommended that FDA continue the general enforcement discretion approach with respect to certain requirements for currently marketed IVDs offered as LDTs that were first marketed prior to publication of the *proposed rule* whereas other comments recommended such an approach should be for currently marketed IVDs offered as LDTs that were first marketed prior to publication of the *final rule*, or prior to the effective date of the final rule. One comment suggested that FDA continue the general enforcement discretion approach with respect to certain requirements for IVDs offered as LDTs that are marketed within the next 4 years. Another comment suggested that FDA continue the general enforcement discretion approach with respect to certain requirements for IVDs offered as LDTs that have been marketed for at least 3 years prior to March 31, 2024, and that are supported by post-market data that provide evidence of device performance and safety.

(Response 123) As discussed in section V.B.3, FDA has keyed the policy for currently marketed IVDs offered as LDTs to the date of this final rule, rather than the proposed rule. FDA chose this date because patients and the healthcare community may have begun relying on these IVDs during the period between publication of the proposed and final rule. Patients and the healthcare community also may have begun relying on IVDs offered as LDTs that were marketed before March 31, 2024 (and that are currently marketed), even if such IVDs were marketed for fewer than 3 years prior to that date. By contrast, for IVDs offered as LDTs that are introduced after the date of issuance of the final rule (e.g., within the next 4 years), the decisions of laboratories, patients, and the healthcare community would be made taking into account the expectation of compliance and not presuming the same reliance. Furthermore, given the timing

of the phaseout policy and the enforcement discretion policy for currently marketed IVDs offered as LDTs, FDA anticipates that laboratories should be able to comply with premarket review and QS requirements by the time of stages 3-5 for IVDs offered as LDTs that are marketed after the publication date for this final rule.

(Comment 124) Some comments stated that if FDA were to continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs, the approach should apply to such IVDs even if the IVDs are modified. One comment argued that modifications are essential to the evolution of patient care. However, most comments suggested that a general enforcement discretion approach for currently marketed IVDs offered as LDTs should not apply to such IVDs after certain types of modifications are made. These comments generally proposed that an enforcement discretion approach should not apply to currently marketed IVDs offered as LDTs after any changes to intended use, indications for use, and/or performance. One comment proposed that a general enforcement discretion approach for currently marketed IVDs offered as LDTs apply to those IVDs if modified in ways that do not significantly change the indications for use, except for some changes to specimen type; that do not significantly change performance claims or significantly and adversely change performance; or that do not adversely change the safety for individuals who come in contact with the IVD. Another comment proposed that a general enforcement discretion approach for currently marketed IVDs offered as LDTs apply to those IVDs if modified in ways that do not alter methodology, intended use, or performance, arguing that this would allow laboratories to continue innovating and address emerging scientific understanding and patient needs. One comment suggested that a laboratory manufacturing a currently marketed IVD offered as an LDT should not be expected to submit a premarket submission for modifications that are properly validated by the laboratory, stating that the utility of currently marketed IVDs offered as LDTs will diminish over time if overly restrictive constraints are placed on modifications.

Some comments emphasized that FDA should provide clear guidance regarding what IVDs offered as LDTs would fall within an enforcement discretion policy for currently marketed IVDs offered as LDTs, including regarding the types of modifications that would be included within that policy.

(Response 124) FDA agrees that the policy should apply to currently marketed IVDs offered as LDTs when they are modified in certain limited ways.

As discussed in response to comment 261, FDA's regulations require premarket review when an authorized device is modified in a way that affects safety and effectiveness (for a device approved under a PMA, with certain exceptions) or in a way that could significantly affect safety and effectiveness (for a device subject to 510(k)). Following a similar approach in this context, and as discussed in more detail in section V.B.3, FDA generally intends to exercise enforcement discretion with respect to premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in relatively minor ways. This policy is intended to preserve access to beneficial IVDs on which patients and the healthcare community currently rely, including versions of that IVD with minor changes. However, once the IVD is changed in certain, more significant ways that could affect its basic safety and effectiveness profile, the policy no longer applies. Thus, FDA generally expects compliance with premarket review and QS requirements for currently marketed IVDs offered as LDTs when a laboratory's modifications (individually or in aggregate) change the indications for use of the IVD, alter the operating principle of the IVD (e.g., changes in critical reaction components), include significantly different technology (e.g., addition of artificial intelligence/machine learning to the test algorithm, a change from targeted sequencing to whole genome sequencing, a change from immunoassay to mass spectrometry, or a change from manual to automated procedures), or adversely change the performance or safety specifications of the IVD. These modifications are generally consistent with the types of

modifications that comments suggested should not fall within an enforcement discretion policy for currently marketed IVDs offered as LDTs. Although some comments suggested that the policy should encompass all modifications to currently marketed IVDs offered as LDTs, FDA does not agree that this type of broad policy would appropriately serve the public health purpose of this rulemaking.

(Comment 125) FDA received several comments that proposed specific circumstances under which FDA might continue the general enforcement discretion approach with respect to certain requirements for currently marketed IVDs offered as LDTs. Some comments stated that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs that are “standard of care” or otherwise well established in the literature; that are widely adopted and incorporated into professional society treatment guidelines; that are developed and offered locally; that are “already in known published medical classifications”; that have “proven performance serving a vital part of healthcare”; for which there are long-term safety and effectiveness records, or evidence of analytical and clinical validity and clinical utility; and/or that are not high risk. One comment stated that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs that, among other types of IVDs, have been modified from FDA-authorized devices with respect to certain parameters (in some cases supported by further studies), or that have been developed by a government or reference laboratory in good standing under CLIA. Another comment stated that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs that have “demonstrated concordance with FDA-approved companion diagnostics.” Yet another comment suggested FDA continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs that are used “without issues” within public health laboratories.

(Response 125) As discussed in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements

(except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs as long as they are not modified following issuance of this final rule, or are modified but only as described in section V.B.3. FDA is adopting this policy based on careful consideration of the comments and the economic projections in the proposed rule, and after weighing competing interests at issue here, as described in section V.B.3.

FDA does not believe that the alternative policies suggested by stakeholders in the comments summarized above would strike the appropriate balance between these competing interests. For example, policies only for some currently marketed IVDs offered as LDTs would not adequately address concerns that patients and providers may have reasonably made choices based on an assumption of continued access to certain IVDs that may not be offered as a result of the phaseout policy, and specifically if FDA were to expect compliance with premarket review and most QS requirements. These include policies that are limited only to currently marketed IVDs offered as LDTs that are offered by certain types of laboratories; that have been modified from FDA-authorized devices with respect to certain parameters; or that have “demonstrated concordance” with certain FDA-authorized IVDs. For discussion of FDA’s determination not to phase out the general enforcement discretion approach only for IVDs that are high-risk, see section VI.L.4.

In addition, many of the policies suggested in comments would be difficult to administer or would not set clear expectations for stakeholders. For example, a policy for currently marketed IVDs offered as LDTs that are “standard of care,” or otherwise well established in the literature, may not be clear for stakeholders. There may be different opinions regarding what IVDs offered as LDTs are standard of care or well established in the literature, and defining those terms in a manner that could be consistently and predictably applied may not be feasible. Similar concerns apply to policies for currently marketed IVDs offered as LDTs that are “widely adopted” and incorporated into professional society treatment guidelines; that are developed and offered locally; that are “already in known published medical classifications”; that have “proven

performance serving a vital part of healthcare”; or for which there are “long-term” safety and effectiveness records or evidence.

(Comment 126) One comment suggested that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs upon request.

(Response 126) FDA believes that continuing the general enforcement discretion approach for currently marketed IVDs offered as LDTs only upon request would not set clear expectations for stakeholders and would be administratively difficult to implement.

(Comment 127) Some comments suggested that FDA should continue the general enforcement discretion approach only for specific types of currently marketed IVDs offered as LDTs (depending on the impact to different patient populations), or for currently marketed IVDs offered as LDTs that are intended for unmet needs or for rare diseases or indications or where there is a strong public health need for the IVD, linked to ensuring access to accurate and reliable IVDs and facilitating a smooth transition for FDA oversight. Other comments suggested that FDA should continue the general enforcement discretion approach for currently marketed IVDs offered as LDTs that have been approved by other regulatory bodies, Federal agencies, or certain other programs or entities, in some cases only when the IVD has been offered for a minimum period of time without any reported adverse consequences, or when there is no credible information establishing a lack of validity, false or misleading claims, or a probability that the IVD will cause serious adverse health consequences.

(Response 127) Regarding the comments about a policy for LDTs for unmet needs, we note that FDA is adopting a policy for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. Moreover, regarding the comment about a policy for currently marketed IVDs offered as LDTs that have been approved by other regulatory bodies, FDA is adopting an enforcement policy for LDTs that are approved by NYS CLEP. In addition, FDA is adopting an

enforcement policy for LDTs offered within DOD's and VHA's oversight programs. For further discussion of these aspects of the phaseout policy, see sections V.B.2 and V.B.3.

Further, similar to our response to comment 125, FDA is concerned that a policy for IVDs offered as LDTs for a certain period of time without issues or that meet a strong public health need would be difficult to administer and would not set clear expectations for stakeholders as there may be different opinions regarding what IVDs offered as LDTs meet these, or any similar, descriptions.

(Comment 128) One comment suggested that IVDs falling within the policy for currently marketed IVDs offered as LDTs be labeled with a statement disclosing they have not been authorized by FDA.

(Response 128) The Agency does not believe such a policy would be appropriate at this time. FDA expects that most IVDs offered as LDTs subject to premarket review requirements will lack required FDA authorization for several years following issuance of this final rule. Under the phaseout policy described in section V.C, the phaseout of enforcement discretion with respect to premarket review requirements will begin 3.5 years (for high-risk IVDs offered as LDTs) to 4 years (for other IVDs offered as LDTs subject to premarket review) from the date of issuance of this rule. After a complete premarket submission for an IVD offered as an LDT has been submitted within these timeframes, FDA generally does not intend to enforce against the IVD for lacking FDA authorization during the pendency of FDA review. Thus, in the context of the phaseout policy, including such a statement in the labeling for currently marketed IVDs offered as LDTs could create confusion by suggesting a distinction that does not exist between those IVDs that are in the process of coming into compliance with premarket review requirements and those that are not. If our experience with implementation of the phaseout policy indicates that a different approach to inclusion of such a statement is warranted as more IVDs offered as LDTs come into compliance with premarket review requirements, FDA would

consider making appropriate policy changes in accordance with good guidance practices (§ 10.115).

To the extent anyone may seek information regarding whether a particular test has been authorized by FDA, such information can be found in FDA databases. For example, tests that have been approved, cleared, or had a De Novo request granted by FDA appear in the PMA, 510(k), and De Novo databases, respectively (Refs. 165,166, and 224). We expect that most tests, including those offered without premarket review (e.g., because they are exempt from premarket notification or fall within an enforcement discretion policy), will be listed in the Registration & Listing database in Stage 2 of the phaseout policy. Where a test has been approved, cleared, or had a De Novo request granted, this database will also indicate the applicable premarket submission number.

(Comment 129) Several comments stated that if FDA continues the general enforcement discretion approach for currently marketed IVDs offered as LDTs, “FDA should retain the authority to require additional regulatory evaluation where there is a need to do so.”

(Response 129) We agree that regardless of the policy for currently marketed IVDs offered as LDTs or any other enforcement discretion policy included in the phaseout policy, FDA retains the authority to enforce any applicable requirements and pursue enforcement action at any time against violative IVDs. Moreover, we note that as discussed above, suggestions that an unauthorized IVD is authorized by FDA would misbrand the IVD under section 502(a) of the FD&C Act.

(Comment 130) One comment stated that if FDA continues the general enforcement discretion approach with respect to premarket review requirements for currently marketed IVDs offered as LDTs, FDA should allow submission of predetermined change control plans (PCCPs) for currently marketed IVDs offered as LDTs without additional submissions, to allow for “controlled, pre-approved test modifications.”

(Response 130) Under section 515C of the FD&C Act, FDA may approve or clear a PCCP that is submitted in a PMA, supplemental PMA, or 510(k) notification. A PMA supplement or new 510(k) is not required for a modification to a device that would otherwise be required if the change is consistent with a PCCP previously approved or cleared by FDA. As set forth in section 515C, a PCCP can only be approved under section 515 of the FD&C Act or cleared under section 510(k) of the FD&C Act. For additional discussion of PCCPs, see our response to comments in section VI.M. FDA notes, however, that the policy for currently marketed IVDs offered as LDTs does encompass modifications to such IVDs when the modification involves a minor change, as discussed in section V.B.3.

(Comment 131) One comment stated that if FDA continues the general enforcement discretion approach with respect to premarket review for currently marketed IVDs offered as LDTs, those IVDs should be able to serve as predicate devices if laboratories subsequently modify the IVDs and submit 510(k)s for those modified IVDs.

(Response 131) Under section 513(i) of the FD&C Act and part 807, subpart E of FDA's regulations, a predicate device (for purposes of FDA clearance of a 510(k) submission) is a "legally marketed" device. FDA's regulations establish that "[a] legally marketed device to which a new device may be compared for a determination regarding substantial equivalence is a device that was legally marketed prior to May 28, 1976, or a device which has been reclassified from class III to class II or I (the predicate), or a device which has been found to be substantially equivalent through the 510(k) premarket notification process" (§ 807.92(a)(3)). An IVD that does not satisfy this definition, including a currently marketed IVD offered as an LDT that requires but does not have premarket authorization, would not be eligible to serve as a predicate device.

3. Small Laboratories

(Comment 132) FDA received comments stating that FDA should structure the phaseout of the general enforcement discretion approach for LDTs differently for small laboratories, as

such laboratories will be more heavily affected by the phaseout. Some comments stated that small laboratories often develop and validate innovative assays or modify existing tests to serve specific populations, which can be costly. One comment stated that compliance with FDA requirements is a large and costly undertaking which only the largest corporations would be able to do, and that providing a longer phaseout period for LDTs offered by laboratories with annual receipts below \$150,000 would still not be sufficient for small laboratories to come into compliance. Another comment recommended FDA have a ten-year phaseout for IVDs offered as LDTs by small laboratories and define small laboratory using the definition proffered by the Small Business Administration.

(Response 132) FDA recognizes that some small laboratories may be disproportionately impacted by the phaseout of the general enforcement discretion approach for LDTs from a financial perspective, as discussed in section III of the FRIA (Ref. 10). However, the final phaseout policy includes several enforcement discretion policies that we anticipate will reduce costs for laboratories compared to what was estimated in the PRIA, including for small laboratories (see section V.B). As shown in table 48 of the FRIA, annualized costs per entity under the final phaseout policy (taking into account the enforcement discretion policies described in section V.B of this preamble) are estimated to be about 6 percent of receipts for small laboratories (for further discussion see section III.B of the FRIA).

In light of the anticipated costs to small laboratories associated with the final phaseout policy, and the additional considerations discussed in comment 133, FDA does not believe it is appropriate to adopt an enforcement discretion policy for small laboratories' IVDs offered as LDTs or to extend the phaseout policy to 10 years for such laboratories.

We understand that small laboratories may manufacture innovative LDTs or modify existing IVDs to serve specific populations. For small laboratories that are integrated within a healthcare system, certain of their LDTs may fall within the unmet need policy, discussed further in section V.B.3. Small laboratories that are not integrated within a healthcare system would fall

outside that policy including because there are not the same risk mitigations present in such situations (see further discussion in section V.B.3).

(Comment 133) Some comments expressed opposition to FDA having a different enforcement approach for small laboratories and advocated for uniform treatment of all laboratories. Several comments stated that the size of the laboratory should not determine how certain tests are treated, noting that this type of approach would not be acceptable if applied to non-laboratory manufacturers and would be inconsistent with a risk-based approach. Some comments also stated that the harm to patients from faulty tests does not change based on the size of the laboratory and remarked that a longer phaseout period may allow for continued patient harm due to problematic IVDs offered as LDTs. One comment stated that small laboratories with fewer LDTs may actually be better able to comply with FDA requirements than larger laboratories and AMCs with hundreds of LDTs and suggested that any extension of the implementation period be based on the number of LDTs that a laboratory performs rather than annual receipts. Another comment noted that some small laboratories are associated with large hospital systems, which may prevent them from qualifying for any exemption or special considerations afforded to small laboratories.

(Response 133) FDA agrees that the phaseout of the enforcement discretion approach for LDTs should not be determined by laboratory size, as a different enforcement approach for small laboratories would not be in the best interest of the public health where we are unaware of any evidence supporting that IVDs manufactured by small laboratories are any less likely to be problematic than IVDs manufactured by large laboratories. We note that this approach is generally consistent with FDA's device regulations and policies, which generally do not distinguish small businesses from other regulated entities (though small businesses are eligible for a waiver or reduction of certain MDUFA user fees as a matter of statute). FDA also anticipates that features of the final phaseout policy will address many of the concerns of small

laboratories as discussed in response to comment 132 above. FDA's phaseout policy is described in detail in section V.

4. Academic Medical Centers

(Comment 134) We received many comments responding to the questions posed in the NPRM (88 FR 68006 at 68023-24) about whether FDA should continue the general enforcement discretion approach with respect to any requirements for tests manufactured by AMC laboratories. We received a wide variety of comments spanning all sides of the issue: comments in favor of continuing an enforcement discretion approach for tests manufactured by AMC laboratories, comments recommending that FDA also continue an enforcement discretion approach for tests manufactured by other similarly situated laboratories, comments that suggested limitations to an enforcement discretion approach for tests manufactured by AMC laboratories, and comments against the continuation of an enforcement discretion approach for tests manufactured by AMC laboratories. We also received various suggestions on possible ways to define an AMC.

(Response 134) As stated in section V.B, FDA is adopting several enforcement discretion policies that may apply to certain IVDs manufactured by AMC laboratories. First, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs as long as they are not modified following issuance of this rule, or are modified but only in certain limited ways as described in section V.B.3. This includes IVDs currently offered as LDTs by AMC laboratories. Second, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP, as described in section V.B.2. We anticipate that some LDTs manufactured by AMC laboratories may fall within this policy. Third, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs

manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. We anticipate many LDTs made in AMC laboratories will fall within this policy.

For the reasons set forth in section V.B and discussed in the response to comment 135, FDA does not think it is appropriate to have an enforcement discretion policy for: all LDTs manufactured by AMC laboratories; all requirements for LDTs manufactured by AMCs laboratories; or LDTs manufactured by AMC laboratories but not LDTs manufactured by other laboratories integrated within a healthcare system (as such, and because we are not adopting an enforcement policy for AMC laboratories, we have not included a definition of AMCs in the phaseout policy).

(Comment 135) Comments suggested that FDA should continue its general enforcement discretion approach with respect to tests manufactured by AMC laboratories for various reasons. Some argued that a continued enforcement discretion approach for AMCs is necessary because increased FDA oversight of their LDTs would negatively impact the public health, access, medical training, and innovation. Comments also claimed that AMC laboratories cannot afford the cost of compliance with FDA requirements as they perform tests on hospitalized patients, with no additional revenue stream or resources to cover the cost of compliance with FDA requirements. Other comments claimed that continuing an enforcement discretion approach is necessary because AMC laboratories already operate with tight budgets, are short staffed, and struggle to find qualified talent. Similar comments indicated that due to budgets, AMC laboratories may be prevented from performing FDA-authorized alternative tests where such tests require specialized capital equipment, additional training, and inventory management, whereas a continued enforcement discretion approach for LDTs made by AMC laboratories would account for consolidation of testing platforms for efficiency. Comments hypothesized that increased FDA oversight would cause AMC laboratories to limit their testing offerings, detrimentally impacting the most vulnerable populations, raising costs to patients, and hurting

access. Many comments stated that AMC laboratories manufacture and provide tests for unmet needs to provide care for the most complex adult and pediatric patients. This includes tests for rare diseases, which are low volume or do not have a “commercial” alternative. For example, a comment indicated that there are less than 20 laboratories that perform advanced immunologic testing, and all such laboratories are AMC laboratories. Comments expressed concern that patients might not otherwise have access to these and other tests. Other comments focused on the role of AMCs in training medical students, research, and innovation. Some pointed out that AMC laboratories create and develop test methods that “commercial” laboratories later adopt and use for their tests, and that AMC laboratories are nimble and able to explore and employ creative applications of new technology to enhance clinical testing. These comments expressed concern that increased FDA oversight would inhibit training and research to the detriment of the public health.

Comments also stated that the integration of AMC laboratories into patient care at the AMC provides a direct feedback loop between providers and patients that helps to mitigate the risks of the tests by providing context about the patient, their condition, and the particular purpose a test serves in this patient’s care, and thereby allowing for conversation about the interpretation of results between the physician, patient, and test manufacturer. The commenters posit that these factors allow test manufacturers to troubleshoot as needed.

(Response 135) As described in response to comment 134, FDA is adopting several enforcement discretion policies that may apply to certain IVDs manufactured by AMC laboratories, including an enforcement discretion policy for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. As discussed in section V.B.3, in the circumstances described in the unmet needs policy, FDA has greater confidence that ordering physicians will communicate any questions about LDTs or concerns regarding the safety and effectiveness of the LDT (e.g., when the patient’s symptoms point to another diagnosis; when subsequent test results

contradict the original test result) to a laboratory given the built-in communication mechanisms present. Moreover, FDA generally has greater confidence that laboratories will communicate any limitations of the LDT or other relevant information to the ordering physician given these mechanisms. We think this is particularly likely to happen in the context of LDTs for unmet needs, which are likely to be a focus of attention and communication between laboratorians and providers given the uncommon nature of the issues presented.

FDA anticipates that this and other enforcement discretion policies (described in response to comment 134) that may apply to IVDs manufactured by AMC laboratories will help to avoid the access concerns discussed in the comments. Specifically, FDA anticipates that these policies will reduce the compliance costs associated with the phaseout policy for many laboratories, including AMC laboratories, thereby addressing many of the financial concerns referenced in the comments. As described in the FRIA, the costs of compliance with premarket review and QS requirements are a significant portion of the overall anticipated costs to laboratories of complying with applicable FDA requirements (see section II.F.5 of the FRIA (Ref. 10)). Of the total estimated discounted costs to industry of \$1.17 billion, the average estimated costs of compliance with stages 1 and 2 are approximately \$9,522 per test (\$74,783 per laboratory) and the average estimated costs of compliance with premarket review and QS requirements are approximately \$3.02 million per test (\$1.26 million per laboratory). Therefore, these policies may help to avoid AMC laboratories from no longer offering currently marketed IVDs or from manufacturing LDTs for unmet needs in the future due to the perceived costs of compliance with premarket review and QS requirements, as discussed further in section V.B.3. We also anticipate these policies will help to address the other concerns raised in comments, such as regarding AMC laboratories' role in training medical students to understand tests.

As discussed in the response to comment 142, we believe that for unmet need LDTs, the risk mitigations present in laboratories integrated within healthcare systems will help to address some of the concerns raised regarding problematic IVDs offered as LDTs discussed in the

NPRM and this preamble. Notably, this policy is limited to exercising enforcement discretion for premarket review and most QS requirements (not all FDA requirements) and LDTs for unmet needs (not LDTs for which there are available FDA-authorized alternatives).

FDA believes it is important that an enforcement discretion policy for laboratories integrated within a healthcare system be limited to premarket review and QS requirements. Compliance with other applicable requirements will help provide assurances regarding safety and effectiveness and help FDA monitor for potentially poor performing LDTs that should be addressed. Moreover, we understand that compliance with premarket review and QS requirements are what is likely to lead laboratories integrated within a healthcare system to stop manufacturing LDTs for unmet needs in the future due to perceived compliance costs.

(Comment 136) Other comments pointed out features they assert mitigate the risk of tests manufactured by AMC laboratories. Comments noted that such laboratories are already regulated under/by CLIA, CAP, and other state and local accreditation bodies and that most hospital systems have mechanisms for reporting and tracking of events that have the potential for negative patient impact in order to comply with accreditation requirements. Some pointed to the not-for-profit nature of AMCs and the fact that AMCs are working to educate providers and enhance patient care--not generate profit or “commercialize” the tests they manufacture. Some claimed AMC laboratories have a demonstrated track record for developing safe and effective tests. Comments stated that AMCs were not subject to the lawsuits involving misleading information which FDA cited in the NPRM. Another posited that tests developed by AMCs do not have the problems observed in “commercial” tests.

(Response 136) FDA does not agree with comments that assert that an enforcement discretion policy is appropriate for all requirements for all LDTs manufactured and performed by AMC laboratories. FDA does not agree with the assertion that there are no problems with IVDs offered as LDTs by AMC laboratories nor does FDA agree that CLIA and other accreditations and the not-for-profit nature of AMCs are sufficient mitigations to justify such a policy. As

described in the NPRM and memorandums to file prepared by FDA that were included in the docket for this rulemaking, we are aware of problems with certain IVDs offered as LDTs manufactured and performed by AMC laboratories (see Refs. 16 and 18).

FDA does not believe it would be appropriate to have an enforcement discretion policy for all LDTs manufactured by AMC laboratories because such laboratories must comply with CLIA, as some comments asserted. In our response to comments in section VI.C, we explain that CLIA requirements and accreditation activities serve a complementary and distinct purpose from FDA oversight, and are therefore insufficient on their own to justify FDA continuing its general enforcement discretion approach for IVDs offered as LDTs.

Although healthcare systems may already have mechanisms addressing the reporting and tracking of adverse events, that does not negate the need for FDA oversight, including of MDR requirements. FDA uses adverse event information to monitor safety signals and identify trends, so that we can inform healthcare providers about issues the Agency has identified and work with manufacturers to correct problems with their devices. Reports to FDA about corrections and removals are also important in assuring that healthcare providers, patients, and caregivers are aware of problems and how to address them.

Finally, we note that even if an AMC is a not-for-profit entity, as raised in the comments, whether or not a test is sold for profit does not determine the quality of the test itself, which is the focus of FDA's attention.

(Comment 137) In response to FDA's question whether to continue its general enforcement discretion approach for tests made by AMC laboratories, many comments made various suggestions to FDA about continuing its general enforcement discretion for LDTs made by other types of health systems that are responsible for patients' complete clinical course of care. Some comments asserted that FDA should continue its general enforcement discretion approach for LDTs: (1) made by laboratories within hospitals that provide immediate patient care or any community healthcare delivery system, (2) manufactured by laboratories in

accredited hospitals and healthcare systems where the laboratory directors meet prerequisite education and experience requirements, or (3) manufactured by CLIA-certified laboratories that are integrated as part of a healthcare organization providing direct medical care. These comments claimed that a continued enforcement discretion approach for these LDTs would be appropriate, either because an AMC is too hard to define, or because some of the aspects of AMCs described in the NPRM, i.e., integration into patient care, and CLIA certification and meeting requirements to perform high-complexity testing, also apply to clinical laboratories in other health systems.

(Response 137) For the reasons discussed further in section V.B.3, FDA is adopting an enforcement discretion policy for LDTs manufactured and performed by laboratories integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. FDA is not adopting an enforcement policy specific to AMC laboratories based on FDA's understanding that AMCs are not the only healthcare systems in which integrated laboratories make LDTs to meet the needs of patients being cared for in the same healthcare system.

FDA believes that the risk mitigations present when the patient tested is receiving care within the same healthcare system as the laboratory offering the unmet need LDT, along with the other risk mitigations discussed in section V.B.3, help to address some of the concerns raised regarding problematic IVDs offered as LDTs discussed in the NPRM and this preamble. Specifically, in such situations, FDA generally has greater confidence that ordering physicians will communicate any questions about LDTs or concerns regarding the safety and effectiveness of the LDT (e.g., when the patient's symptoms point to another diagnosis; when subsequent test results contradict the original test result) to a laboratory given the built-in communication mechanisms present. Moreover, FDA generally has greater confidence that laboratories will communicate any limitations of the LDT or other relevant information to the ordering physician given these mechanisms. We think this is particularly likely to happen in the context of LDTs for unmet needs, which are likely to be a focus of attention and communication between

laboratorians and providers given the uncommon nature of the issues presented. For further discussion on these risk mitigations, please refer to section V.B.3. While we recognize that these features do not mitigate all risk and there may still be some uncertainty about the performance of tests subject to this policy, we believe that these features support enforcement discretion for premarket review and quality system requirements in the specific context of LDTs for unmet needs.

Thus, and as described further in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. This policy may include, but is not limited to, AMC laboratories' LDTs. We believe this policy generally encompasses the scenarios described in the comments summarized above (e.g., where LDTs are made by laboratories within hospitals or that are part of a healthcare organization providing direct medical care), albeit it applies only to LDTs that are intended to meet an unmet need of patients receiving care within the same healthcare system as the laboratory. As described in section V.B.3, an enforcement discretion policy whereby FDA generally would not enforce premarket review and most QS requirements for *any* LDTs manufactured by laboratories integrated within healthcare systems would appear to be overly broad, including because it would encompass LDTs for which there are FDA-authorized alternatives that we know have appropriate assurances of safety and effectiveness.

(Comment 138) Some comments suggested that FDA should continue a general enforcement discretion approach only with respect to premarket review, but phase in other requirements, such as reporting of adverse events, for LDTs manufactured by AMC laboratories.

(Response 138) FDA is adopting an enforcement discretion policy for premarket review and most QS requirements for certain unmet need LDTs manufactured and performed by laboratories integrated within a healthcare system where the patient is receiving care. Among

other things, this enforcement discretion policy is intended to avoid laboratories that manufacture unmet need LDTs from no longer manufacturing such LDTs as a result of the phaseout policy and perceived costs with premarket review and QS requirements. FDA is concerned that including premarket review requirements only in the policy would not sufficiently address this concern. As noted in section V.B.3, FDA expects compliance with all other applicable requirements as described in the phaseout policy.

For the reasons discussed in section V.B.3, FDA is not adopting an enforcement discretion policy for all LDTs manufactured and performed by AMC laboratories (or other laboratories integrated within healthcare systems).

(Comment 139) Another comment suggested that FDA continue the general enforcement discretion approach for all regulatory requirements, but only for low-risk tests offered by AMC laboratories.

(Response 139) FDA disagrees that it would be appropriate to adopt an enforcement discretion policy for all FDA requirements for low-risk tests offered by AMC laboratories. As an initial matter, FDA does not believe that AMC laboratories would stop offering low-risk tests as a result of the phaseout policy (including because most low-risk tests are exempt from premarket notification, meaning premarket submissions are not required). Moreover, for the reasons discussed throughout this preamble, compliance with other applicable requirements, such as registration and listing and adverse event reporting, among others, will provide critical assurances regarding these tests and allow FDA to monitor and take action in the event a problematic IVD is offered.

(Comment 140) A comment urged FDA to recognize that some hospitals and integrated patient facilities, including AMCs, may need to use devices “off label,” and asked how certain provisions, like the custom device exemption and IDE expanded access, apply to laboratories.

(Response 140) FDA recognizes that, under the FD&C Act, healthcare practitioners may prescribe or administer a legally marketed device to a patient for any condition or disease within

a legitimate healthcare practitioner-patient relationship (see section 1006 of the FD&C Act (21 U.S.C. 396)). As discussed further in section VI.D.6, however, section 1006 of the FD&C Act does not reach the manufacturing of a device, including by a laboratory.

Regarding the custom device exemption and IDE expanded access, FDA has issued a final guidance document on the custom device exemption (Ref. 168) and has provided information on its website about expanded access for medical devices (Ref. 169) as resources to device manufacturers, including laboratory manufacturers, among others.

(Comment 141) Some comments claimed that AMCs engage in the practice of medicine when they modify or use FDA-authorized tests off-label and so AMCs are not subject to FDA laws and requirements when they engage in these activities. Another comment stated that there are exclusions in the FD&C Act that apply to AMCs. Specifically, the comment quoted the following provision from the FD&C Act: “practitioners licensed by law to prescribe or administer drugs or devices and who manufacture, prepare, propagate, compound or process drugs or devices solely for use in the course of their professional practice,” and cited the following provisions in the FD&C Act: 21 U.S.C. 360(g)(2), 360i(c)(2)⁸⁴, and 374(a)(2)(B).

(Response 141) We do not agree that the “practice of medicine” provision in the FD&C Act is so broad as to encompass all of the activities raised in the comments (see response to comment 74 for a further discussion of this provision). Section 1006 of the FD&C Act expressly states what conduct within the practice of medicine falls outside of FDA’s statutory authority. *See* 21 U.S.C. 396 (“Nothing in this [Act] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship,” with several explicit limitations). Notably, the provision limits FDA’s oversight of

⁸⁴ Although this comment cited 21 U.S.C. 360(i)(c)(2), we believe the commenter may have intended to reference 21 U.S.C. 360(i)(c)(1), which refers to “any practitioner who is licensed by law to prescribe or administer devices intended for use in humans and who manufactures or imports devices solely for use in the course of his professional practice.”

certain practitioners’ “prescrib[ing] or administer[ing]” of a “legally marketed device,” but it does not reach the manufacturing of a device. Thus, to the extent that an AMC or AMC laboratory is manufacturing a device, including by modifying another entity’s device, its actions do not fall within the “practice of medicine” provision.

Regarding the comment asserting that various referenced exemptions in the FD&C Act generally apply to AMCs or AMC laboratories, we note that these exemptions apply when a “practitioner[]”: (1) is “licensed by law to prescribe or administer” a device, such as an IVD, (2) “manufacture[s]” that device, and (3) does so “solely for use in the course of their [or his] professional practice.” As discussed in response to comment 77, these exemptions are only relevant when a particular individual meets all three criteria and, by their plain terms, do not apply to an institution or an entity. Thus, to the extent the commenter is asserting that all AMCs or all AMC laboratories generally fall within these exemptions, we disagree.

(Comment 142) Several comments suggested that AMCs should be subject to the same enforcement approach as all other IVD manufacturers because it is important that patients be able to depend on tests regardless of who develops them. One comment stated that applying the same oversight approach would help to “standardize the development and validation of LDTs.” Another comment thought that FDA should not continue an enforcement discretion approach for LDTs manufactured and used in an AMC laboratory because it falsely gives the impression that LDTs manufactured by AMCs are superior to LDTs manufactured by non-AMCs. Another comment highlighted that FDA’s memorandum to file entitled “Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2” concluded that the deficiencies found in design, validation, and performance of COVID-19 tests were similar across all types of laboratories, including AMCs (see Ref. 18). Other comments suggested that any continuation of enforcement discretion should be test-based, with comments highlighting that FDA should focus on continuing its enforcement discretion approach

for tests developed to meet needs of those impacted by pediatric and rare diseases, regardless of where the test is manufactured.

(Response 142) FDA agrees that patients should be able to depend on IVDs regardless of who manufactures them, which is why FDA is phasing out the general enforcement discretion approach for LDTs. This phaseout policy includes several enforcement discretion policies for certain requirements for specific categories of IVDs manufactured by a laboratory. This phaseout policy is intended to better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance.

Regarding the enforcement discretion policies FDA is adopting, as discussed further in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. We understand that AMCs generally integrate their laboratories within their respective healthcare systems, and so this policy generally applies to their LDTs for unmet needs, as well as the unmet need LDTs manufactured and performed by other laboratories integrated within a healthcare system.

As discussed further in section V.B.3, FDA understands that laboratories integrated within a healthcare system may no longer manufacture and perform many critical LDTs for unmet needs due to a lack of financial incentive and the perceived costs of premarket review and QS requirements for such tests if expected to comply with such requirements. FDA is aware, however, of problems with certain IVDs offered as LDTs manufactured and performed by AMC laboratories (see response to comment 32). Certain evidence of problematic IVDs offered as LDTs described in the NPRM addressed tests from AMCs, including the memorandum described above entitled “Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories

for Molecular Diagnostic Tests for SARS-CoV-2” (Ref. 18). In addition, another FDA memorandum and several of the studies referenced in the NPRM referenced IVDs manufactured by AMC laboratories (see Refs. 20 and 92). We believe the risk mitigations present in laboratories integrated within healthcare systems, and various other risk mitigations, as described in section V.B.3, help to address some of the concerns raised regarding problematic IVDs offered as LDTs discussed in the NPRM and this preamble.

As discussed further in section V.B.3, while we recognize that these features do not mitigate all risk and there may still be some uncertainty about the performance of tests subject to this policy, we believe that these features support enforcement discretion for premarket review and quality system requirements in the specific context of LDTs for unmet needs. FDA considers an LDT to be for an unmet need where there is no available FDA-authorized IVD that meets the patient’s needs. This may be because: (1) there is no FDA-authorized IVD for the disease or condition (for example, because it is for a rare disease or condition); (2) there is an FDA-authorized IVD for the disease or condition but it is not indicated for use on the patient, or a unique attribute needs to be added to the LDT to meet the patient’s needs; or (3) there is an FDA-authorized IVD but it is not available to the patient.

We also acknowledge statements in the comments that applying the same oversight approach would help to standardize the development and validation of LDTs. In light of unique validation issues for many IVDs for unmet needs, FDA intends to consider whether issuing additional guidance regarding validation of tests, including those for rare diseases that takes into consideration the challenges in obtaining a robust number of samples for validation, would be helpful, as discussed in section V.B.3. In the event FDA were to issue any such guidance, FDA would do so in accordance with good guidance practices (see § 10.115). FDA anticipates that such guidance could result in more consistently robust validation practices across laboratories that develop tests for unmet needs and reduce the potential for introduction of poorly performing LDTs.

Finally, we do not think it is appropriate to adopt an enforcement discretion policy for all LDTs developed to meet the needs of those impacted by pediatric and rare diseases, regardless of where the LDT is manufactured and performed. As discussed further in section V.B.3, such a policy would appear to be overly broad, as there are not the same risk mitigations present for all such LDTs that would help address and avoid the use of problematic LDTs.

(Comment 143) A number of comments expressed concern that if FDA were to continue its general enforcement discretion approach for AMCs, it would distort the market and negatively impact underserved and rural regions. Comments indicated that AMCs are generally concentrated in urban areas and that many patients in rural areas are not able to access AMCs due to lack of proximity or insurance coverage. Another comment stated that community health centers provide more cancer treatment than AMCs. The comments expressed fear that continuing an enforcement discretion approach for AMCs will exacerbate the disparities in care between urban and rural regions and would be detrimental to the ability of community centers to provide tests for cancer patients. Similarly, another comment stated that non-AMCs will have trouble attracting talent if FDA continues to exercise enforcement discretion for AMCs.

(Response 143) As discussed in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

FDA believes that this policy will help to address the concerns raised in the comments for patients in underserved and rural regions and should mitigate concerns about attracting talented laboratorians. The policy applies to all laboratories integrated within a healthcare system, not only AMCs. FDA anticipates that this policy will help to avoid laboratories integrated within healthcare systems, wherever such healthcare systems are located, from no longer manufacturing

LDTs to meet the unmet needs of patients receiving care within the same healthcare system due to the costs of compliance with premarket review and QS requirements.

(Comment 144) Several comments suggested that FDA not extend its general enforcement discretion approach to AMCs if AMCs were to “commercialize” the tests they develop at a significant volume.

(Response 144) FDA believes that an enforcement discretion policy for LDTs manufactured and performed by a laboratory integrated within a healthcare system should be limited only to those LDTs for which there is an unmet need, and should not apply when there is an FDA-authorized test available that meets the needs of the patient. There may be an unmet need because--(1) there is no FDA-authorized IVD for the disease/condition (for example, because it is for a rare disease/condition); (2) there is an FDA-authorized IVD for the disease/condition but it is not indicated for use on the patient, or a unique attribute needs to be added to the test to meet the patient’s needs; or (3) there is an FDA-authorized IVD but it is not available to the patient. Moreover, as described in section V.B.3, this enforcement discretion policy is limited to LDTs for patients who are receiving care within the same healthcare system as the laboratory offering the test.

(Comment 145) Multiple comments indicated that it will be difficult to develop a consistently implementable definition of AMCs. Many other comments stated that AMC laboratories serve patients beyond a single physical location and that such a “requirement” would be too narrow. These comments indicated that it is rare for specimen collection, testing in a clinical laboratory, and treatment of the patient to all take place in the same building. Comments also pointed out that real estate availability and patient needs may force AMCs to take advantage of multiple physical spaces. Other comments indicated that while AMCs may span multiple physical locations, they may all be connected by one electronic management record system. Some comments suggested FDA consider an enforcement discretion policy for AMCs that have closely affiliated health systems or where the laboratories work directly or in coordination or

collaboration with the academic institution. Other comments questioned what it meant to have a medical residency training or fellowship program involving test development, and whether this applied to pathology. Others wanted clarity on the meaning of “direct patient care.”

We also received many comments providing various possible definitions of an AMC. Common across many comments was that AMCs are high-complexity CLIA-accredited laboratories and that the leadership or a portion of the laboratory leadership have an academic appointment at an Accreditation Council for Graduate Medical Education (ACGME)-accredited school with a training program in pathology or laboratory medicine. Some comments suggested an AMC laboratory should provide testing for patients in their AMCs. Another comment suggested an AMC laboratory should accept at least 50 percent of its samples from patients being tested within the institution-affiliated healthcare system. Another comment suggested that FDA should not limit an enforcement discretion policy to tests where samples come from within the AMC because AMCs are often referral centers. A comment suggested that an AMC be defined as a nonprofit 501(c)(3) with a Liaison Committee on Medical Education-accredited medical school, teaching hospital, residency training program, and a mission to educate medical professionals. Other comments suggested an AMC use a single EMR where testing is performed within the system and reported into the system EMR. Another comment suggested an AMC is a unit where the physician ordering the specimen is either employed by the healthcare system or has active clinical privileges at a hospital owned by the healthcare system.

(Response 145) Based on these and other comments submitted to the docket for this rulemaking and for the reasons described in section V.B.3, FDA will not have a separate enforcement discretion policy for AMC laboratories. Instead, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. As such, FDA is not

defining an AMC in this preamble and many of the concerns raised in the comments summarized above have been addressed or are no longer relevant (e.g., concerns regarding limiting the policy to manufacturers at a single physical location; questions regarding what it means to have a medical residency training or fellowship program involving test development; questions regarding the meaning of “direct patient care”).

5. New York State Department of Health Clinical Laboratory Evaluation Program (NYS CLEP)

(Comment 146) FDA received several comments in support of “leveraging” LDT approval under established programs, specifically NYS CLEP, in lieu of ending FDA’s general enforcement discretion approach for LDTs with respect to premarket review requirements, in order to prevent duplicative efforts and reduce burden for both FDA and laboratories. Some comments expressed general support for relying on established programs such as NYS CLEP, but noted that these programs would need to be aligned with FDA’s regulatory review standards. Some comments noted that NYS CLEP provides a robust system of oversight and furthers the same goals as FDA’s 510(k) process, but they suggested that adverse event data collection and registration and listing should be conducted at the Federal level. Other comments recommended using NYS CLEP as a model when structuring FDA’s enforcement of requirements for IVDs offered as LDTs. Some comments supported the idea of continuing the general enforcement discretion approach for all FDA requirements for tests that have already been approved by NYS CLEP. One comment noted that relying on existing programs and continuing enforcement discretion for these tests would reduce concerns about bottlenecks in FDA’s review capacity and constraints on innovation and alleviate concerns about increased costs.

NYS provided a comment indicating support for continued enforcement discretion with respect to premarket review requirements for LDTs they have reviewed and approved. They explained that their “technical review is designed to determine whether the test is analytically and clinically valid. The laboratory must submit all applicable standard operating procedures, validation data demonstrating accuracy and reliability of the test results, documentation that the

results are associated with a clinical or public health need, examples of reports, and other material necessary to evaluate the test.... CLEP's LDT oversight process is designed to address the risk for each LDT and considers all parts of the test, including test method, intended use, specimen type, and claims, as well as the laboratory performing the test. Each LDT application is reviewed by subject matter experts with post-graduate experience and training in the field and reviews are not conducted during onsite survey. An LDT approval is specific to the laboratory.... Tests that cannot meet CLEP requirements are denied. Approval may be revoked or modified if an approved test is found subsequently to be no longer analytically and/or clinically valid.” However, NYS supported the collection of adverse event information and registration and listing information at a national level.

(Response 146) As discussed in section V.B.2, FDA intends to exercise enforcement discretion with respect to premarket review requirements for LDTs approved by NYS CLEP. FDA notes that this is an enforcement discretion policy and not a substitute for FDA premarket review. FDA believes that the term “leveraging” in the NPRM (88 FR 68006 at 68024) might have caused confusion. FDA recognizes that NYS CLEP's regulatory framework is not the same as FDA's (e.g., NYS CLEP has a different risk classification and premarket review program). However, as explained in section V.B.2, FDA believes that NYS CLEP has a program that provides for certain mitigations that help reduce the risk of harm from inaccurate and unreliable LDTs. Specifically, NYS CLEP has a program under which high risk and moderate risk LDTs generally are evaluated for analytical and clinical validity. Based on the available information, FDA believes that generally NYS CLEP's review of analytical and clinical validity of LDTs helps to mitigate the risk of harm from inaccurate and unreliable LDTs and that, rather than enforcing premarket review requirements by FDA, it would be more efficient and effective to use our resources for other oversight activities regarding IVDs offered as LDTs. See section V.B.2. for further information. We have accounted for this enforcement discretion policy in the FRIA. Specifically, as discussed in appendix A of the FRIA (Ref. 10), we estimate that 12.1 percent of

IVDs offered as LDTs would not experience new costs associated with submission preparation and review as a result of FDA's enforcement discretion policy with respect to LDTs approved by NYS CLEP.

However, as discussed in section V.B.2, FDA intends to phase out its general enforcement discretion approach with respect to other regulatory requirements, such as registration and listing and MDR requirements, for these LDTs. Enforcement of other requirements will help to protect and promote the public health, e.g., by providing FDA and the public with important information about these tests. See section V.B.2 for further information.

(Comment 147) Some comments stated that an external program such as NYS CLEP should not “replace FDA regulation,” but noted that such programs could be used to streamline FDA review or provide additional “flexibility” to tests certified under such regimes. Some comments expressed concern that such external programs would be unable to handle the volume of requests from laboratories, and others noted that if FDA were to “leverage” such external programs and continue its general enforcement discretion approach, this may lead to an overly broad approach with FDA accepting foreign standards like the EU CE Certificate.

(Response 147) FDA's policy with regard to LDTs approved by NYS CLEP does not “replace FDA regulation.” As described in section V.B.2, FDA intends to exercise enforcement discretion with respect to premarket review requirements, but not other FDA requirements such as MDR reporting, for LDTs approved by NYS CLEP. See section V.B.2. for further information. Additionally, as noted above, this is an enforcement discretion policy and not a substitute for FDA premarket review. As described in section V.B.2, FDA intends to exercise enforcement discretion and generally not enforce the premarket review requirements for LDTs approved by NYS CLEP because NYS CLEP has a program under which high risk and moderate risk LDTs generally are evaluated for analytical and clinical validity. Based on the available information, FDA believes that generally NYS CLEP's review of analytical and clinical validity

of LDTs helps to mitigate the risk of harm from inaccurate and unreliable LDTs and that, rather than enforcing premarket review requirements by FDA, it would be more efficient and effective to use our resources for other oversight activities regarding IVDs offered as LDTs. Further, as stated in section V.B.2, FDA retains its discretion to pursue enforcement action at any time against violative IVDs when appropriate.

This enforcement discretion policy for LDTs approved by NYS CLEP does not apply to tests with foreign approvals if those tests are not approved by NYS CLEP. With respect to concerns regarding potentially overwhelming NYS CLEP, the likelihood of this result is unclear. However, FDA anticipates collaborative communication with NYS CLEP. Should experience with this policy indicate that changes are warranted, FDA would consider appropriate policy changes through guidance in accordance with good guidance practices (see § 10.115).

(Comment 148) A few comments stated that FDA should not “leverage” outside programs and continue applying the general enforcement discretion approach for tests under those programs. They stated that these programs as they exist today do not have the same scope and standards as FDA’s device regulations. Further, they stated that “allowing” external programs with different standards to “stand in for FDA regulation” would not further the goal of implementing a single risk-based regulatory framework.

(Response 148) As discussed in the response to comment 146, FDA believes that the term “leveraging” in the NPRM (88 FR 68006 at 68023) might have caused confusion. FDA recognizes that NYS CLEP’s regulatory framework is not the same as FDA’s (e.g., NYS CLEP has a different risk classification and premarket review program). However, as discussed in section V.B.2, FDA intends to exercise enforcement discretion with respect to premarket review requirements for LDTs approved by NYS CLEP because FDA believes that NYS CLEP has a program that provides for certain mitigations that help reduce the risk of harm from inaccurate and unreliable LDTs. See section V.B.2 for further information. FDA notes that this is an enforcement discretion policy and not a substitute for FDA premarket review or a “stand in for

FDA regulation.” Further, as described in section V.B.2, FDA generally intends to exercise enforcement discretion with respect to premarket review requirements, but not other FDA requirements such as MDR reporting, for LDTs approved by NYS CLEP. See section V.B.2 for further information.

(Comment 149) One comment asked whether an enforcement discretion policy for NYS CLEP-approved LDTs would include those used on people across all states, or whether the policy would be limited to NYS CLEP-approved tests used only in New York State.

(Response 149) FDA generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs approved by NYS CLEP. As explained in section V.B.2, these are LDTs with NYS CLEP approval, conditional approval, or within an approved exemption from full technical documentation granted by NYS CLEP. The enforcement discretion policy with respect to LDTs approved by NYS CLEP applies regardless of whether that LDT is performed on specimens from NYS or elsewhere, as the risk mitigations upon which the policy is based apply regardless of where the specimens are coming from. This enforcement discretion policy only applies to the version of the LDT approved by NYS CLEP. If the laboratory is offering and using a different version of the LDT that is not approved by NYS CLEP, this enforcement discretion policy would not apply.

(Comment 150) FDA received comments suggesting that NYS CLEP should be granted “deemed” status and tests subject to NYS CLEP should be exempt from the phaseout of FDA’s general enforcement discretion approach for LDTs.

(Response 150) As described in section V.B.2, FDA generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs approved by NYS CLEP. FDA’s policy with respect to LDTs approved by NYS CLEP is an enforcement discretion policy and not a substitute for FDA premarket review. Further, FDA intends to phase out its general enforcement discretion approach with respect to other regulatory requirements, such as registration and listing and MDR requirements, for these LDTs. Enforcement of other

requirements will help to protect and promote the public health, e.g., by providing FDA and the public with important information about these tests. For additional discussion of FDA's policy with respect to LDTs approved by NYS CLEP, see section V.B.2.

6. Timing and Structure of the Phaseout Policy

(Comment 151) FDA's proposed phaseout policy described a gradual phaseout of the general enforcement discretion approach for LDTs that would occur in stages over a total period of 4 years. FDA received several comments stating that this timeline is too short and should be extended. These comments generally proposed that FDA modify the phaseout period to last a total of 7-10 years, though at least one comment proposed a significantly longer phaseout period of 15 years. One comment suggested that each stage of the phaseout period should be extended by an additional year. These comments generally characterized the length of the phaseout period as unreasonable or not workable, and emphasized laboratories' lack of experience and infrastructure for complying with FDA requirements; the number of tests that laboratories will have to address and associated resource demands; FDA's resource limitations; the time required for laboratories to become familiar with applicable requirements; and general uncertainty regarding how laboratories will navigate the phaseout process. One comment noted that in a survey of 39 laboratories, only 1 laboratory stated that it would likely be able to implement all applicable requirements within the 4-year timeframe (this survey is described in Ref. 170). In describing this survey finding, the comment characterized the proposed phaseout timeline as "unrealistic since the requirements for FDA approval cannot be conducted in a timely fashion due to the large number of LDTs and insufficient resources," and further stated that "[FDA's] review process is also lengthy once data is submitted." Some comments suggested that the length of the phaseout period be extended for certain types of tests, such as diagnostic flow cytometry leukemia and lymphoma immunophenotyping tests, due to the challenges associated with preparing premarket submissions for such tests.

In addition, one comment noted that the average time to bring a medical device to market has been estimated to range from 2-7 years, and several comments noted that FDA had proposed a longer phaseout period of 9 years in 2014. One comment noted that the VALID Act had proposed a transition period of up to 10 years. Another comment stated that the reliance interests of laboratories would be harmed if the length of the phaseout period were not extended, given the challenges that laboratories would face from competing demands for limited resources.

FDA also received comments stating that the overall length of the phaseout period should be reduced. One comment stated that if laboratories have been doing “the right thing,” they should not require 4 years to comply with applicable requirements, and patients should not have to wait 4 years to be able to rely on accurate tests. Another comment suggested that FDA consider the Agency’s expectations for a startup conventional IVD manufacturer and apply the same expectations to laboratory manufacturers, stating that a conventional manufacturer could not take 4 years to come into compliance. One comment stated that FDA should shorten the phaseout period for premarket approval requirements for tests that pose a higher risk of harm from 4 years to 1-2 years.

FDA also received a comment that agreed with FDA’s phaseout timeline. This comment stated that the timeline would give laboratories adequate time to come into compliance with applicable requirements while allowing FDA to gather information on the LDT market and prioritize review of high-risk tests.

(Response 151) After considering the public comments and the impact of new enforcement discretion policies included in the final phaseout policy, FDA has determined that it should retain a 4-year, gradual phaseout of the Agency’s general enforcement discretion approach for LDTs.

As described in section II.F of the FRIA (Ref. 10), FDA has estimated the time and resources that will be required for laboratories to comply during each stage of the phaseout policy. We estimate total costs to be approximately \$101 million for stage 1 in year 1 for 1,275

affected laboratories, \$113 million for stages 1 and 2 in year 2 for 1,275 affected laboratories, \$386 million for stages 1 through 4 in year 3 for 858 affected laboratories, and \$1.65 billion for stages 1 through 5 for 849 affected laboratories with 7,554 premarket submissions in subsequent years (year 4 to year 20).

Based on these estimates, and in consideration of the factors discussed for each stage of the phaseout policy in section V.C, FDA has determined that the time allotted for each stage of the phaseout will give laboratories adequate time to comply with the requirements that are the focus of that stage. For example, FDA has determined that a 1-year time period is adequate to phase out the general enforcement discretion approach for LDTs with respect to MDR requirements and correction and removal reporting requirements under stage 1 of the phaseout policy, given that laboratories should already have some processes in place for detecting problems with their IVDs to comply with CLIA regulations, and in stage 1 laboratories will be reporting adverse events and malfunctions to FDA in accordance with part 803. Additional discussion of the timeframe associated with stage 1 and the timeframes associated with other stages of the phaseout policy is provided in response to comments 154-159. Additional discussion of FDA's phaseout of the general enforcement discretion approach with respect to particular requirements under each stage of the phaseout policy is provided in sections VI.F.7-13 of this preamble.

In addition, changes have been made to the phaseout policy that directly address the concerns raised in comments that laboratories' reliance interests will be harmed if the phaseout period is not extended, and that laboratories will not be able to come into compliance during the time periods set forth in the phaseout policy (e.g., due to the lack of experience with FDA oversight, the cost of compliance, etc.). FDA recognizes that some laboratories may lack familiarity, experience, or existing infrastructure for complying with FDA requirements. However, we note that, as discussed elsewhere in this preamble, there are numerous existing final guidance documents and educational resources made available by FDA to help companies

comply with requirements applicable to devices. FDA also intends to issue guidance documents or make other resources available to provide further clarity to stakeholders regarding implementation of certain aspects of the phaseout policy following issuance of this rule. FDA also recognizes that the time and resource demands associated with each stage of the phaseout policy may be significant for laboratories, and a laboratory's efforts to come into compliance with the requirements associated with different stages of the phaseout policy may need to take place concurrently. However, as described in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs. As discussed further in section V.B.3, this policy takes into account that laboratories may have made financial investments and other decisions based on a past assumption about the presence of the general enforcement discretion approach.

In addition, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs that are approved by NYS CLEP. As a result of these policies, the time and resources associated with stages 3, 4, and 5 of the phaseout policy are estimated to be significantly reduced as compared to the estimates in the PRIA (see sections II.F.3, 4, and 5 of the FRIA (Ref. 10)). With fewer competing demands, laboratories may be better able to comply with the requirements that are the focus of stages 1 and 2 of the phaseout policy.

While the Agency appreciates the information provided in a comment regarding a survey in which only 1 out of 39 laboratories stated that the laboratory would likely be able to implement all applicable requirements within the proposed 4-year phaseout period, this survey did not take into account the enforcement discretion policies described in the preceding

paragraph. The comment that described this survey emphasized the perceived burden of compliance with FDA's premarket review requirements, yet under many of the enforcement discretion policies included in the final phaseout policy, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements. FDA also notes that this survey was conducted with a small sample size and reflects the subjective views of entities that would be subject to increased FDA oversight under the phaseout policy.

Regarding the comments on extending the phaseout policy in light of demands on FDA resources, we note that the enforcement discretion policies included in the final phaseout policy will significantly reduce these demands. The annualized costs to FDA over 20 years are approximately \$408 million less than the estimates in the PRIA (in the FRIA, the primary estimate for FDA review costs over 20 years at a 7 percent discount rate are \$121 million, as compared to \$530 million in the PRIA). These policies, and in particular the policy for currently marketed IVDs offered as LDTs, also address concerns that FDA should modify the length of the phaseout period for certain types of tests to account for perceived challenges associated with preparing premarket submissions for such tests.

FDA does not believe it would be in the best interest of public health to adopt a longer phaseout period or to extend the time allotted for any of the stages in the phaseout policy. Based on information currently available to the Agency regarding the risks associated with IVDs offered as LDTs (as discussed in the NPRM and sections III.B and VI.C of this preamble), an extension of the phaseout policy to a period longer than 4 years would be inconsistent with FDA's mission to protect the public health. FDA encourages manufacturers to begin working towards compliance with applicable requirements as early as possible, and to engage with FDA through a Pre-Submission or other available mechanism.

FDA recognizes that the Agency proposed a different timeline for phasing out its general enforcement discretion approach for LDTs in 2014, which, if finalized, would have involved a longer overall phaseout period. However, as noted in section III.B and described in the NPRM,

FDA's concerns regarding the risks associated with IVDs offered as LDTs have grown in recent years, and more recent evidence from a variety of sources underscores the pressing need to better assure the safety and effectiveness of IVDs offered as LDTs (88 FR 68006 at 68009). Diagnostic testing is increasingly important; for example, as time goes on, more novel treatments will require use of a specialized test to identify patients likely to benefit from those treatments.⁸⁵ Furthermore, IVDs offered as LDTs are a growing sector of the diagnostic testing market (Ref. 4). FDA anticipates that IVDs will continue to become more complex and play a greater role in modern healthcare (Ref. 3). The U.S. LDT market size is anticipated to grow 6 percent from 2023 to 2030 due to varying factors including increased use in personalized medicine and rising prevalence of chronic diseases. (Id.) FDA is therefore taking steps to oversee the safety and effectiveness of IVDs regardless of where they are manufactured, so that both now and in the future, patients can have confidence about the tests used in their care.

Moreover, the longer timeline proposed in 2014 included a phaseout of enforcement discretion for LDTs already on the market, whereas the phaseout policy described in this preamble phases out enforcement discretion with respect to premarket review for IVDs offered as LDTs entering the market after publication of the final rule.

We disagree with comments that the time to bring a device to market or any timing provisions in the proposed VALID Act should dictate the timeline of the phaseout policy. For example, we note that even if the average time to bring a medical device to market ranges from 2-7 years, as one comment asserted, this does not mean that 7 years is needed to prepare and submit a premarket submission to FDA, even if new data must be collected to support the submission. FDA is aware of estimates that refer to the time required to bring a new device all the way from concept to market as 3-7 years (Ref. 171). Not only does this cover development time prior to FDA review, but it is also based on all devices including permanent implants, which generally take longer to develop and evaluate than IVDs.

⁸⁵ See, e.g., Ref. 23 ("Demand is increasing in the CDx market, due to the paradigm shift to precision medicine.").

FDA also does not agree that the length of the phaseout period should be reduced to less than 4 years. A reduced timeline would mean phasing out the general enforcement discretion approach with respect to premarket review requirements before the start of a new user fee cycle, which would not provide industry with a prior opportunity to participate in user fee negotiations with the knowledge that laboratory manufacturers will be expected to comply with premarket review requirements for new IVDs offered as LDTs. A shorter overall phaseout timeline would also place greater concurrent demands on laboratory resources. For the same reasons, FDA does not believe that the phaseout period for premarket review requirements for high-risk IVDs offered as LDTs should be shortened from 4 years to 1-2 years. FDA notes that the phaseout policy already prioritizes phasing out the general enforcement discretion approach for high-risk IVDs offered as LDTs by phasing out enforcement discretion with respect to premarket review requirements for high-risk tests prior to doing so for moderate-risk and low-risk tests.

Finally, some comments suggested that the length of the phaseout period be extended for certain types of tests, such as diagnostic flow cytometry leukemia and lymphoma immunophenotyping tests, due to the challenges associated with preparing premarket submissions for such tests. We believe the timelines for premarket review are reasonable and appropriate, as discussed further in section V.C and the responses to comments in section VI.F.13. Moreover, providing different timelines for the phasing out of the enforcement discretion approach for different types of IVDs would be overly complicated for laboratories to follow and for FDA to implement.

(Comment 152) FDA received comments stating that the timing of certain stages of the phaseout policy should be measured from when FDA issues final guidance documents or other educational materials regarding implementation of the phaseout policy, rather than from publication of the phaseout policy itself.

(Response 152) FDA disagrees with these comments. Although FDA intends to issue guidance documents or make other resources available to provide further clarity to stakeholders

regarding implementation of certain aspects of the phaseout policy, and intends to issue any such guidance documents or provide other resources expeditiously, there are numerous existing final guidance documents and educational resources on FDA's website to help companies comply with FDA requirements applicable to devices. Moreover, this preamble includes extensive information about the phaseout policy and FDA's expectations, as well as references to final guidance documents and resources available to laboratories.

(Comment 153) One comment stated that it was unclear whether FDA intended the stages of the phaseout policy to run concurrently or consecutively. The comment requested that FDA clarify this point.

(Response 153) The timing for each stage of the phaseout policy is based on the date that FDA publishes this final rule and not when the previous stage ends. For example, stage 3 will begin after 3 years, measured from the date of publication of this final rule and not relative to the timing of any other stages. However, because each stage will begin after a different length of time has passed from the date of publication of this final rule, the stages will commence in sequence. For example, as described in section V.C, stage 1 will commence 1 year after publication of this final rule. Upon the start of stage 1, FDA will generally expect compliance with applicable MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files). Stage 2 will commence 2 years after publication of this final rule. Upon the start of stage 2, FDA will generally expect compliance with applicable requirements discussed under stage 2, in addition to continued compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files) for which the general enforcement discretion approach was phased out at the beginning of stage 1.

(Comment 154) One comment stated that ending the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements 1 year after publication of the phaseout policy is appropriate, as this timeline will enable FDA to

quickly identify LDTs potentially associated with safety or performance issues. This comment further stated that laboratories that are in compliance with CLIA requirements should already have systems in place for detecting problems with their tests. Another comment stated that FDA should end the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements 6 months after publication of the phaseout policy. According to this comment, 6 months is more than adequate to establish procedures for identifying events that need to be reported and for implementing a reporting mechanism (e.g., through the FDA eSubmitter software). In addition, this comment recommended that all subsequent stages of the phaseout policy commence 6 months sooner than proposed by FDA, as a result of the shorter timeline for phasing out the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements under stage 1.

(Response 154) FDA agrees with the comment that stated that phasing out the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements 1 year after publication of the phaseout policy is appropriate, for the reasons discussed in section V.C. FDA also agrees that most laboratories should be able to establish and implement procedures for complying with MDR requirements and correction and removal reporting requirements within 6 months; however, we also believe it is appropriate to provide a little more time to help to ensure compliance with the requirements.⁸⁶ In recognition that phasing out the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements too quickly may lead to less effective reporting, FDA has determined to phase out the general enforcement discretion approach with respect to these requirements 1 year after publication of this final rule. As such, FDA also disagrees that all subsequent stages of the phaseout policy should commence 6 months sooner than proposed by FDA in the proposed phaseout policy.

⁸⁶ Some comments submitted on the draft guidance documents that FDA issued in 2014, in which FDA proposed a 6-month timeframe for laboratory compliance with MDR requirements, suggested that a longer period would be appropriate.

(Comment 155) FDA received one comment which expressed concern that FDA had not proposed to phase out the general enforcement discretion approach with respect to the requirements addressed in stage 2 of the phaseout policy in a manner that would distinguish between IVDs of different risk levels. The comment stated that a decision not to pursue such an approach, which FDA had previously considered, would be arbitrary and not justified.

(Response 155) FDA does not agree that the phaseout of the general enforcement discretion approach with respect to the requirements addressed in stage 2 of the phaseout policy should be conducted in a manner that distinguishes between IVDs of different risk levels, or that the Agency's decision not to structure the phaseout policy in the manner suggested by the comment is arbitrary and unjustified. The requirements for which FDA will expect compliance in stage 2 of the phaseout policy, including registration and listing requirements under 21 U.S.C. 360, part 607, and part 807 (excluding subpart E), labeling requirements under 21 U.S.C. 352 and parts 801 and 809, subpart B, and investigational use requirements under 21 U.S.C. 360j(g) and part 812, are general controls under section 513(h)(1) of the FD&C Act, and are thus generally applicable to all devices. FDA has determined that it would best serve the public health to phase out the general enforcement discretion approach with respect to these requirements 2 years after publication of this final rule, irrespective of the risk classification of the device.

In the NPRM, FDA acknowledged that this proposal was different from FDA's prior statements in the 2017 Discussion Paper (88 FR 68006 at 68025), wherein FDA discussed a scenario in which the timing of FDA's expectations for compliance with certain requirements might depend on the type of premarket review applicable to the device (Ref. 57). FDA anticipates that 2 years is adequate time for laboratories to come into compliance with the requirements addressed in stage 2, and structuring the phaseout policy in this manner is easier for laboratories to comprehend and follow, easier for FDA to implement, and more responsive to the pressing need for additional FDA oversight of IVDs offered as LDTs.

(Comment 156) One comment requested clarification as to whether FDA intends to phase out the general enforcement discretion approach with respect to QS provisions regarding complaint files under § 820.198 during stage 1 of the phaseout policy (when FDA generally intends to phase out the general enforcement discretion approach with respect to MDR requirements), rather than during stage 3 of the phaseout policy, given that FDA’s regulations regarding MDR requirements state that “[i]f you are a manufacturer, you may maintain MDR event files as part of your complaint file, under part 820 of this chapter, if you prominently identify these records as MDR reportable events. We will not consider your submitted MDR report to comply with this part unless you evaluate an event in accordance with the quality system requirements described in part 820 of this chapter” (§ 803.18(e)).

(Response 156) FDA has modified the phaseout policy to clarify that while FDA generally intends to phase out the general enforcement discretion approach with respect to QS requirements in stage 3 of the phaseout policy (as described in section V.C), FDA intends to phase out the general enforcement discretion approach with respect to the QS requirements under § 820.198 (complaint files) in stage 1 of the phaseout policy, given the connection between the complaint investigation and complaint file requirements and the MDR reporting regulations.

(Comment 157) FDA received one comment which stated that it could take up to a year for a sizable healthcare system to prepare a list of LDTs, before the healthcare system could list those LDTs with FDA.

(Response 157) FDA appreciates that it may take time for laboratories to identify and prepare a list of their IVDs offered as LDTs before being able to comply with device listing requirements under the FD&C Act and FDA’s regulations. Under FDA’s phaseout policy, FDA is phasing out the general enforcement discretion approach with respect to registration and listing requirements 2 years after publication of this final rule, which will provide sufficient time for laboratories to come into compliance even if a year is needed for some laboratories to prepare a comprehensive list of their IVDs offered as LDTs.

(Comment 158) One comment stated that 3 years could be sufficient to develop a quality management system that complies with QS requirements, but that developing a quality management system that is both QS-compliant and CLIA-compliant will be complex and require uncommon knowledge and expertise. This comment also stated that to develop a quality management system that meets FDA's expectations, laboratories will require guidance from FDA with detailed descriptions of the differences that exist between QS requirements and CLIA regulations. The comment urged FDA to phase out the general enforcement discretion approach with respect to QS requirements 4 years after publication of the phaseout policy or 1 year after FDA issues a guidance document regarding the differences that exist between the QS requirements and CLIA regulations, whichever comes later. The comment also stated that this approach should provide FDA sufficient time to amend the QSR to harmonize with international standards.

(Response 158) FDA does not agree that the Agency should phase out the general enforcement discretion approach with respect to QS requirements 4 years after publication of the phaseout policy, or 1 year after issuance of a guidance document describing differences that exist between QS requirements and CLIA regulations, rather than 3 years after publication of the phaseout policy as proposed by FDA. While FDA recognizes that laboratories will be complying with applicable CLIA requirements as well as applicable QS requirements, laboratories already comply with CLIA requirements.

Moreover, as discussed in section V.C, compliance with CLIA requirements provides certain quality assurances that may be relevant to laboratories' manufacturing practices, and laboratories may be able to apply concepts set forth under CLIA requirements to manufacturing activities regulated by FDA. As such, and as further discussed in section V.C.3, FDA intends to phase out the general enforcement discretion approach with respect to only a subset of QS requirements rather than all applicable requirements for LDTs. This subset of QS requirements is listed in section V.C.3.

FDA also notes that it has already finalized amendments to the QSR (effective in February 2026), and the amended QS requirements, which align more closely with international consensus standards for devices, will be in effect prior to the beginning of stage 3 (see 89 FR 7496). FDA anticipates providing to all its stakeholders, including laboratories, timely guidance on compliance with the regulatory requirements in that rule. In addition, several educational resources regarding the QS requirements currently applicable under part 820 are currently available on FDA's website (see Ref. 72).

(Comment 159) One comment stated that FDA should phase out the general enforcement discretion approach with respect to premarket review requirements after 4 years for PMAs and after 9 years for 510(k)s and De Novo submissions. Another comment stated that FDA should phase out the general enforcement discretion approach with respect to premarket review requirements after 5 years for PMAs, after 7 years for De Novo requests, and after 9 years for 510(k)s. In addition, one comment stated that if FDA does not continue the general enforcement discretion approach with respect to premarket review and QS requirements for "existing LDTs," FDA should, in the alternative, consider "exempting or more gradually phasing in premarket review and QSR requirements for LDTs that meet certain criteria," such as those "certified by [NYS CLEP]." Another comment stated that FDA should extend the phaseout by 5 years for premarket review and QS requirements for LDTs introduced or modified after the effective date of the rule that have approval from NYS CLEP, receive coverage from the MoIDx Program, or are performed in a CLIA-certified clinical laboratory accredited by CAP, unless there is credible information establishing that the LDT is marketed with insufficient evidence of analytical or clinical validity, that the LDT is marketed with false or misleading analytical or clinical claims, or that it is probable that the LDT will cause serious adverse health consequences.

(Response 159) After considering the public comments and the impact of other policies included in the phaseout policy, for the reasons discussed in section V.C, FDA has determined that it should phase out the general enforcement discretion approach: (1) with respect to QS

requirements (other than requirements under § 820.198 (complaint files)), 3 years after publication of this final rule; (2) with respect to premarket review requirements for high-risk IVDs, 3½ years after publication of this final rule; and (3) with respect to premarket review requirements for moderate-risk and low-risk IVDs (that require premarket submissions), 4 years after publication of this final rule. For further discussion of these stages and the QS and premarket review requirements, see sections V.C.3-5, VI.F.12, and VI.F.13.

FDA disagrees that the phaseout policy should be modified as suggested by these comments. As discussed in response to comment 151, FDA has determined that extending the timelines for stages of the phaseout policy is not necessary to provide an adequate opportunity for laboratories to comply with applicable requirements or to effectively implement the phaseout policy, and is not in the best interest of the public health. This is true even in the case of IVDs offered as LDTs covered by the MolDx Program or performed in a CAP-accredited CLIA-certified laboratory. As discussed in response to comments in section VI.C.3, neither the MolDx Program nor CAP accreditation provides a substitute for FDA oversight or mitigates the need for FDA oversight. With respect to LDTs approved by NYS CLEP, as described in section V.B.2, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP. As further discussed in section V.B.2, compliance with the QS requirements that FDA intends to enforce for these LDTs will help provide for quality manufacturing of these LDTs. FDA understands that NYS CLEP's clinical laboratory standards (which exceed CLIA requirements in certain respects) and its premarket review requirements collectively could generally satisfy these QS requirements except as to certain aspects of design control documentation, and FDA therefore does not anticipate significant additional burden with respect to compliance with these QS requirements for laboratories offering LDTs approved by NYS CLEP.

We further note that the absence of “credible information” establishing a lack of evidence of analytical or clinical validity, false or misleading claims, or a probability that the

IVD offered as an LDT will cause serious adverse health consequences does not justify delaying the phaseout of FDA's general enforcement discretion approach with respect to QS and premarket review requirements. Even in the absence of such "credible information," risks may exist that will be mitigated by compliance with applicable QS and premarket review requirements.

In addition, as described above, one comment submitted to the docket suggested that FDA exempt or more gradually phase in premarket review and QS requirements for certain LDTs as an alternative option in the event that FDA determined not to continue the general enforcement discretion approach with respect to premarket review and QS requirements for existing tests. As described in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways.

(Comment 160) FDA received several comments which stated that the Agency should end the general enforcement discretion approach with respect to MDR requirements and/or registration and listing requirements prior to deciding whether and when to phase out the general enforcement discretion approach with respect to other applicable requirements. These comments generally asserted that FDA lacks certain information necessary to inform the feasibility of the phaseout policy. For example, one comment stated that FDA is missing information regarding how many clinical laboratories currently offer LDTs, how many LDTs are on the market, how frequently LDTs are modified, the nature of those modifications, and the intended use(s) of those LDTs. In addition to these comments, a comment suggested that FDA's 4-year phaseout policy should apply only to high-risk IVDs offered as LDTs, after which FDA should determine how best to proceed with respect to other IVDs offered as LDTs.

(Response 160) FDA does not agree that the Agency should phase out the general enforcement discretion approach only with respect to MDR requirements and/or registration and listing requirements prior to determining how to proceed with respect to other applicable requirements. Although FDA is prioritizing the phaseout of the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements (followed by registration and listing requirements) to obtain additional information about potentially harmful IVDs offered as LDTs as soon as feasible (see discussion in section V.C), FDA already possesses enough information to determine that there is no longer a sound basis to generally treat LDTs differently from other IVDs and that the general enforcement discretion approach for LDTs does not best serve the public health. As discussed in response to comment 151, recent evidence from a variety of sources underscores the pressing need to better assure the safety and effectiveness of LDTs. Adopting a phaseout policy that only addresses MDR and registration and listing requirements at this time would inevitably delay the phaseout of the general enforcement discretion approach for other requirements beyond a 4 year period, and thus would be inconsistent with FDA's mission to protect the public health.

In addition, the FRIA (Ref. 10) provides estimates of much of the information that the comments characterized as "missing," such as how many laboratories currently offer IVDs as LDTs and how many IVDs offered as LDTs are on the market. Although we acknowledge that these are estimates, and we do not have exact numbers, we do not believe that should delay the phaseout of the general enforcement discretion approach, which we have determined is not in the best interest of public health. FDA also does not agree that certain information, such as the intended use(s) of all IVDs offered as LDTs, is necessary for FDA to determine whether and when to phase out the general enforcement discretion approach with respect to certain requirements.

FDA likewise does not agree that the Agency should phase out the general enforcement discretion approach for high-risk IVDs offered as LDTs prior to determining how to proceed

with respect to other IVDs offered as LDTs. As FDA explained in the NPRM and in this preamble, the Agency is aware of information showing that there is a high variability in the performance of IVDs offered as LDTs even in circumstances where the test technology is relatively simple and well-understood, and where the tests are low risk (88 FR 68006 at 68010-11).

(Comment 161) Some comments suggested that FDA consider stratifying the phaseout policy by annual test volume, due to the potential impact of high-volume LDTs on larger patient populations.

(Response 161) FDA does not agree that FDA's general enforcement discretion approach for LDTs should be phased out on a different timeline, in a different sequence, or otherwise in a different manner based on annual test volume. The importance of having assurances regarding the safety and effectiveness of IVDs offered as LDTs does not depend on whether IVDs are offered in low or high volume. Moreover, we think stratifying the phaseout in this way would be overly complicated for laboratories to comprehend and follow, and for FDA to implement.

(Comment 162) Some comments stated that FDA did not provide sufficient clarity or specificity regarding how it intends to implement the phaseout policy, resulting in uncertainty among laboratories which may have a "chilling effect." Another comment stated that the phaseout policy is too complicated for laboratories to follow.

(Response 162) We believe the information included in the phaseout policy, including the timeline for the various stages in the phaseout policy and information regarding enforcement discretion policies described in this preamble, provides clear expectations for laboratories that offer IVDs as LDTs. FDA appreciates that additional guidance regarding implementation of the phaseout policy may facilitate efforts by laboratories to comply with applicable requirements. As discussed more fully in response to comment 291, FDA anticipates issuing a small entity compliance guidance, issuing guidance documents, and/or making additional resources available on specific topics over the course of the phaseout period.

(Comment 163) A comment sought clarification regarding how the phaseout policy will apply to LDTs that are developed during the phaseout period, for example, LDTs that are developed between issuance of the rule and the start of stage 1 of the phaseout policy, or that are developed between successive stages of the phaseout policy.

(Response 163) Laboratories that first introduce IVDs offered as LDTs after the publication of the final rule and during the phaseout period will be expected to comply with requirements consistent with the dates identified for each stage of the phaseout policy. For example, an IVD offered as an LDT introduced 2½ years after publication of this final rule, which would be after the start of stage 2 of the phaseout policy but before the start of stage 3, would be expected to comply with requirements for which FDA has already phased out the general enforcement discretion approach under stages 1 and 2. FDA would expect compliance with QS requirements upon the start of stage 3 (other than requirements under § 820.198 (complaint files), for which FDA would have already phased out the general enforcement discretion approach under stage 1), and so on for stages 4 and 5 as applicable. Laboratories should also be aware of the enforcement discretion policies included in the phaseout policy, including those set forth in section V.B.

7. MDR Requirements

(Comment 164) Many comments supported FDA's proposal to end its general enforcement discretion approach with respect to the MDR requirements within 1 year from publication of the final rule. A comment suggested that this approach was reasonable regardless of the risk or volume of the LDTs the laboratory distributed. However, another comment suggested that FDA would need to provide additional guidance on the types of events it is interested in to avoid being flooded with reports about events that are of the type that are within CLIA's purview. This comment stated that the vast majority of laboratory adverse events are due to human error (e.g., manual mispipetting or a lost specimen) and not due to a design flaw with an LDT. Along these lines, another comment requested that FDA provide definitions of certain

terms in the context of laboratories, such as: FDA reportable adverse event, causal for MDR requirements, malfunction, and recall. Another suggested that such definitions align with reporting for “conventional” IVDs. Yet another comment suggested that FDA continue the general enforcement discretion approach for the MDR requirements until FDA provides education on this topic.

(Response 164) FDA agrees with the comments supporting FDA’s proposed phaseout of enforcement discretion regarding MDR reporting for IVDs offered as LDTs. As stated in section V.C, FDA is phasing out the general enforcement discretion approach with respect to the MDR requirements within one year from publication of the final rule for IVDs offered as LDTs. FDA acknowledges that some laboratories may not be familiar with FDA’s MDR requirements in part 803. However, FDA disagrees that this justifies waiting to phase out the general enforcement discretion approach with respect to those requirements. Laboratories should already have some processes in place for detecting problems with their IVDs to comply with CLIA regulations. In addition, FDA already has a number of resources to assist manufacturers in complying with MDR requirements, including guidance, information on FDA’s website, and webinars. These include, for example, FDA’s final guidance document entitled “Medical Device Reporting for Manufacturers” (Ref. 172), and information on “How to Report Medical Device Problems” on the Agency’s website (Ref. 173). Laboratories can better understand their responsibilities under part 803 by consulting these resources. FDA also intends to develop additional educational resources on MDR reporting to assist laboratories transitioning to compliance with these requirements.

With respect to the comment requesting that FDA provide definitions of certain terms in the context of laboratories, we note that the following terms are already defined in part 803 for purposes of MDR reporting requirements: “MDR reportable event” (§ 803.3(o)(2)), “caused or contributed” (§ 803.3(c)), and “malfunction” (§ 803.3(k)). These definitions apply to MDR reporting requirements regardless of whether the manufacturer of a device is a laboratory and

regardless of whether the device at issue is an IVD or another kind of device. Although the term “recall” is not used in FDA’s MDR regulations, we note that FDA regulations define the term “recall” at 21 CFR 7.3(g) (voluntary recalls) and 21 CFR 810.2(k) (mandatory device recalls). FDA has multiple resources for industry regarding recalls available on its website (see, e.g., Ref. 174).

Further, we note that MDR reportable events can include events caused by user error and are not limited to events resulting from a flaw in device design. For example, under the regulations, a device manufacturer must submit a report to FDA when it becomes aware of information that reasonably suggests that the manufacturer’s device may have caused or contributed to a death or serious injury (§ 803.50(a)(1)). Section 803.3(c) defines “caused or contributed,” to specifically include death or serious injury events occurring as a result of labeling or user error, among other things. However, if the manufacturer determines that an event is solely the result of user error with no other performance issue, and there has been no device-related death or serious injury, the manufacturer is not required to submit an MDR report. It would therefore generally be unlikely that a laboratorian losing a specimen (as referenced in the comment) would be considered a reportable event.

Importantly, CLIA does not require laboratories to report suspected device-associated adverse events to any Federal oversight authority. Therefore, we disagree with the comment suggesting that the phaseout of enforcement discretion for MDR requirements will result in a flood of MDRs for events “of the type within CLIA’s purview.”

(Comment 165) Several comments argued that MDR requirements should not apply to laboratories. Some of these comments indicated that the framework is not appropriate for laboratories, while others asserted that CLIA already covers the MDR activities. In particular, a comment stated that CLIA requires laboratories to identify, document, and perform corrective measures for any laboratory errors, including patient harm and that this documentation is reviewed by a CLIA inspector, its accrediting bodies, or exempt States. Further, the comment

stated that CMS-approved accrediting organizations are required to notify CMS within 10 days of any deficiency identified in an accredited or CLIA-exempt laboratory if the deficiency poses an immediate jeopardy to the patient or a hazard to the general public. Another comment suggested that FDA should not “subject” laboratories that have a system for reporting errors, and which are integrated within a health system, to the MDR requirements. Another comment opined that compliance with the MDR requirements was not warranted because events were rare and for most laboratories never occur.

(Response 165) FDA disagrees with the suggestion that laboratory compliance with the MDR requirements is not warranted. MDR reporting is an important postmarket surveillance tool that FDA uses to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of medical devices. FDA also disagrees that CLIA “covers” activities equivalent to complying with MDR reporting requirements. As explained in our responses to comments in section VI.C.2, the CLIA requirements are geared towards identifying issues and problems with the laboratory operations, not with an LDT itself. Further, unlike FDA’s MDR regulations, CLIA regulations do not require centralized reporting of suspected, device-associated adverse events to inform tracking and trending by a Federal oversight authority. FDA’s MDR regulations require that a manufacturer report to FDA within specified timeframes when the manufacturer receives or otherwise becomes aware of information reasonably suggesting that a device it markets may have caused or contributed to a death or serious injury, or has malfunctioned and the device or a similar device that the manufacturer markets would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur (§§ 803.50(a) and 803.53). It is important that FDA receive this information to enable it to identify trends and detect safety signals. For example, FDA received MDRs regarding incorrect test results due to “carryover” in automated test systems. “Carryover” is when a falsely high result is obtained due to residual analyte from a high concentration sample that was tested immediately prior. Upon review of trends across MDRs and further investigation,

FDA found that “carryover” caused inaccurate results across multiple automated test systems. Based on this finding, FDA worked to ensure that manufacturers of affected automated test systems addressed this issue. This included FDA classification of recalls for affected tests and manufacturer notification to users. As another example, FDA received MDRs indicating that ambient temperature in laboratories was affecting test results for common tests. Upon review of trends across MDRs and further investigation, we found that temperature interference caused inaccurate results across different tests that used different instruments from different manufacturers in different laboratories. Based on this finding, manufacturers redesigned affected tests to address this issue and submitted the changes for FDA review.

For similar reasons, FDA disagrees that there generally should be continued enforcement discretion for MDR requirements for laboratories that have a system for reporting errors, and which are integrated within a health system. Being integrated within a health system does not ensure centralized reporting of suspected, device-associated adverse events to inform tracking and trending by a Federal oversight authority in accordance with the manufacturer reporting requirements in part 803. Continuing to exercise enforcement discretion for the MDR requirements for all the entities identified in the comment would undermine FDA’s ability to identify trends or issues with the performance of IVDs offered as LDTs.

Moreover, FDA disagrees with the comment indicating that adverse events associated with LDTs are rare. In the absence of the type of reporting required by the MDR regulations, FDA has no assurance that adverse events associated with IVDs offered as LDTs are “rare.” Laboratories may not be tracking or reporting these adverse events currently, but that does not mean that they do not occur. However, if MDR reportable events are truly rare for certain laboratories, that should minimize additional burden of complying with the MDR requirements.

8. Registration and Listing Requirements

(Comment 166) FDA received many comments supporting the need for and rationale behind the proposal to phase out the enforcement discretion approach for registration and listing

requirements. One comment emphasized the need to create an active and accurate account of LDTs offered. Some comments voiced the need for FDA to identify and address poorly performing tests and the importance of transparency in terms of LDTs currently in use and any related adverse events.

(Response 166) FDA agrees that registration and listing information will provide FDA with a better understanding of the exact universe of IVDs offered as LDTs and facilitate oversight. FDA is phasing out the general enforcement discretion approach with respect to registration and listing requirements under 21 U.S.C. 360 and part 807 (excluding subpart E) 2 years after publication of this final rule. Under this timeline, FDA will be able to utilize registration and listing information to obtain an understanding of the universe of IVDs offered as LDTs to facilitate premarket review of those IVDs.

FDA also agrees with comments supporting FDA addressing poorly performing IVDs offered as LDTs and noting the importance of transparency in terms of any IVD adverse events. Beginning 1 year after the publication date of this final rule, FDA no longer intends to have the general enforcement discretion approach for MDR requirements, among other requirements. Enforcement of MDR requirements will enable FDA to systematically monitor significant adverse events to identify problematic IVDs offered as LDTs, such as those with poor performance or other safety issues.

(Comment 167) One comment suggested that FDA accelerate the phaseout timeline for registration and listing requirements, emphasizing the importance of this information in implementing the rest of the phaseout policy. Some comments agreed with the need to enforce registration and listing requirements but requested that FDA enforce only the elements that are currently required for IVDs and other devices, as it is “not appropriate to require more elements for LDTs than are currently required for IVDs and medical devices.”

(Response 167) As described in section V.C, FDA has determined that it will best serve the public health to phase out the general enforcement discretion approach with respect to

registration and listing requirements 2 years after publication of this final rule. We believe laboratories will have sufficient time to come into compliance with these requirements, and that any less time may not be sufficient. Moreover, FDA is first prioritizing the phaseout of the enforcement discretion approach for MDR requirements (and related complaint file requirements) and correction and removal requirements to obtain information about potentially harmful IVDs offered as LDTs as soon as possible (stage 1).

We note that the registration and listing requirements applicable to IVDs offered as LDTs are the same as those applicable to other IVDs and other devices; FDA is not establishing any new registration and listing requirements as part of this rulemaking.

(Comment 168) Several comments supported the enforcement of registration and listing requirements but urged FDA to phase out the general enforcement discretion approach for registration and listing requirements before phasing out the general enforcement discretion approach for other requirements. In particular, some comments suggested phasing out the general enforcement discretion approach with respect to registration and listing requirements before MDR requirements.

(Response 168) Under the final phaseout policy, FDA intends to phase out the general enforcement discretion approach for registration and listing requirements in stage 2, after first phasing out the general enforcement discretion approach for MDR requirements and correction and removal reporting requirements (as well as requirements regarding complaint files, given the connection between the complaint investigation and complaint file requirements and the MDR reporting regulations) in stage 1. FDA does not agree that the phaseout policy should address registration and listing requirements before the requirements described in stage 1. FDA has structured the phaseout policy to facilitate obtaining information about potentially harmful IVDs offered as LDTs as soon as feasible. As detailed in this preamble, FDA is concerned that some LDTs on the market may be posing risks to patients. Phasing out the general enforcement discretion approach for MDR requirements and correction and removal reporting requirements

(stage 1) will help FDA to systematically monitor significant adverse events and identify problematic IVDs offered as LDTs. In addition, under this phaseout structure, laboratory manufacturers will have sufficient time to comply with registration and listing requirements (stage 2).

FDA therefore intends to phase out the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements before registration and listing requirements. We note that, as stated in section V.C, FDA generally does not intend to enforce requirements to include certain information (e.g., registration numbers, premarket submission numbers) in reports or other submissions to the Agency until the information is addressed in a later stage of the phaseout policy.

(Comment 169) FDA received comments requesting guidance on the information required for registration and listing. One comment suggested that FDA consider creating temporary product codes in order to advance the registration and listing process while product codes are developed.

(Response 169) FDA has instructions and educational resources relating to registration and listing requirements available on FDA's website (Ref. 175). For more information on product codes, see FDA's final guidance on "Medical Device Classification Product Codes." FDA intends to consider creating product codes to be used during the registration and listing process where no product code exists for a given test type. FDA also intends to consider providing additional or more targeted resources on registration and listing requirements over the course of the phaseout period, as appropriate.

(Comment 170) One comment encouraged FDA to establish a clear and publicly available mechanism that would allow patients and providers to "ascertain the test's level of review."

(Response 170) As detailed in section V.C, FDA intends to phase out the general enforcement discretion approach with respect to registration and listing requirements 2 years

after publication of this final rule. The registration and listing database generally will provide patients and healthcare providers with information about specific IVDs as required by FDA regulation (*see, e.g.*, § 807.26(g)), including information regarding an IVD’s “level of review.” In particular, we note that the device listing database includes information indicating the type of premarket submission (if any) for the listed device. We recognize that this information may not be included for currently marketed IVDs offered as LDTs, as well as for IVDs offered as LDTs after the publication of the final rule prior to stages 4 and 5.

(Comment 171) FDA received comments regarding the potentially prohibitive costs of registration and listing for some laboratories. One comment recommended FDA enforce “limited” registration and listing requirements for existing tests and allow laboratories to provide an “electronic, internet-based test menu” housed on the laboratory’s website in lieu of individual test listings. Another comment noted that some laboratories maintain publicly available test catalogs online that include such information on tests’ intended use, test method, and specimen requirements, and urged FDA to continue to exercise enforcement discretion if laboratories submit links to these test catalogs instead of providing all the information required for listing.

(Response 171) FDA disagrees with these comments. As described in section II.F.2.a of the FRIA, FDA estimates the cost of compliance with registration and listing requirements (this does not include registration fees) to range between \$0.20 million and \$0.82 million in initial costs and between \$0.08 million and \$0.34 million in recurring costs for between 590 and 2,362 affected laboratories (as well as between \$0.02 million and \$0.07 million in initial costs for between 47 and 189 new affected laboratories each year). This amounts to less than \$500 per laboratory for compliance with initial registration and listing requirements and slightly over \$100 per laboratory for compliance with annual requirements. In addition, under current user fee rates, laboratories must pay an annual establishment registration fee of \$7,653. FDA believes it is unlikely for these costs of registration and listing to be prohibitively expensive for laboratories.

FDA also disagrees with the suggestions provided in these comments. FDA has determined that collecting registration and listing information for all laboratories and IVDs offered as LDTs in a uniform and systematic manner will provide the Agency with a holistic and comprehensive view of the universe of IVDs offered as LDTs and better enable FDA to help assure the safety and effectiveness of LDTs. FDA does not believe “limited” registration and listing information or the submission of electronic internet-based test menus/catalogs would allow the Agency to have such a comprehensive view.

(Comment 172) One comment stated that laboratories with multiple locations operating under a common quality management system should be allowed to register as a single entity with multiple sites.

(Response 172) With the phaseout of the general enforcement discretion approach, manufacturers of IVDs offered as LDTs generally will be expected to comply with registration and listing requirements under 21 U.S.C. 360, part 607, and part 807 (excluding subpart E) in the same way as other medical device manufacturers. FDA’s regulations define establishment in the registration context as “a place of business under one management at one general physical location at which a device is manufactured, assembled, or otherwise processed.” 21 CFR 807.3(c); see also 21 CFR 607.3(c) (defining “establishment” in the context of registration requirements for licensed devices as “a place of business under one management at one general physical location”). To the extent a laboratory has multiple sites in different physical locations, each of these sites would be registered separately. This information is important to inform FDA’s oversight, including with respect to conducting inspections. If a laboratory with multiple sites were to register as a single entity that would impede such oversight and FDA’s ability to conduct inspections in a timely and efficient manner.

(Comment 173) One comment suggested that FDA should reduce the burden of registration and listing for clinical laboratories by continuing an enforcement discretion approach

for low-risk tests with regard to registration and listing requirements if the laboratory “documents” all low-risk LDTs it performs as required by CAP accreditation.

(Response 173) As discussed in section VI.L.4, FDA does not think it is appropriate to continue an enforcement discretion approach for low-risk LDTs, including with respect to registration and listing requirements. Moreover, specifically regarding registration and listing requirements, comprehensive registration and listing is critical to inform FDA’s understanding of the universe of IVDs offered as LDTs and to help FDA identify, monitor, and address any issues with IVDs offered as LDTs. In addition, as discussed in response to comment 171, FDA does not anticipate the costs of registration and listing to be prohibitively expensive for laboratories. We also note that under the phaseout policy, FDA expects compliance with registration and listing 2 years after publication of the final rule (stage 2), which we anticipate will be sufficient time to come into compliance with the registration and listing requirements.

9. Corrections and Removals Reporting Requirements

(Comment 174) A comment stated that it did not agree with FDA’s proposal to end the general enforcement discretion approach with respect to the correction and removal reporting requirements because it perceives CLIA as adequately covering these requirements. Another comment suggested that FDA continue the general enforcement discretion approach for correction and removal reporting requirements if laboratories have documented corrective action and removal processes.

(Response 174) FDA disagrees with these comments. As described in sections V.C, VI.C.2, and VI.D.8, CLIA requirements are complementary and distinct from FDA requirements. They do not provide adequate oversight of IVDs offered as LDTs to render FDA oversight unnecessary. Under the FD&C Act, certain entities are required to report device malfunctions, adverse events, and corrections and/or removals of a device. Moreover, FDA has authority to take steps when a device presents a risk to the public health, including utilizing its mandatory recall authority. There are not the same requirements and authorities under CLIA.

Enforcement of correction and removal reporting requirements along with the MDR requirements will enable FDA to systematically monitor adverse events, identify problematic IVDs offered as LDTs, and monitor corrections and removals of IVDs offered as LDTs. Moreover, as FDA stated in response to comment 165, MDR is one of the postmarket surveillance tools that FDA uses to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of medical devices. Under § 806.10, manufacturers and importers are required to submit a written report to FDA of any correction or removal of a device initiated by such manufacturer or importer if the correction or removal was initiated: (1) to reduce a risk to health posed by the device or (2) to remedy a violation of the FD&C Act caused by the device which may present a risk to health (subject to the limitation and exemption described in § 806.10(a)(2)), within 10 working days of initiating such action. This information is critical to FDA's ability to assure that patients, healthcare providers, and other stakeholders have information about safety or other issues with a device, and to monitor the effectiveness of corrective actions.

Laboratories having "documented processes" relating to corrections and removals does not provide the same types of critical assurances. If laboratories do have existing internal processes, however, that should ease the burden of complying with FDA's correction and removal reporting requirements.

10. Investigational Device Exemption Requirements

(Comment 175) Several comments suggested clarification around when investigational use requirements apply to IVDs offered as LDTs. One comment requested that FDA address how the phaseout would impact laboratories that validate reagents for use in a clinical trial where the reagent has been labeled by its manufacturer as being RUO, or validate kits that have been manufactured by a third party but which are validated by the laboratory for a specific purpose for use in a clinical trial, e.g., for clinical trial stratification, inclusion/exclusion determinations, or safety assessments of enrolled subjects. This comment further stated that FDA should be

cognizant of the time that is required to get a test ready for use in a clinical trial. Another comment sought clarification regarding potential impacts of the phaseout on clinical research organizations (CROs). This comment observed that it would be redundant for both CROs and their clients to make submissions to FDA for the same IVDs, and further stated that if “CRO LDTs” are “restricted” by the phaseout, there could be significant delays with respect to drug and IVD development. The comment recommended that FDA consider granting all accredited CRO laboratories “an exemption” from applicable requirements. Multiple comments requested clarification regarding clinical trial assays that have no direct impact on patient care, such as for pharmacokinetic analyses for dosing studies. Others cited the importance of IVDs offered as LDTs in drug trials and suggested continued enforcement discretion to support therapeutic product development.

(Response 175) The IDE requirements under section 520(g) of the FD&C Act and part 812 apply to clinical investigations of devices. However, certain categories of clinical investigations of devices are exempt from most IDE requirements under § 812.2(c), and certain other categories of device investigations are deemed to have an approved IDE application under § 812.2(b) if the conditions therein are met. Sponsors and investigators of investigational devices have obligations under the IDE regulations (and related regulations such as parts 50 and 56 (21 CFR parts 50 and 56), regarding protection of human subjects and institutional review boards, respectively). Thus, if a laboratory is a sponsor or investigator of an investigational IVD (including a reagent or instrument), that laboratory is responsible for ensuring compliance with all applicable requirements under the FD&C Act and FDA’s regulations. Investigational IVDs may include an IVD that was previously labeled RUO by a third-party manufacturer, an IVD that was previously labeled by a third party manufacturer for a use different from the use in the clinical investigation, or an IVD manufactured by a third party but modified by the laboratory for purposes of the clinical investigation. Additional information regarding RUO-labeled products is

available in FDA's final guidance document entitled "Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only" (Ref. 176).

Under the phaseout policy described in section V.C, FDA expects compliance with applicable IDE requirements and other applicable requirements, such as parts 50 and 56, for investigations that involve investigational IVDs offered as LDTs 2 years after publication of this final rule. FDA has several resources available to help sponsors comply with IDE requirements in the context of clinical investigations of IVDs, including a final guidance document entitled "In Vitro Diagnostic (IVD) Device Studies--Frequently Asked Questions," which has been available to stakeholders since June 2010 (see Ref. 177).

We recognize that some sponsors of clinical investigations of investigational IVDs may choose to engage with a CRO, including a CRO laboratory, to perform certain duties, including certain obligations under the IDE regulations. It is up to the sponsor and CRO to decide which duties and obligations the CRO will undertake. The obligations that apply under the IDE regulations must be met regardless of which party performs them. If an IDE application is required, either the sponsor or the sponsor's CRO may submit the application, i.e., it is not necessary for both parties to submit an IDE application for the same clinical investigation of the investigational IVD. We note that to the extent a CRO submits an IDE application to FDA, this application would be distinct from the premarket submission (such as a 510(k), De Novo, or PMA) that the CRO's client may subsequently submit to FDA if the client intends to offer the IVD.

With respect to use of IVDs offered as LDTs in clinical investigations of drugs, FDA has issued a draft guidance document entitled "Investigational IVDs Used in Clinical Investigations of Therapeutic Products" (this guidance has not been finalized at this time but it includes information that may be helpful, such as a discussion of certain IDE requirements) and a final guidance document entitled "Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry," which

provide additional information regarding investigational use requirements in such settings (see Refs. 178 and 179). As FDA has explained, sponsors should already be aware that all investigational IVDs used in therapeutic product trials are subject to IDE requirements, and may require the submission of an IDE application separate from an investigational new drug application (IND) to the extent an IDE application is required under part 812 of FDA's regulations (Ref. 178). When an IDE application is not required, a therapeutic product trial that uses an investigational IVD must still comply with other IDE requirements as applicable under part 812. An IDE and an IND may be held by the same entity or may be held by different entities (for example, a CRO and its client); however, IDE and IND applications may cross-reference each other through a letter of authorization, or in cases where either an IND or an IDE application is not required, information may be provided through the use of a master file (MAF). As explained in section V.C, FDA generally expects compliance with the device investigational use requirements 2 years after publication of the final rule. Given this time period to prepare, FDA does not anticipate that compliance with IDE requirements will meaningfully delay drug or IVD development activities. Further, FDA notes that investigations of diagnostic devices are exempt from most IDE requirements, provided that certain labeling requirements are met and the testing: is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure (§ 812.2(c)(3)). Additionally, investigations of diagnostic devices that are not significant risk are deemed to have an approved IDE (without submission of an IDE application) if the conditions in § 812.2(b) are met.

Finally, in response to comments that inquired regarding the applicability of IDE requirements to certain types of assays, FDA would generally need additional information regarding the specific assay and the investigation in which the assay is intended to be used. FDA encourages stakeholders to consult the materials that have been made available by the Agency

regarding IDE requirements, including the final guidance documents referenced above.

Laboratories may also contact FDA with product-specific questions, as discussed elsewhere in this preamble.

11. Labeling Requirements

(Comment 176) FDA received several comments inquiring about labeling requirements for LDTs and requesting clear guidance on the required information and where such information needs to be located. One comment asked whether labeling for LDTs should be written with the performing laboratory as the audience or the ordering physician, noting that this distinction “is critical as it directly impacts the communication of clinical information, essential for accurate patient diagnosis and treatment.” Another comment stated that FDA should not consider the “test menu, educational and interpretive information, and scientific publications included on the laboratory website” as labeling and must not treat this information in the same way as product advertisement. Another comment stated that information listed as part of test menus “cannot be subject to rigid labeling requirements and should not be considered ‘promotional.’”

(Response 176) FDA appreciates the comments requesting clarification regarding the labeling requirements for LDTs. FDA’s regulations in § 809.10 set forth specific labeling requirements for IVDs, including specific information that must be included. FDA anticipates that this information might be encompassed in more than one document, such as the test protocol, test report template, and test menu.

FDA intends to provide more targeted guidance and/or additional resources regarding the applicable labeling requirements prior to stage 2 of the phaseout period.

(Comment 177) One comment expressed concern that FDA labeling requirements would be duplicative because similar information is provided in the test ordering form or as part of the electronic order entry process. The comment also expressed concern that FDA labeling requirements would be impractical because there is limited space on the label after compliance with CLIA and other requirements, and that data elements of electronic health records would

need to be added and then standardized and harmonized. This comment recommended FDA continue the general enforcement discretion approach for labeling requirements if the “LDTs’ information” is documented and made available to FDA upon request.

(Response 177) FDA disagrees with this suggestion. FDA is phasing out the general enforcement discretion approach with respect to labeling requirements under 21 U.S.C. 352 and parts 801 and 809, subpart B. FDA believes that generally enforcing the labeling requirements for IVDs offered as LDTs will provide for consistent and comprehensive information that will benefit healthcare providers and patients and help FDA to better protect and promote the public health. As noted in response to comment 176, FDA anticipates that the information required under § 809.10 might be encompassed in more than one document, such as the test protocol, test report template, and test menu. In addition, in the case of insufficient space with respect to the label, to the extent there is an immediate container onto which a label could be affixed, we note that § 809.10(a)(10) provides that some of the required information may appear on the outer container labeling. These and other labeling requirements are additionally discussed in FDA’s final guidance document entitled “Labeling: Regulatory Requirements for Medical Devices” (Ref. 180).

As noted in response to comment 176, FDA intends to provide more targeted guidance and/or additional resources regarding labeling requirements prior to stage 2 of the phaseout period.

(Comment 178) FDA received one comment stating that significant problems for laboratories could be expected when “adhering to guidance for manufacturers regarding labeling practices.” The comment also stated that LDTs cannot reasonably be expected to adhere to the label requirements under § 809.10 as there is no physical container onto which a label could be affixed. Similarly, the comment noted that creation of a package insert would not be practical in a laboratory setting.

(Response 178) It is unclear what “guidance” the comment is referring to as the comment did not identify any specific guidance. To the extent the comment is referring to the labeling requirements in § 809.10, as noted in response to comment 176, FDA anticipates that the information required under § 809.10 might be encompassed in more than one document, such as the test protocol, test report template, and test menu.

FDA’s IVD labeling requirements in § 809.10(b) specify the information that must be included in labeling and provides a package insert as an example of labeling. However, the regulations do not require that the labeling be a package insert.

FDA recognizes that guidance and/or additional resources on the labeling requirements for LDTs would be helpful for laboratory manufacturers. Therefore, FDA intends to provide more targeted guidance and/or additional resources on labeling requirements, including label requirements, prior to phase 2 of the phaseout period.

(Comment 179) One comment requested that FDA clarify expectations regarding compliance with UDI requirements for IVDs offered as LDTs.

(Response 179) FDA recognizes that the labeling requirements under part 801 of FDA’s regulations, for which FDA intends to phase out the general enforcement discretion approach under stage 2 of the phaseout policy (see section V.C), include UDI requirements. FDA intends to provide more targeted guidance and/or additional resources regarding UDI requirements prior to stage 2 of the phaseout period.

12. Quality System Requirements

(Comment 180) A number of comments agreed with FDA that laboratories should have quality systems to help ensure that there are less errors with IVDs offered as LDTs. These comments went on, however, to express concerns with FDA’s proposal to exercise enforcement discretion with respect to certain QS requirements in part 820 for those IVDs for which all design and manufacturing activities occur within a single CLIA-certified laboratory that meets the regulatory requirements to perform high complexity testing and for which distribution of the

IVD does not occur outside that single laboratory. In particular, comments thought that having two different systems could result in confusion about what is “required.”

(Response 180) FDA agrees that quality systems are important to assuring that a manufacturer consistently manufactures IVDs that have appropriate assurance of safety and effectiveness, and FDA generally expects laboratories to comply with the QS requirements at the 3-year mark under stage 3 of the phaseout policy (other than requirements under § 820.198 (complaint files), for which FDA will phase out the general enforcement discretion approach under stage 1 of the phaseout policy). As stated in section V.C, FDA is also finalizing the QS policy for LDTs as proposed. For LDTs, FDA will expect compliance at the 3-year mark with some, but not all, of the QS requirements.

FDA recognizes that this policy creates a more nuanced approach in terms of expectations for QS compliance, but we believe this nuance is justified because it may be important for some laboratories while still serving FDA’s public-health goals. FDA has set forth the reasoning for this policy, which is based on certain quality assurances provided through compliance with CLIA requirements, in section V.C. This policy is consistent with the Agency’s least burdensome approach for devices. FDA also welcomes compliance with the full QSR, including to avoid confusion. As with any enforcement discretion policy, this policy is subject to change as circumstances warrant.

(Comment 181) Many comments sought additional clarity about the QS requirements. These comments explained that laboratories do not have experience with FDA’s QS requirements and may need substantial assistance in understanding the requirements and whether they can “leverage” their existing quality system to meet FDA’s requirements. Another comment questioned the requirements that would be included in FDA’s final rule amending part 820 and whether FDA would require certification to the relevant ISO standard (i.e., ISO 13485). A similar comment asked whether FDA would make guidance available to clinical laboratories on this topic and whether such guidance would be issued with enough time for laboratories to take

necessary actions to come into compliance. Another comment requested that FDA provide guidance on the gaps that exist between the QSR and CLIA.

(Response 181) FDA understands that compliance with the FD&C Act and its implementing regulations, including part 820, is unfamiliar for many laboratories. We intend to engage in various educational activities, including issuing timely guidance, to assist laboratories with understanding and complying with applicable requirements. Additionally, FDA has just issued its final rule amending part 820 (see 89 FR 7496). This rule will take effect 2 years from publication on February 2, 2026. FDA anticipates providing to all its stakeholders, including laboratories, timely guidance on compliance with the regulatory requirements in that rule. Laboratories can take advantage of these efforts to obtain a better understanding of the applicable requirements.

As for the specific question about certification to ISO 13485, FDA is not requiring certification and such certification will not substitute for an FDA routine inspection under section 704 of the FD&C Act (89 FR 7496, 7518).

(Comment 182) We received several comments about the relationship between FDA's QSR and CLIA. A comment suggested that FDA should harmonize its QSR with CLIA. Another comment stated that FDA should specify whether compliance with part 820 obviates the need to maintain CLIA certification.

(Response 182) First, the requirement to comply with part 820 does not obviate the need for a laboratory to maintain CLIA certification. CMS administers CLIA and its implementing regulations, whereas FDA administers the FD&C Act and its implementing regulations, including the QSR. As FDA has explained elsewhere in this preamble, the schemes implemented by CMS and FDA are complementary and not duplicative; both are important to help assure quality testing with laboratory-manufactured tests.

Second, FDA disagrees that the QSR and CLIA regulations require harmonization because, as stated previously, the two schemes are complementary, not duplicative or conflicting.

In addition, to the extent that the comments were suggesting that FDA needs to revise the QSR in light of CLIA, FDA disagrees. CLIA and its implementing regulations and FDA's QSR are two different regulatory frameworks based in different statutory authorities intended to achieve different goals. Unlike CLIA and its implementing regulations, the QSR provides a basic framework of requirements critical for a quality system for manufacturing devices. These requirements are flexible, apply to many device types, and recognize that manufacturing circumstances may vary. Under the QSR, manufacturers are responsible for complying with those parts of the regulation that are applicable to their operations, and the QSR is intended to be sufficiently flexible to be applied to the spectrum of devices as well as manufacturers of varying size and operation type. Although FDA has adopted a policy described in this preamble that takes into account certain assurances provided by CLIA for LDTs (see section V.C), that policy does not mean that the requirements are duplicative or conflicting or that amendments to the QSR are required (see comment response 82).

(Comment 183) Some comments argued that the QSR is not appropriate for laboratory testing and it does not cover all aspects of laboratory operation. A comment suggested that this is because laboratories that develop LDTs do not engage in manufacturing. Other comments stated that ISO 15189: Medical Laboratories (ISO 15189) is the more appropriate standard.

(Response 183) As stated above, the QSR provides a basic framework of requirements critical for a quality system for manufacturing devices. These requirements are flexible, applying to many device types, and recognize that manufacturing circumstances may vary. Under the QSR, manufacturers are responsible for complying with those parts of the regulation that are applicable to their operations, and the regulation is intended to be sufficiently flexible to be applied to the spectrum of devices as well as manufacturers of varying size and operation type. In this manner, the QSR is suited to the manufacture of IVDs in laboratories. Furthermore, because the QSR focuses on assuring the quality of the device itself, it need not cover "all aspects of laboratory operation."

FDA also disagrees with the comment that laboratories that develop LDTs do not engage in device manufacturing. Section 820.3(o) defines a manufacturer as “any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions.” As explained in the NPRM and in section VI.D. of this preamble, LDTs are devices (88 FR 68006 at 68015-16). As such, when laboratories design, assemble, or process an LDT, they are manufacturers of a finished device and as such are subject to the QSR (for further discussion, see comment response 71).

ISO 15189, similar to CLIA, specifies requirements for quality and competence in medical laboratories, focusing on the competencies and qualifications of laboratory personnel and testing processes. The QSR is focused on a robust quality system that promotes safety and effectiveness of the device itself through controls such as adequate management oversight, procedures for validating changes, monitoring, and audits, and plans for handling non-conformances. In contrast, ISO 15189 does not address the processes involved in manufacturing an IVD, including design controls. Thus, ISO 15189 is not the appropriate standard for laboratory activities relating to device manufacturing.

(Comment 184) Several comments suggested that compliance with the QSR is not warranted because of the quality management systems laboratories already have in place. One comment went on to state that such systems comply with Federal and State facility licensure requirements, CLIA certification, medical test site requirements, CAP accreditation, and participation in CLIA-required proficiency testing surveys/challenges. Another suggested that CLIA regulation and CAP combined are sufficient. Another comment suggested that FDA did not present scientific data that having multiple quality systems produces a better test result.

(Response 184) FDA disagrees with these comments. As explained throughout this preamble, none of the requirements the comments referenced address the quality and

manufacturing of the device itself. For example, the focus of CLIA is on the testing process as it is implemented in a given laboratory, focusing on the qualifications, responsibilities, and ongoing competencies of laboratory personnel, rather than the manufacture of the IVD itself. For more information about the differences between CLIA and FDA regulation, see our responses to comments in section VI.C.2.

Some commenters pointed to participation in CLIA-required proficiency testing surveys/challenges, but those surveys/challenges are only required for certain analytes; the majority of IVDs offered as LDTs test for analytes that do not have required proficiency testing (Refs. 181 and 182). Proficiency testing events are performed on a regularly scheduled basis to assess whether laboratories are performing tests appropriately. Such testing is not intended to assess a laboratory's ability to continually manufacture safe and effective IVDs, nor does it establish the performance of a particular test, as further described in response to comment 9.

With regard to CAP accreditation, as discussed in more detail in response to comment 18, CAP accreditation addresses the manner in which the laboratory performs a test and does not assess the laboratory's processes for making the test. Further, CAP accreditation is voluntary. As for state licensure requirements, the comment did not identify specific states or their requirements for FDA to assess. When FDA considered comments about New Jersey's laboratory certification program and Washington's medical test site program, it concluded that they are focused on laboratory operations, like CLIA, and do not provide assurances regarding the analytical and clinical validity of LDTs (Ref. 84), see response to comment 22. FDA has included a policy for LDTs that are approved by NYS CLEP (see section V.B.2).

While none of the existing requirements discussed here are duplicative of the QSR, FDA is adopting an enforcement discretion policy with respect to QS requirements for LDTs in recognition that compliance with CLIA requirements provides some quality assurances that may be relevant to laboratories' manufacturing practices, as described in section V.C.

Finally, we disagree that FDA is required to produce or cite scientific data showing that “having multiple quality systems produces a better test result.” Regardless of the presence of other quality systems, the question is whether laboratory compliance with the quality system requirements under the FD&C Act, as applicable, will advance public health by helping assure that IVDs are safe and effective. FDA has determined that it will, based on the evidence before it. FDA need not “conduct or commission [its] own empirical or statistical studies” to draw this conclusion. *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150 at 1160.

(Comment 185) A comment concurred with the QS requirements that FDA proposed to focus on for LDTs; however, the comment indicated that FDA should also focus on § 820.70; production and process controls. The comment went on to state that CLIA does not fully address any of these regulations.

(Response 185) FDA agrees that CLIA does not duplicate QS requirements. However, CLIA does provide some relevant assurances, including with respect to § 820.70, in the context of manufacturing activities occurring within a single CLIA-certified laboratory that meets the regulatory requirements to perform high complexity testing and for which the IVD is not transferred outside that single laboratory. Section 820.70 requires manufacturers to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications and to establish and maintain process control procedures where deviations from device specifications can occur due to the manufacturing process. This provision also has requirements addressing environmental controls, personnel cleanliness, contamination control, building suitability, equipment sufficiency, manufacturing material use and removal, and validation of software used in automated processes. CLIA regulations require that the laboratory have control procedures to monitor test accuracy and precision and detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance (42 CFR 493.1256). This provision also addresses requirements for supply checks. Additionally, other CLIA requirements address facility requirements, including equipment, and personnel

competency (42 CFR 493.1101 and 1235). FDA determined that these requirements, in combination with the QS requirements on which FDA is focusing oversight (such as the design controls in § 820.30), provide assurances relevant to § 820.70.

(Comment 186) Several comments raised concerns about the costs of compliance with the QSR. A comment took issue with FDA's statement, as characterized by the comment, that the final rule amending part 820 would not impose new requirements because that was a comparative statement about the differences between FDA's proposed rule and the current part 820, but that many LDT manufacturers would be complying with part 820 for the first time. Other comments asserted that the cost of QS compliance will prohibit small companies from marketing tests, hurting patients.

(Response 186) FDA acknowledges that many laboratories may not have experience with part 820. In the NPRM, FDA stated that FDA's proposed amendment of part 820 was substantially similar to the current QS requirements simply to explain that laboratories can use the current part 820 to understand FDA's requirements with respect to quality systems, and to prepare for compliance even though the final QS rule had not been issued at that time--not to diminish the effort needed to comply (see 88 FR 68006 at 68026).

FDA continues to believe that QS compliance is important to help assure the safety and effectiveness of IVDs offered as LDTs, as explained throughout this preamble (see, e.g., section III.B.1). However, FDA has also considered the costs associated with QS compliance for laboratories, and has taken those costs into account in developing the policy for currently marketed IVDs offered as LDTs (see section V.B.3). Under that policy, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)), for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3. This policy applies to all laboratories, including small laboratories. In light of this policy, FDA disagrees that the cost of compliance

with the QSR, alone, would cause small laboratories to close. (For more information about impacts on small businesses, see section VI.G). We note that in the FRIA, we estimate \$71 million less in one-time costs for compliance with QS requirements for all affected entities compared to the PRIA, and \$354 million less in annual recurring costs (see Ref. 60).

Further, as discussed in the NPRM and in this preamble, FDA intends to exercise enforcement discretion with respect to certain QS requirements for LDTs as discussed in section V.C.3, which may reduce costs for such laboratories.

(Comment 187) A comment indicated that enforcing QS requirements for laboratories could have negative impacts on manufacturers of laboratory tools and instruments, and on producers of reagents and antibodies, because they may not be able to meet the supplier requirements. Another comment stated that the supplier requirements in § 820.50 (purchasing controls) expand the responsibility of the laboratory professional beyond the CLIA requirements, and inappropriately place “liability” on laboratory professionals, who are acting as healthcare providers, for ensuring the quality of reagents instead of placing that responsibility on suppliers.

(Response 187) The manufacturers of test components that are themselves finished devices, such as instruments, reagents, and antibodies, intended for clinical purposes should already be complying with the QSR, including requirements in § 820.50, and thus we would not expect negative impacts on suppliers as a result of this phaseout policy. FDA agrees that when a laboratory manufacturer makes a test system using components that are not intended for clinical use, such as components labeled RUO, the laboratory is subject to the purchasing controls set forth in § 820.50, which may require validation of such components for the clinical use.⁸⁷ FDA acknowledges that laboratory manufacturers may prefer to source components manufactured under a QS to help assure the quality of their test.

⁸⁷ See Ref. 176, which states that it is important that research and investigational use only products should not be distributed for clinical diagnostic uses.

Section 820.50 (purchasing controls) requires that manufacturers of finished devices assess the capability of their suppliers to produce acceptable components. When the manufacturer ensures that components, such as laboratory instruments, reagents, and antibodies, are adequate for the IVD's intended use, this helps to ensure the accuracy of the IVD being manufactured. Ultimately, the laboratory manufacturer cannot be sure that the specifications for a finished IVD are met if they did not take steps to ensure that the individual components of the finished device meet specifications. As such, FDA disagrees that such a supplier requirement is inappropriate. Enforcement of supplier requirements will provide assurances that IVDs continue to be manufactured with quality components over time.

(Comment 188) A comment argued that the QSR does not translate well to laboratory activities, and that CLIA addresses many of the QS requirements on which FDA proposed to focus in the QS policy for LDTs. The comment stated that the acceptance activities in §§ 820.80 and 820.86 do not translate well to laboratories, specifically highlighting the requirements in § 820.80(d) and indicating, according to the commenter, that it is unclear how a laboratory might comply with the requirement that manufacturers establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. The comment also specified that a number of CLIA provisions in 42 CFR part 493, subparts J and K serve the same purposes as or cover the activities in § 820.30 (design controls), § 820.100 (corrective and preventive action), and part 820, subpart M (records requirements).

(Response 188) FDA disagrees that the CLIA regulations cited in the comment provide assurances relevant to the cited QS requirements in part 820. CLIA covers laboratory operations, including processes for handling and dealing with components and specimens, as well as documenting and responding to patient test result errors as a result of laboratory operations. None of the CLIA provisions include requirements for designing or monitoring issues with the IVD itself. For example, 42 CFR 493.1241 addresses the need for a test request, 42 CFR

493.1242 addresses policies for specimen handling, storage, and processing, 42 CFR 493.1252 addresses proper storage of reagents and specimens, 42 CFR 493.1253 addresses performance specification with regards to accuracy, precision, and range (without tying those specifications to the design of the test and without addressing design input and output review), and 42 CFR 493.1290 and 1291 address other issues related to laboratory operations rather than faulty device design, including the content of test reports, handling of abnormal results, error reporting requirements, and assessment and resolution of identified problems with regard to patient test result errors.

In contrast, the design controls in § 820.30, at a high level, address: design and development planning, procedures for ensuring that the design requirements are appropriate for the device intended use, including design inputs, procedures for defining and documenting design outputs, procedures for design review, verification, and validation, and procedures for documenting and validating design changes. Each of these requirements aims to ensure that devices perform as intended, which is a concept not covered by the CLIA requirements.

Similarly, the CLIA requirements on correcting errors (42 CFR 493.1291) and records requirements (42 CFR 493.1251 (procedure manual), 42 CFR 493.1101 (facilities), 42 CFR 493.1105 (retention requirements), 42 CFR 493.1291 (test report), and 42 CFR 493.1283 (test records)) are focused on addressing laboratory errors and laboratory recordkeeping. The QS requirements are focused on assuring the quality of the IVD offered as an LDT itself, and compliance with these requirements addresses issues of device quality. As detailed in comment 182, CLIA and the QSR are complementary but different in focus.

While FDA acknowledges that the terminology of the QSR may not be familiar to many laboratories, as stated in comment 181, FDA intends to engage in educational activities to assist laboratories in understanding compliance with the QSR. FDA disagrees that lack of familiarity means that the requirements are inappropriate for laboratories. The QSR is written in a flexible manner and there are many ways that a laboratory may comply with the QSR. For example, the

comment cited uncertainty about how a laboratory would comply with acceptance activities in §§ 820.80 and 820.86 generally, and specifically questioned the ability for laboratories to comply with finished device acceptance requirements in § 820.80(d), which requires that manufacturers, including laboratories, establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets specified requirements; in other words, assessing whether the finished device is what you expected. For example, laboratories procure reagents from external sources for use as part of their LDT. The laboratory would need suitable methods to identify reagents in a way that distinguishes between those that have just been received and not yet evaluated, those that have been received and found unacceptable according to their purchasing controls, and those that have been received and found acceptable according to their purchasing controls and are therefore adequate for use as part of the final LDT. Manufacturers have the flexibility to choose a combination of methods to comply with these requirements, including finished device inspection and testing, acceptance criteria, and identification methods, provided such methods will accomplish the required result. For example, for final acceptance activities, laboratories may have a procedure that specifies the methods and materials and acceptance criteria (including confidence intervals) that would be used to assess whether the final LDT meets those specified acceptance criteria, prior to the LDT being used for clinical use.

(Comment 189) A comment recommended that FDA establish an “umbrella approval” for CGMP and software modules from each laboratory and that FDA should recognize results from third party quality efforts.

(Response 189) In general, FDA does not “approve” manufacturing practices, although they are reviewed within the context of a PMA. We note that, in premarket applications, manufacturers may rely on information that they previously submitted to FDA by referencing where the information was provided in a previous submission. Establishment of an “umbrella approval” for CGMP and software modules is outside the scope of this rulemaking.

With regards to third-party quality efforts, to the extent that the comment is referring to CAP accreditation or NYS CLEP assessments, see our response to comment 18 and section V.B.2 for more information on that topic.

13. Premarket Review Requirements

(Comment 190) Several comments expressed concern that compliance with premarket review requirements would be infeasible and cost-prohibitive for laboratories with limited resources and stated that FDA should take into account that these laboratories also pay fees to CMS associated with CLIA. One comment stated that FDA should “[s]et reasonable pricing for LDT review and registration.” One comment suggested that FDA should consider temporarily reducing user fees for premarket submissions during the phaseout timeline.

(Response 190) In the final phaseout policy, in recognition of patient reliance and cost considerations, among other things, FDA has included policies for enforcement discretion with respect to premarket review for several categories of IVDs, as described in section V.B. These policies should help address some of the concerns raised by the comments.

With respect to fees, FDA is unable to unilaterally change user fee amounts or adjust user fees to take into consideration other fees that laboratories may pay to CMS pursuant to CLIA. User fees associated with establishment registrations and certain premarket submissions are established by Congress in MDUFA. Under the current reauthorization of MDUFA, payment of either a standard fee or a small business fee is required for each submission type identified in 21 U.S.C. 379j(a)(2)(A) (unless the applicant qualifies for a fee waiver or for an exception under 21 U.S.C. 379j(a)(2)(B)). Payment of an establishment registration fee is required at the time of initial or annual registration (as applicable), except as provided in 21 U.S.C. 379j(a)(3)(B). More information about user fees is available on FDA’s user fee website (see Ref. 183). However, FDA will have an opportunity to negotiate with industry regarding user fees at the time of the next reauthorization of MDUFA, which will occur in advance of stages 4 and 5 of the phaseout

policy (when FDA intends to phase out the general enforcement discretion approach for premarket review requirements).

FDA disagrees that compliance with premarket review requirements is likely to be infeasible for laboratories with limited resources. As just noted, the existing program incorporates a different user fee amount for small businesses (see 21 U.S.C. 379j(d) and (e)), and review can occur relatively quickly when an IVD has been appropriately validated for its intended use. In addition, FDA implements premarket review consistent with several “least burdensome” statutory provisions and in accordance with Agency policy. This topic is discussed in detail in FDA’s final guidance document entitled “The Least Burdensome Provisions: Concept and Principles,” which defines “least burdensome” to mean the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time (Ref. 72). FDA also encourages IVD manufacturers to take advantage of FDA’s industry resources, including final guidance documents and resources available through the Division of Industry and Consumer Education within CDRH (see Ref. 184). These resources may facilitate efforts by laboratories to comply with premarket review requirements and other applicable requirements. Ultimately, FDA recognizes that laboratories will need to make investments to comply with premarket review requirements, but these investments are important to help ensure that IVDs are appropriately safe and effective, so that patients and providers can rely on test results for clinical decision-making.

(Comment 191) We received several comments asking specific questions about what and how different types of data should be presented in premarket submissions, and how to know when a premarket submission is required, especially for modifications. For example, comments asked what specific data are necessary to bridge a premarket authorization to new specimen types, how to handle database curation for sequencing assays, and what types of software applications are considered part of a test system. Another comment stated that the NPRM did not provide sufficient guidance on what amount or type of data may be required.

(Response 191) FDA appreciates that many laboratory manufacturers may not be familiar with FDA’s regulations and the premarket submission process. FDA intends to consider providing guidance on various topics and making additional resources available over the course of the phaseout period as appropriate, including on the topic of premarket review of IVDs offered as LDTs. FDA has already made resources available on several of the specific topics identified by the comments, including FDA’s final guidance documents entitled “Deciding When to Submit a 510(k) for a Change to an Existing Device” and “Modifications to Devices Subject to Premarket Approval (PMA)--The PMA Supplement Decision-Making Process,” regarding modifications to devices (Refs. 61 and 185); information regarding the CLSI EP35 standard (1st Edition), “Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures,” regarding bridging to new specimen types (Ref. 186); FDA’s final guidance document entitled “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics,” regarding database curation (Ref. 187); and FDA’s final guidance documents entitled “Clinical Decision Support Software,” “General Principles of Software Validation,” and “Content of Premarket Submissions for Device Software Functions,” regarding software (Refs. 188 to 190). The amount and type of data needed in premarket submissions varies depending on the circumstances. For questions that are specific to a particular IVD, laboratory manufacturers may request feedback from FDA through a Pre-Submission, which is further explained in FDA’s final guidance document entitled “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program” (Ref. 65).

(Comment 192) One comment questioned how premarket submissions may account for the various components of a test (e.g., extraction kits, instrument platform, software, or reagent) when those components may not be manufactured by the laboratory manufacturer and the laboratory manufacturer may consider them to be interchangeable.

(Response 192) In the scenario described in the comment, the laboratory manufacturer is expected to establish specifications for such components and have purchasing and acceptance controls to ensure each component meets specifications. This is critical to help ensure the quality of the test over time. While evidence of purchasing and acceptance controls are generally not part of premarket review for 510(k) and De Novo submissions, they are required elements of a quality system. In addition, under the design control provisions of the QSR, the laboratory would be expected to validate its test system, including all components per established specifications, for its intended use. During premarket review, FDA would review analytical and clinical validation information for the test system. For PMAs, FDA would also review applicable quality system information.

(Comment 193) Some comments addressed what FDA should consider as evidence of a reasonable assurance of safety or effectiveness in premarket submissions for IVDs offered as LDTs. Some comments stated that clinical trials “should not be required” because they are too burdensome. One comment stated that FDA should expect less information in premarket submissions when tests are designed for use on “commercially” available instruments and using “commercially” available reagents. Another comment suggested that FDA consider peer-reviewed evidence of clinical validity and clinical utility and prior reviews by other regulatory bodies.

(Response 193) The content that must be included in a premarket submission can vary greatly based on several factors, including the type of submission and the type of device. Data relevant to the evaluation of a submission for one type of test may not be relevant to evaluating submissions for other types of tests. However, in general, FDA does not agree that the amount and type of evidence included in a particular submission should vary based on whether the IVD is manufactured by a laboratory or another manufacturer. FDA encourages IVD manufacturers to request feedback on individual submissions through FDA’s Pre-Submission program, which is further explained in FDA’s final guidance document entitled “Requests for Feedback and

Meetings for Medical Device Submissions: The Q-Submission Program” (Ref. 65). FDA also implements premarket review consistent with several “least burdensome” statutory provisions and in accordance with Agency policy. This topic is discussed in detail in FDA’s final guidance document entitled “The Least Burdensome Provisions: Concept and Principles” (Ref. 72).

With respect to the consideration of peer-reviewed evidence, FDA would not expect laboratories to generate additional clinical validity data when available literature is adequate to demonstrate that the IVD is clinically valid. In reviewing submissions for IVDs, FDA considers applicable information from the literature submitted by the applicant. In addition, as discussed in response to comment 203, FDA has published a final guidance document describing a recognition program for publicly accessible databases of human genetic variants as sources of valid scientific evidence for genetic and genomic tests (Ref. 188). Under this policy, test manufacturers can use information in FDA-recognized databases to support the clinical validity of their tests.

FDA disagrees that FDA should expect less information in premarket submissions when tests are designed for use on “commercially” available instruments and with “commercially” available reagents. FDA’s expectations for validation apply to the test system, which includes use of all components together. Any given instrument or reagent may be a part of a test system that works well and part of another test system that does not.

With respect to the comment suggesting that FDA consider prior reviews by other regulatory bodies, as described elsewhere in this preamble, FDA anticipates expanded use of the Third Party review program and intends to exercise enforcement discretion with respect to premarket review requirements for LDTs approved by NYS CLEP. Further, FDA will continue ongoing efforts towards international harmonization with other regulatory bodies.

(Comment 194) One comment expressed concern that FDA does not have the level or depth of expertise necessary to review premarket submissions for highly complex LDTs.

Another comment stated that the NPRM was focused largely on clinical pathology, and that FDA

has not considered that the large quantity of premarket submissions FDA will receive will be more varied and challenging, and include digital pathology products incorporating artificial intelligence/machine learning, liquid biopsies, multiplex assays, multianalyte tests incorporating complex algorithms, and whole genome sequencing.

(Response 194) FDA disagrees with the comment's suggestion that FDA has failed to consider a wide range of IVDs in connection with this rulemaking, such as the products listed in the comment. FDA is familiar with these products, as discussed below, and has taken into account its experience with IVDs generally in issuing this rule. FDA also notes that the term "clinical pathology" is broad. According to the Association of Academic Medical Centers, clinical pathology includes many subspecialties, including blood banking-transfusion medicine, chemical pathology, clinical informatics, cytopathology, hematology, microbiology, and molecular genetic pathology, among others.

FDA also disagrees that it lacks the level or depth of expertise necessary to evaluate premarket submissions for a wide variety of challenging and varied highly complex IVDs offered as LDTs. FDA employs hundreds of scientists with expertise in the review of IVD safety and effectiveness, including those who have worked in clinical laboratories and developed LDTs. This expertise includes knowledge of digital pathology products, liquid biopsy-based tests, multiplex assays, multi-analyte tests incorporating complex algorithms, and whole genome sequencing, among other things. FDA also works with experts across offices, including experts in the Digital Health Center of Excellence on artificial intelligence/machine learning matters. For example, FDA has already authorized artificial intelligence/machine learning-based software (see Ref. 191), digital pathology tests incorporating artificial intelligence/machine learning (see Ref. 192), liquid biopsy assays (see, e.g., Refs. 144 and 193), multiplex assays (see, e.g., Refs. 194 and 195), multi-analyte tests incorporating complex algorithms (see, e.g., Refs. 196 and 197), and exome sequencing based NGS tests (see, e.g., Refs. 198 and 199).

(Comment 195) Several comments requested clarity around device classification and offered suggestions for how FDA should classify IVDs offered as LDTs, including what factors should be considered. One comment suggested FDA determine and continuously seek input on classification of tests through a public process. Another comment suggested FDA use a request for information process to gather information on currently available IVDs offered as LDTs and use that data to establish classification panels that IVD manufacturers could look to as a resource in the premarket submission process, which would save them time and resources. Some comments stated that, when classifying tests, FDA should consider context, including how widely a test is distributed; whether it is offered by a laboratory that is integrated into patient care; and the history of the test manufacturer, including with respect to validation generally and for specific tests.

(Response 195) As discussed more fully in section VI.P of this preamble, FDA already has processes in place and has made multiple resources available to industry to help manufacturers determine the classification of their devices. FDA notes that some IVDs offered as LDTs may already be classified under existing classification regulations. FDA recommends that stakeholders consult FDA's classification database for more information (Ref. 200). Laboratory manufacturers may also seek feedback from FDA through a Pre-Submission, or may submit a request for information regarding the class in which a device is classified or the requirements applicable to a device under section 513(g) of the FD&C Act.

We note that standards for classification of a device are set forth in statute (21 U.S.C. 360c(a)). The existing device classification processes focus on the risk of the IVD itself and availability of controls to address such risk. In classifying devices, FDA considers, among other things, the device's intended use and indications for use, which includes consideration of the intended patient population. The risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Refer to FDA's webpage for more information on classification (Ref. 201).

With regard to the request for FDA to continuously seek input on classification of tests through a public process, we agree that public input can be important, and in fact required, in certain circumstances.

Among other things, there is a public process when FDA classifies a preamendments device for the first time under section 513(d) of the FD&C Act. This process involves a public meeting of the appropriate advisory committee panel and notice and comment rulemaking.

Postamendments devices are deemed to be class III by operation of law under section 513(f)(1) of the FD&C Act, but such devices can be reclassified under different processes. Under section 513(f)(3) of the FD&C Act, for example, stakeholders can petition FDA to change the classification of these devices (see § 860.134(b) (21 CFR 860.134(b))). FDA can also initiate reclassification under section 513(f)(3) of the FD&C Act, and under that process, the public would have an opportunity to review and comment on the proposed classification and special controls, if applicable, which are published first by proposed order in the *Federal Register* (see § 860.134(c)). In addition, a manufacturer can submit a De Novo classification request under section 513(f)(2) of the FD&C Act requesting reclassification to class II or class I. FDA acts on such requests through written order, without a public comment process.

(Comment 196) Some comments stated that FDA's three-tier classification system for devices does not translate well to IVDs offered as LDTs. These comments expressed concern that FDA would inappropriately classify many IVDs offered as LDTs as high risk "when in reality their risk is mitigated by the fact that they are part of a multi-faceted medical assessment and are rarely used in isolation for clinical decision-making." Some comments stated that most LDTs should be considered low- or moderate-risk because they are typically used as only one part of a more comprehensive patient evaluation and not the singular factor for clinical decisions. One comment stated that "LDTs are comprised of not only medical products, but also analytic processes," and suggested that "A regulatory review process for LDTs should consider both and achieve an appropriate balance between the two given where the risk lies in a particular test."

(Response 196) FDA disagrees that FDA’s device classification system does not translate well to IVDs offered as LDTs. FDA determines the risk class of devices, including IVDs, by applying the statutory standards set forth in the FD&C Act, including standards for class I (low-risk), class II (moderate-risk), and class III (high-risk) devices. *See* 21 U.S.C. 360c(a)(1). FDA’s classification decisions take into account the risk of a device, which may depend on whether the device is the sole determinant for clinical decision-making, among other things. FDA is not aware of any unique feature of IVDs offered as LDTs that renders the statutory standards less applicable or less appropriate for these IVDs.

To the extent that the comments were suggesting that IVDs offered as LDTs are unique because they are “part of a multi-faceted medical assessment and are rarely used in isolation for clinical decision-making,” FDA disagrees. Many IVDs are indicated for use in conjunction with clinical assessments and not as the sole basis for clinical decisions, so IVDs offered as LDTs are not unique in that respect. For example, class III prostate specific antigen tests are intended to be used in conjunction with a digital rectal exam to aid in the detection of prostate cancer in men aged 50 years and older. Class II Duchenne muscular dystrophy newborn screening tests are intended to be used in conjunction with other clinical and diagnostic findings to aid in the screening of newborns. Class I cholesterol tests are intended to be used to aid in the diagnosis of lipid disorders. In general, any IVD, regardless of class, that is indicated to “aid in the diagnosis” of a clinical condition is intended to be used in conjunction with clinical assessments. Therefore, use in the context of a “multi-faceted medical assessment” is not unique to IVDs offered as LDTs.

FDA also disagrees that IVDs offered as LDTs should be considered low or moderate risk whenever they are part of a multifaceted medical assessment (i.e., are not used in isolation for clinical decision-making). Even if such tests are used as a part of a multifaceted medical assessment and are not the sole determinant for clinical decision-making, false positive or false negative test results can still lead to unwarranted interventions or progression of disease without

necessary intervention. Given the role that IVDs offered as LDTs play in modern medical care, test validity has a significant impact on the public health. However, FDA notes that most currently classified IVDs have been determined by FDA to be low or moderate risk (class I or class II).

With regard to the suggestion that FDA’s regulatory review process should consider that LDTs are comprised of both “medical products” and “analytic processes,” the comment provided no additional discussion of these terms, and FDA is not clear on the distinction the commenter intended to draw. To the extent the commenter meant to distinguish between medical devices and the “practice of medicine,” see our responses to comments in section VI.D.6. With regard to the suggestion that FDA take a balanced approach in light of a test’s risks, FDA agrees. We take a risk-based approach to the devices we regulate and determine the level of regulation warranted to provide reasonable assurance of safety and effectiveness. On January 31, 2024, FDA announced that it is undertaking an effort to initiate the process to reclassify most IVDs that are currently class III into class II because FDA believes there is sufficient information to establish special controls that, together with general controls, will provide a reasonable assurance of safety and effectiveness for these tests. The majority of these tests are infectious disease and CDx IVDs (Ref. 66). FDA aims to complete this reclassification process before stage 4 of the phaseout policy.

(Comment 197) One comment questioned how a high-risk IVD offered as an LDT that uses a class I instrument could be classified into a different class than the instrument, and whether the instrument would need to go through premarket review based on the classification of the high-risk IVD offered as an LDT.

(Response 197) The regulatory requirements applicable to a particular device can vary depending on the device’s intended use. For example, the same instrument may be subject to certain requirements when it is not intended for use as part of a particular test system and subject to a different set of requirements when it is intended for use as part of a particular test system.

Most instruments not intended for use as part of a particular test system are classified as class I 510(k)-exempt. However, if a manufacturer seeks to market a test system that includes such an instrument as a component, the instrument would be reviewed under the standards applicable to the overall test system. For example, in the context of a submission for a high-risk test system, FDA would review information to support use of the instrument in that test system.

(Comment 198) Several comments proposed that FDA streamline premarket submission or review for some or all IVDs offered as LDTs. Comments stated that FDA review should be expedited so that care is not delayed, and that quick turnaround times are particularly needed for infection prevention and control. Some comments suggested specific approaches FDA could take. One comment asked FDA to consider maintaining a MAF containing core data submitted by a manufacturer, which other laboratories could then draw from and use rather than repeat a data collection. Another comment suggested FDA provide standardized templates to help the manufacturers of IVDs offered as LDTs present data in a consistent and understandable format. Another comment suggested that FDA identify strategies to streamline validation of tests when there are well characterized biomarkers or numerous tests with a similar intended use.

(Response 198) Premarket pathways and certain submission requirements are set forth in the FD&C Act,⁸⁸ and FDA cannot change those requirements. In addition, to the extent that the comments were suggesting that FDA should have a different approach to implementing premarket review for IVDs offered as LDTs compared with other IVDs, FDA disagrees.

However, in general, FDA supports tools for more efficient premarket review as consistent with applicable law. For example, FDA's device MAF system is available to device manufacturers, including laboratory sponsors of IVDs offered as LDTs. A laboratory sponsor can, with the data owner's permission, reference specific MAFs in a premarket submission for a third party's data and other information related to the subject IVD offered as an LDT. The MAFs would allow FDA's confidential review of such information to facilitate scientific evaluation of

⁸⁸ Some devices that are also biological products are licensed under the PHS Act.

the IVD without disclosing trade secret or confidential information to the sponsor laboratory (see Ref. 202 for more details). Such use of MAFs in a manner that eliminates unnecessary burdens is consistent with the least burdensome principles directed by Congress.

FDA appreciates that standardized templates or additional guidance regarding data presentation and test validation may facilitate efforts by laboratories to comply with applicable premarket review requirements. As discussed more fully in response to comment 291, FDA anticipates issuing a small entity compliance guide, and intends to consider issuing additional guidance documents as appropriate and making additional resources available on specific topics, including test validation, over the course of the phaseout period. As described further in response to comment 293, there are multiple resources to help manufacturers, including laboratories, understand the type of data and information, including validation data and information, that is included in support of premarket submissions for IVDs. As stated elsewhere, FDA implements premarket review, including its review of analytical and clinical validation data, consistent with several “least burdensome” statutory provisions and in accordance with Agency policy. This topic is discussed in detail in FDA’s final guidance document entitled “The Least Burdensome Provisions: Concept and Principles,” which defines “least burdensome” to mean the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time (Ref. 75). Consistent with FDA’s least burdensome principles, if available literature is adequate to demonstrate that the clinical validity of the biomarker detected by the test is well-established, FDA considers such applicable information from the literature submitted by the applicant.

(Comment 199) One comment suggested that FDA collaborate with CDC and other Federal agencies so that each public health laboratory does not need to submit a separate PMA to obtain premarket approval for their shared test types. The comment noted that this suggested approach would alleviate challenges when the public health laboratory does not hold the

validation dataset, which, for some test types, is validated by Homeland Security and the Laboratory Response Network.

(Response 199) When a laboratory submits an application for premarket approval of an IVD, that application can include information to support the distribution of that IVD to other laboratories; for example, CDC can obtain approval for a test that involves the distribution of that test to the Laboratory Response Network. In addition, as discussed above, data owners may choose to submit a MAF and provide a right of reference to specific laboratories, which in turn can reference the data and information in the MAF in their PMA applications.

(Comment 200) One comment suggested that FDA work with CMS, CAP, and the Joint Commission to align requirements for clinical laboratories when performing validation experiments to avoid creating redundant and misaligned regulations that will lead to costly delays.

(Response 200) FDA is responsible for implementing the requirements of the FD&C Act with respect to IVDs, including requirements for safety and effectiveness of IVDs offered as LDTs. FDA takes a least burdensome approach in its implementation of premarket review requirements, in a manner that strives to eliminate redundancy and unnecessary burdens. However, this approach does not change the applicable statutory and regulatory requirements for premarket review, including premarket submission content requirements and requirements for valid scientific evidence. As discussed more fully in sections VI.C.2 and VI.C.3, CMS and laboratory accreditation bodies, such as CAP and the Joint Commission, address clinical laboratory operations and personnel, but do not address critical aspects of laboratory development, such as clinical validity. FDA has both the authority and the expertise to oversee IVDs offered as LDTs to better assure the safety and effectiveness of these devices. In addition, FDA and CMS meet regularly to share information and coordinate our approaches, as appropriate, and will continue to do so upon implementation of this rule.

FDA appreciates that additional guidance regarding IVD validation may facilitate efforts by laboratories to comply with premarket review requirements. FDA intends to consider issuing additional guidance documents as appropriate, and making additional resources available on specific topics, which may include clinical validity, over the course of the phaseout period. See our response to comment 291.

(Comment 201) We received comments asking what standard FDA will apply for IVDs offered as LDTs that remain on the market while FDA reviews a premarket submission for that IVD. One comment urged FDA to “allow” these IVDs to remain on the market while the laboratory manufacturer addresses FDA’s questions unless there is a likelihood of serious harm. Another comment asked FDA to confirm whether the Agency commits to take action on premarket submissions during the same stage in which sponsors are expected to submit them (e.g., during stage 4 for high-risk LDTs).

(Response 201) As described in section V.C, in stage 4 of the phaseout policy (3½ years after publication of this final rule), FDA is phasing out the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs offered as LDTs. In stage 5 (4 years after publication of this final rule), FDA is phasing out the general enforcement discretion approach with respect to premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs (that are subject to premarket submission requirements). As described in section V.C, FDA generally does not intend to enforce against IVDs offered as LDTs for lacking premarket authorization after a complete PMA, HDE application, 510(k), BLA, or De Novo request has been submitted to FDA (by the corresponding stage of the phaseout policy) until FDA completes review of the submission. We note, however, that regardless of the phaseout timeline and enforcement discretion policies in this preamble, FDA retains discretion to pursue enforcement action at any time against violative IVDs when appropriate.

The phaseout policy does not address the timeframe within which FDA will complete review of premarket submissions. FDA’s timeline for phasing out the general enforcement

discretion approach with respect to premarket review requirements aligns with the next reauthorization of MDUFA, which will provide an opportunity for FDA and industry to negotiate regarding user fees and performance goals with the knowledge that laboratory manufacturers will generally be expected to comply with applicable premarket review requirements.

(Comment 202) Several comments asked how premarket authorization will work when it is possible FDA will receive several De Novo requests for the same type of test. One comment stated that there would be a disincentive to being the first to submit a De Novo request for novel tests (specifically in reference to laboratories creating new intended uses for FDA-authorized tests) because such requests require payment of a higher user fee than 510(k) submissions. FDA also received comments asking about the logistics of the premarket review process when sponsors may not know whether another entity has submitted a De Novo request for the same type of test.

(Response 202) FDA has issued multiple final guidance documents outlining our policies for De Novo requests, including “De Novo Classification Process (Evaluation of Automatic Class III Designation)” (Ref. 203) and “Acceptance Review for De Novo Classification Requests” (Ref. 204), in addition to a final rule entitled “Medical Device De Novo Classification Process” (86 FR 54826, October 5, 2021).

With respect to the comments asking about the logistics of the premarket review process when multiple sponsors have submitted De Novo requests for the same type of IVD, FDA generally would not disclose the existence of a De Novo request under review to other submitters, but would notify them if/when a De Novo request for the same device type is granted. As further explained in our final guidance document entitled “De Novo Classification Process (Evaluation of Automatic Class III Designation),” when a De Novo request is granted while other devices of the same type are under review in additional De Novo requests, the additional De Novo requests will be declined. The submitters of the declined De Novo requests will be required to demonstrate substantial equivalence to the IVD that was granted a De Novo in

a 510(k) submission, and comply with any applicable special controls for the device type; the sponsor may use all information in their initial De Novo request by incorporating it by reference into the new 510(k) submission.

To the extent this process and the higher user fees associated with De Novo requests compared to 510(k) submissions may disincentivize submission of De Novo requests for novel IVDs, as suggested in one comment, this concern is not specific to IVDs offered as LDTs, but rather relates to all devices. FDA is not changing the De Novo and 510k frameworks through this rulemaking.

(Comment 203) One comment requested guidance on how to handle database curation for sequencing assays, specifically regarding adding to databases without having to submit an application to FDA, and regarding regulations for curated databases pertaining to the authenticity and security of data and obtaining proper documentation for database submissions prior to inclusion in the database.

(Response 203) FDA has published a final guidance document entitled “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics,” which describes a recognition program for publicly accessible databases as sources of valid scientific evidence for genetic and genomic tests (Ref. 187). This final guidance addresses recommendations for appropriate curation of publicly accessible databases using human expert evaluation, including recommendations around database procedures and operations, data quality and security, variant evaluation and assertions, and professional training and conflicts of interest. FDA recognition of a database indicates that FDA believes the data and assertions contained in the database can be considered valid scientific evidence. Test manufacturers can use the assertions within FDA-recognized databases to support the clinical validity of their tests.

We note that the clearance/approval of a PCCP may help manufacturers avoid the need for PMA supplements or new 510(k)s for modifications to a database that is used as part of test

result generation. PCCPs provide the opportunity for a manufacturer to prospectively outline how changes to a device will be validated and implemented. This may include how a database that is used as part of the test result generation may be updated, such as to add variants. FDA can review and clear or approve the PCCP during review of a premarket submission. Manufacturers would not need to submit a PMA supplement or new 510(k) for subsequent changes when such changes are in accordance with the authorized PCCP. This approach has been successfully employed for various FDA-authorized IVDs.

(Comment 204) FDA received comments with specific questions about FDA premarket review, including the review process, FDA response timelines, associated user fees, and appeal rights, among other subjects.

(Response 204) Notably, neither the regulation amendment nor the phaseout policy changes applicable FDA requirements for IVDs or IVD manufacturers. As noted throughout this preamble, FDA has published numerous final guidance documents and resources for industry with information on how to comply with applicable requirements, including requirements for premarket review. We encourage interested parties to consult these materials, including final guidance documents and resources available through the Division of Industry and Consumer Education within CDRH (see Ref. 184). As appropriate, FDA also intends to develop guidance documents specific to the final phaseout policy, which will be forthcoming during implementation.

G. Impact on Small Businesses

(Comment 205) FDA received comments expressing concern that phasing out the general enforcement discretion approach for LDTs will put financial and administrative pressure on small laboratories, resulting in laboratory closures, consolidation of smaller entities, and monopolies in the testing space as large laboratories take more of the market share. Several comments stated that large laboratories will be advantaged as they have the resources to afford the necessary staffing and other costs related to test development and regulatory submission and

emphasized the thin financial margins with which small laboratories operate. Some comments stated that the impact on small laboratories will result in a loss of expertise and infrastructure. In addition, comments noted that such centralization of LDTs at large laboratories may negatively impact medical education and training in pathology.

(Response 205) FDA appreciates the concerns regarding financial and administrative challenges for smaller laboratories. FDA anticipates that the enforcement discretion policies discussed in section V.B will sufficiently address these concerns and help to avoid undue disruption to the testing market. For example, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3. Premarket review costs and QS costs are a significant portion of the overall costs associated with compliance with applicable requirements under the FD&C Act and FDA's regulations, as described in section II.F.5 of the FRIA (see Ref. 10). Small laboratories that do not incur such costs will face significantly less of the financial and administrative pressure that the comments describe, reducing the likelihood of laboratory closures, laboratory consolidation, and monopolies predicted by the comments. For further discussion see section III.B of the FRIA. FDA also intends to issue a small entity compliance guide, which will assist small entities in complying with applicable requirements. For discussion of the potential impact of the phaseout policy on medical education and training, see our response to comment 301.

(Comment 206) Some comments enumerated specific questions for FDA regarding compliance and requested clarification as to whether FDA will make materials available to help small businesses come into compliance.

(Response 206) FDA intends to provide additional resources on specific topics that may be useful as laboratories come into compliance with applicable requirements, as discussed in

response to comment 291. In addition, as noted in response to comment 205, FDA intends to issue a small entity compliance guide to provide additional guidance to small businesses.

H. Impact on Pricing

(Comment 207) Several comments stated that ending the general enforcement discretion approach for LDTs will lead to higher prices for clinical tests due to the costs of complying with applicable FDA requirements. Some comments further stated that the costs of complying with applicable requirements will result in the closure of many laboratories, the outsourcing of certain laboratory testing, or other supply chain contractions, which in turn will increase the costs of tests due to decreased test availability, decreased market competition, and increased handling costs (e.g., costs associated with shipping samples to a centralized laboratory), or supply chain contractions. One comment expressed skepticism regarding FDA's statement that any losses may be offset by the market entry of IVDs from other manufacturers. FDA also received a comment which argued that increased prices for clinical tests will disincentivize people from seeking preventive care until they suffer an emergency, which will increase costs for the overall healthcare system. Collectively, these comments suggested that laboratories will pass increased costs to their customers, which some comments noted could result in higher insurance premiums. However, one comment stated that insurance companies will be more likely to cover tests (because they will have FDA authorization), which may allow for greater access to more affordable testing. Payors themselves commented in support of the rule "given the proliferation of laboratory developed tests (LDTs) and concerns about the reliability of certain LDTs." One comment noted that it is inaccurate to assume that LDTs are always cheaper.

(Response 207) FDA recognizes that laboratories may pass the costs of compliance with applicable requirements, including the specific examples listed in the comments, to their customers by raising prices for IVDs offered as LDTs. We also recognize that if many laboratories reduce operations or exit the market, production may be concentrated in a few large laboratories, which may cause prices for certain IVDs offered as LDTs to increase. As we noted

in section II.F.6 of the PRIA and the FRIA (Ref. 60 and 10), the exact effect of the phaseout policy on the price of IVDs offered as LDTs is unknown. A few comments received by FDA included discussion of the price differential between unauthorized LDTs and FDA-authorized tests, but comments did not otherwise provide empirical data to inform FDA's assessment of effects on test prices.

However, we note that in the final phaseout policy, after considering the public comments received on the NPRM, FDA has included certain enforcement discretion policies. As described in section V.B.3, FDA intends to exercise enforcement discretion and not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as described in section V.B.3. In addition, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP. FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

As noted in response to comment 205, the costs of compliance with premarket review requirements (as well as QS requirements) are a significant portion of the overall anticipated costs to laboratories of complying with applicable FDA requirements (see section II.F.5 of the FRIA (Ref. 10)). As a result, FDA's determination to include the enforcement discretion policies described above in the final phaseout policy may significantly reduce the costs of compliance under the final phaseout policy, thus reducing the number of laboratories that scale back operations or exit the market. FDA estimates the annualized cost over 20 years to be \$4.6 billion less than the estimates in the PRIA (Ref. 60).

In addition, we anticipate that FDA oversight could help to support coverage and reimbursement determinations for IVDs offered as LDTs, which we anticipate will make certain IVDs offered as LDTs for which there is a reasonable assurance of safety and effectiveness more affordable for patients. As a result, FDA does not agree that patients will necessarily be disincentivized from seeking preventive care resulting in increased costs to the healthcare system as a result of the phaseout policy.

In addition, phasing out the general enforcement discretion approach for LDTs will help to reduce other healthcare costs. Greater oversight by FDA will help to address the hidden costs associated with unsafe or ineffective IVDs (including IVDs promoted with false or misleading claims), such as costs incurred from inappropriate treatments, additional or repeat testing, unnecessary consultations with providers, or additional treatments that become necessary due to the progression or worsening of a disease or condition following misdiagnosis. While certain costs may be passed on to individuals and insurers, we expect some of these costs will be offset by the associated benefits.

A more fulsome discussion of the estimated costs and benefits is provided in FDA's FRIA (Ref. 10).

(Comment 208) FDA received one comment which stated that some laboratories may decide to utilize tests that are more expensive for patients, regardless of medical necessity, in order to recoup the costs of complying with applicable FDA requirements.

(Response 208) FDA does not agree that phasing out the general enforcement discretion approach for LDTs will cause laboratories to utilize more expensive tests regardless of medical necessity. FDA anticipates that, to the extent some laboratories may attempt to recoup costs by utilizing more expensive tests regardless of medical necessity, such laboratories would be likely to engage in such practices irrespective of FDA's determination to phase out the general enforcement discretion approach for LDTs. In addition, the use of any particular test is a decision to be made between patients and their healthcare providers. Finally, FDA anticipates that third

party payors may review the medical necessity of tests for which claims for reimbursement are submitted.

I. Impact on Access and Innovation

(Comment 209) Several comments expressed concern that ending the general enforcement discretion approach for LDTs will negatively impact patient access to clinical testing. These comments generally asserted that the cost or complexity of complying with FDA requirements, and the burdens that may fall on laboratories from the phaseout of the general enforcement discretion approach, will cause many laboratories to reduce activities and stop offering some or all IVDs offered as LDTs, particularly in the context of other challenges that laboratories face with respect to staffing, supply chains, and other challenges. Several comments stated that in a recent American Society for Microbiology survey of its members, over 80 percent of the microbiology laboratories surveyed said they would consider discontinuing LDTs if FDA finalized its proposal. Another comment stated that in an internal survey of members of the Association of Pathology Chairs, out of 39 laboratories surveyed, 37 reported that more outsourcing of tests would be necessary if FDA finalized its proposal. Some comments stated that the impact would be particularly significant for laboratories that currently lack the infrastructure to comply with applicable requirements and for emerging companies.

Based on these concerns, many comments stated that patient access to tests will be reduced, and patients will potentially be deprived of important health-related information. Some comments stated that this would result in worse patient outcomes and higher healthcare costs; comments suggested that patients would lose access to IVDs offered as LDTs that perform well, even some IVDs offered as LDTs that may perform better than FDA-authorized IVDs, while other comments stated that patients would lose access to testing that supports rapid care decisions. A few comments asserted that harm may result from losing access to certain types of tests, such as infectious disease tests or genetic tests. Other comments suggested that reduced access to tests would mean less choice, flexibility, competition, or ability to withstand

disruptions to the test market. One comment stated that more tests would be offered by large laboratories that prioritize financial profits over accountability or patient care and that cannot “keep up with the necessary fine-tuned evolution of these tests.” Another comment suggested that by reducing access to testing, the phaseout policy would infringe on patient and physician “rights to timely and adequate care and the freedom to exercise clinical judgment.” Other comments reiterated the suggestion that the phaseout policy would limit access and thereby constrain a physician’s ability to use his or her discretion to make treatment decisions. Some comments questioned whether the market withdrawal of some IVDs offered as LDTs would be counterbalanced by the introduction of new IVDs.

In addition, some comments stated that by reducing the availability of IVDs offered as LDTs, the phaseout policy would lead to delays in testing, including by potentially increasing reliance on reference laboratories which may increase the time for individuals to obtain test results. Other comments argued that delays will result from FDA’s premarket review process, which will slow down the ability of patients to access tests that they need. Comments also stated that if FDA were to finalize its proposal, delays could result due to less competition, and that if the phaseout policy results in centralization of tests to certain locations, patients who are not in the local area could face additional hurdles.

(Response 209) As described in section V, FDA has made several changes to the phaseout policy that was described in the NPRM, including the addition of certain enforcement discretion policies. These changes significantly reduce the economic impact of the phaseout policy, and thus the likelihood that laboratories may reduce their test offerings or exit the market. Based in part on the inclusion of these enforcement discretion policies in the final phaseout policy, FDA disagrees with concerns that the phaseout of the general enforcement discretion approach for LDTs will have a significant net negative impact on patient access to IVDs that have appropriate assurance of safety and effectiveness.

Most notably, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3.

FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP, and premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system, as discussed in sections V.B.2 and V.B.3.

FDA anticipates that these aspects of the final phaseout policy will substantially reduce the overall impact of the phaseout policy on patient access to clinical tests. In addition, FDA notes that, as explained in the NPRM and discussed in the FRIA, the FD&C Act and FDA's regulations do not require premarket review for all IVDs (88 FR 68006 at 68013). FDA estimates that approximately 50 percent of IVDs offered as LDTs will not require premarket review (see section II.F.2 of the FRIA (Ref. 10)). Moreover, under FDA's phaseout policy, FDA does not intend to phase out the general enforcement discretion approach for premarket review requirements for IVDs offered as LDTs until several years after publication of this final rule. FDA also generally does not intend to enforce against IVDs offered as LDTs for lacking premarket authorization after a complete PMA, HDE application, 510(k), BLA or De Novo request has been submitted to FDA by the start of the corresponding stage of the phaseout policy, until FDA completes review of the submission, so as not to interrupt access to IVDs that are already on the market and available to patients.

To the extent that some IVDs offered as LDTs come off the market because, for example, the IVD cannot meet applicable requirements under the FD&C Act and its implementing

regulations, or the laboratory does not invest resources to meet those requirements, the value of access to such IVDs is diminished in the absence of assurances regarding the IVDs' safety and effectiveness. Neither patients nor providers are helped by access to tests that are not safe and effective for their intended use. In addition, in the event some IVDs offered as LDTs exit the market, FDA expects that other manufacturers may fill the need with IVDs that comply with applicable FDA requirements. FDA also anticipates that applying the same general oversight approach to both laboratory and non-laboratory manufacturers of IVDs will encourage genuine innovation and facilitate access to IVDs for which there is a reasonable assurance of safety and effectiveness, as discussed further in response to comment 218 (see Refs. 15, 22, 88 to 90).

Finally, it is unclear to FDA how generalizable the survey data cited in comments may be. While comments stated that the American Society for Microbiology's survey of its members found that over 80 percent of the microbiology laboratories surveyed would consider discontinuing most LDTs if FDA finalized its proposal, only 88 of the American Society for Microbiology's 36,000 members (0.2 percent) responded to the survey (Ref. 205). Similarly, the Association of Pathology Chairs' survey of its members produced only 39 responses (Ref. 170), while their comment states that the Association of Pathology Chairs "represents the entire academic pathology leadership team of over 160 departments nationwide." Regardless, the policy changes to the phaseout policy, including the addition of certain enforcement discretion policies, help address the concerns identified in these surveys as described above.

(Comment 210) A few comments stated that laboratories may begin offering their tests for "surveillance use only," in reference to a category of tests that FDA proposed in the NPRM would not be affected by the phaseout policy.

(Response 210) Tests for public health surveillance are limited to tests manufactured and offered for use exclusively for public health surveillance and are distinct from tests used for other purposes in that they are intended solely for use on systematically collected samples for analysis and interpretation of health data in connection with disease prevention and control, and

tests results are not reported to patients or their healthcare providers. Tests for which results are returned to a patient or healthcare provider would not be considered public health surveillance tests. Laboratories could not simply label tests “for surveillance use” to avoid oversight of broader use of the tests.

(Comment 211) FDA received a comment which stated that FDA should analyze the totality of circumstances that currently exist “in healthcare” before phasing out the general enforcement discretion approach for LDTs. This comment suggested that such circumstances support the conclusion that the phaseout policy will contribute to a “total disruption” in patient access to tests. Another comment asked whether the Agency has performed, or intends to perform, an impact analysis on patient care, patient access, and patient safety, and one comment expressed concern that action by FDA in the absence of comprehensive data regarding the use of LDTs will result in severe restrictions on access.

(Response 211) As described elsewhere in this preamble, the Agency has determined that increased FDA oversight is necessary to better assure the safety and effectiveness of IVDs offered as LDTs, and that maintaining the general enforcement discretion approach for LDTs is not in the best interest of the public health. In finalizing FDA’s policy for phasing out the general enforcement discretion approach for LDTs, FDA has carefully considered issues related to patient care and access, including through the Agency’s review and analysis of more than 6,500 comments submitted to the docket for this rulemaking. As discussed in response to comment 209, FDA’s final phaseout policy includes several policies that will substantially reduce the overall impact of the phaseout policy on patient access to IVDs offered as LDTs. FDA has also conducted a detailed regulatory impact analysis that considers costs and benefits; please see discussion in the FRIA (Ref. 10).

(Comment 212) FDA received a comment which stated that ending the general enforcement discretion approach for LDTs would impact laboratories’ willingness to share new methods and rare reagents with each other. The comment stated that as a result, the phaseout

policy may impede efforts that aim to address barriers to care, such as the Cancer Moonshot Initiative.

(Response 212) FDA does not agree that ending the general enforcement discretion approach for LDTs will result in less scientific exchange between laboratories, or negatively impact initiatives such as the Cancer Moonshot Initiative. FDA anticipates that the phaseout policy will help to advance the Cancer Moonshot Initiative, as cancer care is often personalized based on the genetic makeup of the tumor, and helping to ensure that IVDs offered as LDTs have appropriate assurance of safety and effectiveness will help patients with cancer get the optimal treatment. Although FDA's phaseout of the general enforcement discretion approach may lead laboratories to incur additional costs, including in connection with premarket review requirements in some cases, FDA does not anticipate that these factors will necessarily cause laboratories that currently share new methods, rare reagents, or other information or materials to cease doing so.

Moreover, better assuring the safety and effectiveness of LDTs may foster test innovation and facilitate the collective efforts of the scientific and medical communities to identify promising technologies, new therapies, or areas worthy of future research (see Refs. 15, 22, 88 to 90). The FD&C Act's premarket review requirements provide an impetus for manufacturers to conduct scientifically sound and robust research to establish the safety and effectiveness of their devices, including IVDs. Basing decisions on scientifically reliable information can help to eliminate or reduce harms to health, such as misdiagnosis or delayed diagnosis with a lost opportunity for effective treatment, as well as the diversion of limited resources to ineffective treatments. *See* January 2017 Discussion Paper at 5-6 (Ref. 57).

(Comment 213) One comment stated that during a past recall of a particular IVD, FDA recommended the use of an LDT as an alternative to the recalled device. The comment expressed concern that ending the general enforcement discretion approach for LDTs may impede FDA's ability to respond to similar recalls.

(Response 213) FDA disagrees with this comment. By phasing out the general enforcement discretion approach for LDTs, FDA seeks to better protect the public health by helping to assure the appropriate safety and effectiveness of LDTs, including IVDs offered as LDTs, which may serve as alternatives to IVDs that are the subject of a recall. Moreover, as discussed in response to comment 209, FDA’s final phaseout policy includes several policies that will substantially reduce the overall impact of the phaseout policy on patient access to IVDs offered as LDTs.

(Comment 214) FDA received comments stating that the phaseout policy would have a negative impact on innovation in the testing space, as laboratories working to come into compliance would be either unable or unwilling to engage in innovative test development. Some comments stated that the regulatory constraints associated with the phaseout policy would cause laboratory manufacturers to develop fewer tests, hindering the timely development and deployment of cutting-edge therapies and diagnostic tools and ultimately harming patients. Comments noted that LDTs are an area of rapid advancement, with some being in use only for short periods of time, and some comments expressed concern that enforcing premarket review requirements for each individual assay or slight modification would not be adequate to keep up with the progress of testing. One comment stated that the phaseout policy would force laboratories to focus efforts on developing premarket applications for current tests instead of innovating to improve patient care. Some comments stated that the phaseout policy would cause delays in the development of new diagnostics, impacting the “competitive edge of U.S. medical research and development.”

(Response 214) FDA does not agree that the phaseout policy will hinder the timely development and deployment of innovative IVDs offered as LDTs. In fact, as discussed in response to comment 218, applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs may facilitate the development of innovative IVDs from non-laboratory manufacturers.

Even when premarket review is required for an IVD offered as an LDT, FDA does not agree that such review generally impairs innovation. The evidentiary requirements of premarket review spur innovation based on reliable scientific evidence that enables an informed determination of the safety and effectiveness of medical devices for each intended use and product labeling that provides information for using the product safely and effectively for such use. The generation of scientific evidence that is independently reviewed by FDA supports physicians in making sound clinical decisions. *See* January 2017 Discussion Paper at 3 (Ref. 57).

We note that sponsors have sought and obtained FDA authorization for innovative IVDs offered as LDTs. For example, a list of authorized CDx IVDs, which include innovative IVDs offered as LDTs, is available on FDA's website (Ref. 206). Furthermore, FDA's Breakthrough Devices program is intended to help expedite the development and review of certain devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions (21 U.S.C. 360e-3).

We agree that test innovation and development is important for patients and the public health, and we recognize the concern that expecting currently marketed IVDs offered as LDTs to come into compliance may cause laboratories to divert resources from the development of new IVDs, due to the time and resources that would be needed to comply with the regulatory requirements for their existing IVDs offered as LDTs. Based on these considerations along with concerns about reliance, and as discussed further in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this final rule. This enforcement discretion policy will improve patient access by allowing laboratories to focus resources on submissions for new, innovative tests based on reliable scientific evidence, rather than expend such resources in support of tests already on the market.

In addition, FDA intends to continue exercising enforcement discretion and generally not enforce premarket review and most QS requirements for such currently marketed IVDs offered as LDTs when they are modified in certain limited ways as described in section V.B.3. This aspect of the enforcement discretion policy will help to facilitate patient access to these tests by permitting certain modifications to be made within the scope of the enforcement discretion policy.

To further facilitate access going forward, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system⁸⁹. In the context of tests for unmet needs, there may be less opportunity to recoup costs of premarket review. This policy is intended to reduce the risk that premarket review costs would dissuade development of and access to such tests, taking into account the mitigations described in section V.B.3.

Moreover, although we acknowledge that the preparation and submission of PMAs and 510(k)s impose the majority of costs estimated for laboratories under the final phaseout policy, we also note that as explained in the NPRM, under FDA's device authorities, FDA premarket review is required only for certain tests (88 FR 68006 at 68009). FDA estimates that approximately 50 percent of IVDs newly offered each year as LDTs will not require premarket review.

For these reasons, FDA does not anticipate that the phaseout policy will hinder the timely development and deployment of cutting-edge diagnostic tools, impair the competitiveness of U.S. medical research and development, or ultimately harm patients, as suggested by the comments. See also our response to comment 218 for discussion regarding how applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs may facilitate the development of innovative IVDs.

⁸⁹ FDA recognizes that innovation often takes place in AMCs. *See e.g.*, Refs. 207-210.

(Comment 215) Several comments noted that laboratories must be able to modify existing tests quickly to diagnose new conditions and monitor the impact of new therapies. Some comments stated that stifling modifications of currently marketed IVDs offered as LDTs would force pathologists and other healthcare providers to use older, less optimal tests, and noted that many patients do not have the time to wait for diagnostic development and rely on laboratories to be nimble and adapt to changing diagnostic criteria. One comment noted the “redundancy and inability to update markers in flow cytometry panels based on new evidence” as a longstanding issue and recommended FDA address the barriers that prevent laboratories from readily adapting tests in response to evolving scientific knowledge.

(Response 215) FDA appreciates the need for improvements to existing tests to better serve patients and providers, and notes that a manufacturer’s modifications to its tests that have already been cleared, approved, licensed, or had a De Novo request granted by FDA require FDA review only in certain circumstances (see §§ 814.39, 807.81(a)(3), and 601.12 (21 CFR 601.12)). FDA has published several resources to help stakeholders determine whether a certain change or modification to a test may require a regulatory submission, including: (1) FDA’s final guidance document entitled “Modifications to Devices Subject to Premarket Approval (PMA)--The PMA Supplement Decision-Making Process” (Ref. 185), (2) FDA’s final guidance document entitled “Deciding When to Submit a 510(k) for a Change to an Existing Device” (Ref. 61), and (3) FDA’s final guidance document entitled “Deciding When to Submit a 510(k) for a Software Change to an Existing Device” (Ref. 211).

FDA recognizes that tests evolve in response to new scientific information, and FDA wants to avoid disincentivizing minor improvements to existing tests. As detailed in section V.B.3, for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) even if the IVD is modified in certain limited ways as described in section V.B.3.

FDA intends to issue a draft guidance with additional details and examples and will seek public comment on such draft guidance.

(Comment 216) Some comments expressed concern regarding the potential impact of the phaseout policy on innovative academic research and clinical trials, suggesting that researchers will have little incentive or ability to develop new LDTs due to the costs associated with compliance with statutory and regulatory requirements. Several comments noted that non-profit AMCs are often the nexus for innovation in medicine and that LDTs developed by AMCs play a critical role in education, development, and quality monitoring for rare disease tests and other conditions that do not have a viable market for commercial test development. One comment stated that the phaseout policy may result in LDTs that are very expensive or limited to common health conditions with established demand.

(Response 216) As discussed above, FDA anticipates that the enforcement discretion policy for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as described in section V.B.3, will address concerns that patient access to new tests would be reduced due to laboratories' focus on premarket submissions, as well as concerns that LDTs will become more expensive due to the cost of resources that would be needed to prepare and submit premarket submissions for currently marketed tests under the phaseout policy as proposed in the NPRM. The Agency believes that the policies described herein will help avoid undue disruption to the testing market, specifically for healthcare providers and patients that are relying on continued access to currently offered tests, and will encourage genuine innovation.

To facilitate access going forward, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. This policy carefully balances the risk of not having a

test available with the risk of not having assurances of premarket review in the context of the mitigations described in section V.B.3.

For additional discussion regarding the application of the phaseout policy in the clinical trial context, see our response to comment 175.

(Comment 217) FDA received some comments disagreeing with the view that increased oversight of LDTs may lead to increased innovation in the IVD space. These comments stated that LDTs and the laboratories that develop them are the catalysts for innovation, as they are typically developed when no “commercial” option is available and later acquired by manufacturers after technology and market development. On the other hand, one comment stated that the investment community and some LDT manufacturers have indicated that FDA’s proposal “will not significantly impede the ability of LDTs to reach the market.”

(Response 217) FDA recognizes the concerns regarding potential impact on innovation, but for the reasons discussed in our response to comment 214, FDA disagrees with the statement that the phaseout policy will not foster innovation and access to IVDs that have appropriate assurance of safety and effectiveness. While continued patient and provider access to certain tests is important, FDA also recognizes that an uneven oversight approach for laboratory and non-laboratory manufacturers of IVDs may discourage test development and innovation, as further discussed in response to comment 218 (see also Ref. 88). By applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, FDA will give stakeholders greater clarity regarding regulatory expectations, and may facilitate investment in the development of innovative IVDs. Additionally, as recently noted in a joint statement issued by CMS and FDA regarding the oversight of LDTs, FDA’s phaseout approach will remove a disincentive for non-laboratory manufacturers to develop novel tests (Ref. 71). We anticipate that phasing out the general enforcement discretion approach for LDTs will spur genuine innovation for IVDs for which there is a reasonable assurance of safety and effectiveness.

(Comment 218) FDA received a few comments discussing the impact of applying the same oversight approach to laboratories and non-laboratories that manufacture IVDs. One comment expressed support for a consistent framework for LDT risk assessment and the enforcement of FDA review requirements according to a test's intended use and stated that "[a] level playing field is critical to maintaining the integrity of FDA review, fostering innovation, and providing patients with high-quality care." Another comment asserted that FDA's statements that application of the same oversight approach to laboratory and non-laboratory manufacturers may remove a disincentive for non-laboratory manufacturers to innovate and thus spur innovation is speculative as FDA has not surveyed manufacturers. The comment added that "market forces, financial considerations, and challenges with patient enrollment in clinical trials for low prevalence pathogens are more likely the disincentivizing factors."

(Response 218) FDA agrees that it is appropriate to apply the same general oversight approach to both laboratories and non-laboratories that manufacture IVDs. The general enforcement discretion approach for LDTs has led to an oversight scheme that does not best serve the public health, and there is no longer a sound basis to have a bifurcated enforcement approach for LDTs and other IVDs. As discussed in section III.B and our responses to comments in section VI.C, most IVDs offered as LDTs are functionally the same as those made by other manufacturers of IVDs, and evidence has exposed problems associated with certain IVDs offered as LDTs.

In addition, FDA agrees that applying the same general oversight approach will result in more stability to the testing market overall, which could help to encourage the manufacture of IVDs for which there is a reasonable assurance of safety and effectiveness. FDA is also aware that some firms have claimed a superficial connection to laboratories and then offered IVDs as LDTs (see Refs. 212 to 215). Given FDA's general enforcement discretion approach for LDTs, firms that use this business model have offered tests to patients in the absence of FDA oversight, with the potential for inaccurate or incomplete results that may impact patients' healthcare

decisions. In addition, FDA is aware of concerns that the use of this type of business model unfairly disadvantages non-laboratory IVD manufacturers that manufacture and market similar tests that comply with applicable FDA requirements. The increase in firms using these business models underscores the need for more oversight.

FDA is also aware of concerns that non-laboratory IVD manufacturers may currently be discouraged from investing time and resources into developing novel tests due to the concern that once the manufacturer receives marketing authorization for its test, laboratories will develop similar tests and market them without complying with FDA requirements, thereby disincentivizing innovation (see response to comment 217).⁹⁰ We anticipate that applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs will address these business strategies that take advantage of the current bifurcated system.

However, FDA also recognizes the effect that its longstanding enforcement discretion approach has had on the market, the role that laboratory-manufactured tests play in modern healthcare, and the presence of other expert regulatory bodies. Many comments emphasized these considerations and FDA agrees with certain comments' concern, for example, that the proposed phaseout policy could lead to the widespread loss of access to safe and effective IVDs on which patients currently rely and certain LDTs for unmet needs. As such, and as further discussed in section V.B, while FDA believes it is appropriate to apply the same general oversight approach to both laboratories and non-laboratories that manufacture IVDs, the Agency has determined that targeted enforcement discretion policies for certain categories of IVDs manufactured by laboratories is appropriate and in the best interest of the public health.

(Comment 219) One comment disagreed with the statement that the phaseout of the general enforcement discretion approach would advance innovation by both laboratory and non-

⁹⁰ FDA also recognizes that challenges in conducting clinical trials for low prevalence pathogens may disincentivize the development of certain novel tests. As noted in section V.B.3 and in response to comment 142, FDA intends to consider whether issuing additional guidance regarding validation of tests, including those for rare diseases that takes into consideration the challenges in obtaining a robust number of samples for validation, would be helpful. In the event FDA were to issue any such guidance, FDA would do so in accordance with good guidance practices (see § 10.115).

laboratory manufacturers, stating that under the general enforcement discretion approach, laboratory manufacturers, especially AMCs, provide innovative, personalized LDTs to fill gaps in test offerings, which then allow conventional manufacturers to assess the market impact of these LDTs and make business decisions based on the LDT experience.

(Response 219) FDA believes that the phaseout of the general enforcement discretion approach for LDTs is necessary to better assure the safety and effectiveness of IVDs offered as LDTs and that the same general oversight approach for LDTs and other IVDs will bring more stability to the market overall. FDA recognizes that laboratory manufacturers of LDTs, including AMCs, may manufacture LDTs that are in lower demand and currently fill gaps in test offerings. As discussed further in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. FDA believes that this policy will address concerns that laboratories integrated within a system and that manufacture LDTs for unmet needs will stop doing so in light of the limited market for such LDTs and the perceived costs of compliance with premarket review and QS requirements.

(Comment 220) One comment noted that FDA's proposal could lead to an unfair playing field between AMCs and for-profit laboratories. The comment indicated that IVDs offered as LDTs by AMCs are typically tests for rare diseases that are not profitable, and suggested that the phaseout policy should perhaps distinguish between for-profit and non-profit laboratories.

(Response 220) As discussed in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. FDA anticipates that this approach will help to reduce the possibility that laboratories in AMCs, or other healthcare systems, may stop manufacturing LDTs for unmet needs.

K. Impact to Specific Patient Populations

(Comment 221) FDA received several comments expressing concern that ending the general enforcement discretion approach for LDTs will negatively impact patient access to necessary tests and thus worsen disparities in healthcare, particularly for racial and ethnic minorities that rely on IVDs offered as LDTs for diagnosis and to inform treatment.

(Response 221) FDA disagrees with the comments stating that phasing out the general enforcement discretion approach for LDTs will exacerbate health inequities for underrepresented patient populations. As detailed in the NPRM, there are concerns that in the absence of greater FDA oversight, IVDs offered as LDTs may be exacerbating health inequities due to higher rates of inaccurate results among underrepresented patient populations, particularly racial and ethnic minorities undergoing genetic testing (88 FR 68006 at 68013; Refs. 21 and 216 to 219). Some IVDs offered as LDTs have not been validated for use across patient populations within a disease state, which may result in decreased accuracy for underrepresented patient populations and further contribute to health disparities (Ref. 220). With increased oversight, FDA will be able to help promote adequate representation of the intended use population in validation studies, and transparency regarding potential differential performance and unknown performance in certain patient populations, which will ultimately help advance health equity.

FDA also recognizes that IVDs offered as LDTs might serve communities in rural, medically underserved areas with disparities in access to diagnostic tests. However, the benefits of test access depend on the ability of tests to work as intended, and the harms of unsafe or ineffective IVDs offered as LDTs might disproportionately occur among medically underserved patient populations that such tests might aim to reach. Without appropriate oversight, IVDs offered as LDTs might exacerbate health disparities.

Nevertheless, FDA recognizes the concerns articulated in these comments regarding potential access issues resulting from the proposed phaseout policy and has adopted several targeted enforcement discretion policies to address those issues, among other things. For

example, FDA acknowledges the importance of avoiding widespread loss of access to IVDs on which patients and the healthcare community currently rely, which ultimately could be more harmful than helpful to the public. As such, and for the reasons further discussed in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3.

FDA is also adopting a targeted enforcement discretion policy for certain unmet need LDTs to help avoid patients being deprived of critically needed LDTs where certain risk mitigations exist (see further discussion in section V.B.3).

(Comment 222) One comment stated that ending the general enforcement discretion approach for LDTs will limit access to necessary tests and make it more difficult to enroll underrepresented patients in clinical trials, which will reduce clinical trial diversity.

(Response 222) As discussed above, FDA is adopting enforcement discretion policies for currently marketed IVDs offered as LDTs and unmet needs LDTs, as described in section V.B.3. These policies will help to address concerns regarding limiting access to such IVDs and resulting difficulties in enrolling diverse populations in clinical trials.

(Comment 223) FDA received one comment that stated that FDA had ignored the special needs of the Native American population, as LDTs are used to analyze mutations with high prevalence in this population, and the population may be “disenfranchised by the loss of LDTs diagnosing their genetic disorders” as a result of phasing out the general enforcement discretion approach for LDTs. The comment suggested that FDA’s tentative determination that “the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes,” as stated in section XII of the NPRM, was incorrect. The comment also suggested that other

populations, specifically “immigrant populations,” would be similarly, negatively affected by the phaseout policy. Another comment stated that there could be legal implications if patients or groups argue that FDA’s actions disproportionately affect certain populations’ access to healthcare.

(Response 223) FDA appreciates the need to consider potential impacts on the Native American population and other specific patient populations. The Agency recognizes that some IVDs offered as LDTs may be currently used to diagnose genetic disorders common in the Native American population. In light of the enforcement discretion policy for currently marketed IVDs offered as LDTs that FDA is adopting, FDA does not anticipate that the Native American population will lose access to such IVDs. In addition, we believe the unmet needs policy described in this preamble, see further discussion at section V.B.3, will help to avoid laboratories integrated in healthcare systems from no longer manufacturing LDTs that meet the unique needs of the Native American population due to the limited market for such tests and perceived costs of compliance with premarket review and QS requirements. As such, FDA does not believe that the Native American population will be disenfranchised as a result of the phaseout policy. For additional discussion regarding FDA’s analysis of the rule in accordance with the principles set forth in EO 13175, please see section XII.

The concepts described above with respect to the Native American population are also applicable to other groups, such as “immigrant populations,” mentioned in the comments.

(Comment 224) FDA received comments regarding the impact of the phaseout policy on medically underserved patient populations. Some comments stated that the phaseout is likely to exacerbate health inequities by further limiting access to testing in rural areas and disproportionately impacting vulnerable patient populations such as pediatric, low-income, lesbian, gay, bisexual, transgender, queer, intersex, and asexual (LGBTQIA+), and minority communities. A few comments stated that the phaseout will further disadvantage underserved populations from both medical and financial perspectives, as AMC laboratories and other

laboratories serving these populations will not have the resources to complete FDA submissions for their tests and will need to outsource testing. One comment voiced concern that FDA has not adequately or accurately assessed the impact of the phaseout on the practice of medicine and patient care, specifically for patients in underserved geographies and those with possible rare diseases. Additionally, a few comments stated that the phaseout will have a detrimental impact on the affordability and speed of testing, which will hinder the ability of some laboratories (particularly public health laboratories) to serve marginalized groups including incarcerated, elderly, and homeless populations.

(Response 224) FDA disagrees that phasing out the general enforcement discretion approach for LDTs will negatively impact medically underserved populations' access to IVDs. FDA recognizes that IVDs offered as LDTs may serve rural communities and other patient populations with disparities in access to diagnostic tests, and recognizes the concern regarding potential disruption of access to IVDs offered as LDTs, particularly for underserved and vulnerable patient populations. However, FDA anticipates that the targeted enforcement discretion policies described in this preamble will help to address the concerns raised in the comments. For example, with respect to AMCs that serve medically underserved populations, as discussed further in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system (including an AMC) to meet an unmet need of patients receiving care within the same healthcare system. We believe this policy addresses the concerns raised in the comment regarding AMCs.

FDA disagrees with the comment that the Agency has not adequately or accurately assessed the impact of the phaseout policy on patients in underserved geographies. As indicated in the PRIA, and again in section II.K of the FRIA (Ref. 10), FDA has considered the potential effects of the phaseout on health inequities to the extent we are able to do so based on available

information. FDA recognizes that IVDs offered as LDTs might serve communities in underserved geographies with disparities in access to diagnostic tests, and the harms of unsafe or ineffective IVDs offered as LDTs might therefore disproportionately occur among individuals in such geographies. As noted in response to comment 221, the benefits of test access depend on the ability of tests to work as intended, and without appropriate oversight, IVDs offered as LDTs might exacerbate health disparities.

FDA has carefully assessed information about IVDs offered as LDTs in scientific literature, news articles, submissions to FDA, and allegations and adverse event reports submitted to the Agency, among other sources, and this information supports a phaseout of FDA's general enforcement discretion approach for LDTs. By phasing out the general enforcement discretion approach, FDA seeks to better prevent and mitigate harm to patients, including those in underserved populations, that may result from inaccurate and unreliable tests, while also accounting for other important public health considerations such as patient access and reliance.

For discussion of the impact of the phaseout policy on the affordability and speed of testing, see our responses to comments 207 and 209 in sections VI.H and VI.I of this preamble.

(Comment 225) FDA received comments expressing concern that ending the general enforcement discretion approach for LDTs will negatively impact Medicare beneficiaries. One comment stated that increased costs for tests will lead to increased Medicare and Medicaid costs, and some comments inquired whether Medicare reimbursements will be adjusted to support the increased costs resulting from the phaseout of the general enforcement discretion approach for LDTs.

(Response 225) As discussed in response to comments in section VI.H, and as noted in section II.F.6 of the PRIA and in the FRIA (Refs. 60 and 10), the exact effect of the phaseout policy on the price of IVDs offered as LDTs is unknown. However, FDA's decision to include certain enforcement discretion policies in the final phaseout policy is predicted to significantly

reduce the costs of compliance under the final phaseout policy, thus reducing the number of laboratories that scale back operations or exit the market, which may in turn reduce any impact of the phaseout policy on pricing. In addition, as noted in response to comment 207, phasing out the general enforcement discretion approach for LDTs will help to reduce other healthcare costs. While certain costs may be passed on to individuals and insurers, we expect some of these costs will be offset by the associated benefits.

In terms of coverage and reimbursement, Medicare is administrated by CMS under different statutory authorities than those governing FDA regulation of IVDs, and future decisions regarding reimbursement are outside the scope of this rulemaking and phaseout policy.

(Comment 226) Other comments articulated concerns regarding the impact of the phaseout policy on laboratory testing for hospitals and providers that serve Medicare and Medicaid patients. These comments expressed concern regarding the potential for the phaseout policy to increase costs for such providers and decrease access to testing for vulnerable patients, particularly children. One comment noted that Medicaid has limited coverage policies for certain laboratory tests and large reference laboratories often do not provide services to Medicaid patients unless the services are covered.

(Response 226) As discussed above, the exact effect of the phaseout policy on the price of IVDs offered as LDTs is unknown, but the enforcement discretion policies described in this preamble are predicted to significantly reduce the costs of compliance associated with the final phaseout policy, thus reducing the number of laboratories that scale back operations or exit the market, which may in turn reduce any impact of the phaseout policy on pricing.

In terms of the comments regarding Medicaid coverage policies, as Medicaid is administrated by CMS and the States under different statutory authorities than those governing FDA's regulation of IVDs, such comments are outside the scope of this rulemaking and phaseout policy.

(Comment 227) FDA received comments stating that the phaseout policy will disproportionately impact pediatric patients. Several comments noted that tests for pediatric patients often do not have any FDA-authorized or “commercial” equivalents, and that tests must be modified to serve the pediatric patient population. As an example, some comments pointed to the lack of FDA-authorized tests to detect sexually transmitted infections (STIs) in children, which must be used in cases of sexual abuse and assault against children. Other comments noted that pediatric patients and their healthcare providers are highly reliant on LDTs because many conventional manufacturers do not seek FDA approval for all age groups and often choose not to develop tests for pediatric diseases, due to the challenges in studying pediatric populations and the relatively slim financial margins for such tests. These comments stated that any action that leads to LDTs not being offered for pediatric patients will result in delayed diagnosis and care for such patients.

(Response 227) FDA understands that laboratories have been using IVDs offered as LDTs to test pediatric patients, and we recognize concerns that phasing out the general enforcement discretion approach for LDTs may lead to a higher chance that laboratories stop offering these tests. FDA believes that the enforcement discretion policies discussed further in section V.B.3, specifically the policies for currently marketed IVDs offered as LDTs and for LDTs for unmet needs, will help to avoid access issues to currently marketed IVDs for pediatric patients as well as LDTs for pediatric patients that meet the unique needs of the patient (see response to comment 228).

(Comment 228) Some comments noted that specialized IVDs offered as LDTs are often vital to medical management for patients with complex medical needs. Comments asserted that the phaseout policy would leave gaps in detection and treatment for these and other vulnerable patients. One comment provided as an example the modification of FDA-authorized assays for more rapid assessment of tuberculosis.

(Response 228) FDA recognizes the need for specialized testing for patients with complex medical needs and for vulnerable populations, like children, who may not have access to FDA-authorized tests. As noted above, FDA intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for currently marketed IVDs offered as LDTs as described in section V.B.3. FDA believes this policy will help to address concerns regarding continued access to currently marketed IVDs for patients with complex medical needs and vulnerable populations. FDA also intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. FDA believes that as a result of this policy, laboratories integrated within healthcare systems will be less likely to not manufacture LDTs for unmet needs due to the limited market for such tests and the perceived costs of compliance with premarket review and QS requirements. Additionally, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements when a laboratory certified under CLIA and meeting the regulatory requirements under CLIA to perform high complexity testing modifies another manufacturer's lawfully marketed test that is not a PMA-approved or BLA-licensed test, in a manner that could not significantly affect the safety or effectiveness of the test or its intended use, as described in sections V.C.4 and V.C.5.

L. Specific Types of IVDs

1. Direct-to-Consumer IVDs

(Comment 229) FDA received comments stating that regulation of direct-to-consumer tests should be prioritized because, unlike in AMCs and hospitals, they are provided to consumers outside of a regulated environment. Comments noted that the direct-to-consumer market is where much of the public concern currently lies regarding unreliable results, as they are not subject to the same controls as LDTs in clinical laboratory settings (i.e., CLIA requirements). Other comments further stated that direct-to-consumer tests are often provided

without accompanying healthcare counseling, which puts users at risk for misinterpretation or patient harm and therefore “should be regulated by FDA.”

(Response 229) FDA agrees with comments that direct-to-consumer tests present risks that are unique and different from some of those posed by IVDs offered as LDTs used in clinical laboratory settings. Indeed, FDA’s general enforcement discretion approach for LDTs has not applied to direct-to-consumer tests, including for this reason. FDA’s general enforcement discretion approach was originally premised, in part, on the participation of medical professionals who, among other things, help determine whether a particular test is appropriate, counsel patients, assist in interpreting results, and assess how the results fit in the overall clinical picture. FDA believes there is a heightened need for oversight of tests where test results are used by consumers to make potentially significant healthcare decisions without the involvement of a learned intermediary in a legitimate healthcare practitioner-patient relationship.

(Comment 230) Some comments stated that the phaseout policy would make it harder for consumers to obtain and use at-home tests, particularly for STIs and human immunodeficiency virus (HIV). Comments noted that this would especially impact those in the LGBTQIA+ community who benefit from at-home tests that can be done discreetly and requested FDA consider “exemptions” for direct-to-consumer tests that further “public health initiatives.”

(Response 230) FDA disagrees that the phaseout policy would make it more difficult for consumers to obtain necessary at-home tests, and notes that FDA has approved a home use test for HIV (Ref. 221) and has authorized an STI test with at-home sample collection for chlamydia and gonorrhea (Ref. 222). As noted in the NPRM and this preamble, FDA’s general enforcement discretion approach for LDTs has not applied to direct-to-consumer tests given the greater risks to consumers presented by these tests (88 FR 68006 at 68022). In situations where consumers may be relying on direct-to-consumer tests to rule out, or otherwise diagnose, a disease or condition, there is a heightened need for FDA oversight. For these tests, FDA has generally

expected compliance with applicable requirements, and the Agency is not changing that approach with the phaseout policy.

(Comment 231) One comment stated that the NPRM “specifies [an] exemption for direct-to-consumer testing,” the danger of which cannot be understated and noted that direct-to-consumer testing “is the exact type of testing the FDA should be focusing on.”

(Response 231) FDA agrees that direct-to-consumer tests should be a focus of FDA oversight due to the risks they present. This comment appears to reflect a misunderstanding of FDA’s proposal. The NPRM indicated that direct-to-consumer tests would not be included in the phaseout policy and, as a result, FDA would continue to expect compliance with applicable regulatory requirements for direct-to-consumer tests. As discussed above and in the NPRM, FDA’s general enforcement discretion approach for LDTs has not applied to direct-to-consumer tests (88 FR 68006 at 68022). FDA has generally expected compliance with applicable requirements for direct-to-consumer tests and the phaseout policy does not change that approach.

2. Forensic Tests

(Comment 231) FDA received several comments regarding the Agency’s proposal to continue its general enforcement discretion approach for tests intended solely for forensic (law enforcement) purposes. The majority of these comments supported FDA’s proposed approach, including one comment which expressed that it was appropriate for FDA to focus on “clinical uses” and to exercise enforcement discretion for tests intended solely for forensic purposes.

(Response 232) FDA agrees with the comments supporting continued enforcement discretion for tests intended solely for forensic (law enforcement) purposes. We described an enforcement discretion approach for tests intended solely for forensic (law enforcement) purposes more than 20 years ago (see, e.g., 65 FR 18230, April 7, 2000). This policy recognized that protections within the judicial process could mitigate risk related to test accuracy and sample collection. Additionally, FDA agrees that it should focus its limited resources on tests that present risks to patients, where sufficient mitigations for test accuracy and sample collection do

not otherwise exist. FDA did not receive any data to justify changing its longstanding policy. FDA, therefore, intends to continue to exercise enforcement discretion for tests intended solely for forensic (law enforcement) purposes. In addition, since the policy on tests for forensic (law enforcement) purposes applies to all tests for forensic (law enforcement) purposes, including those manufactured by non-laboratory manufacturers, changing that policy would not be appropriate in the context of this rulemaking and related policies which are focused on IVDs that are manufactured by laboratories.

(Comment 233) We received a few comments that advocated against FDA's proposal to continue its enforcement discretion approach for tests intended solely for forensic (law enforcement) purposes, primarily because, according to these comments, such tests should be "regulated" the same as other IVDs, and FDA authorization would likely enhance fairness of the judicial system. Another comment indicated that forensic laboratories are not typically CLIA-certified and that NYS CLEP currently requires review of forensic tests. Some laboratories offering forensic tests are accredited by the Substance Abuse and Mental Health Services Administration (SAMHSA), but this level of accreditation is currently required only if a laboratory is testing for certain Federal programs. The comment went on to argue for broader Federal oversight of this test category.

(Response 233) FDA disagrees that ceasing its longstanding enforcement discretion approach for tests intended solely for forensic (law enforcement) purposes is warranted. As FDA explained in the *Federal Register* (65 FR 18230), tests intended solely for forensic (law enforcement) purposes are subject to additional protections such as the use of rules of evidence in judicial proceedings and the representation of the accused (i.e., the person being tested) through the judicial process. The fairness of the judicial process is a separate issue that is not within the scope of this rulemaking.

Further, because FDA’s longstanding enforcement discretion approach for these tests is grounded in the sufficient mitigations in the judicial process, it is inapposite whether these laboratories or their tests are accredited or reviewed by/under CMS, NYS CLEP, or SAMHSA.

(Comment 234) A comment requested that FDA clarify that the general enforcement discretion approach for tests intended solely for forensic purposes includes only tests within FDA’s jurisdiction and that it does not capture tests performed by forensic DNA testing laboratories that fall outside of FDA’s purview. The comment explained that tests at forensic DNA testing laboratories are not “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease,” or “intended to affect the structure or any function of the body.” Rather, relationship testing (DNA) facilities use forensic tests exclusively for legal and immigration proceedings, criminal investigations, and identification of human remains. The comment explained that the National Institute of Justice within the Department of Justice is the lead Federal Government Agency supporting forensic laboratories, including relationship testing facilities accredited by AABB.

(Response 234) A device is defined, in relevant part, as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is...(B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals.” Section 201(h)(1) of the FD&C Act. The determination of whether a product meets the definition of a device is a highly fact-dependent analysis and the context of use may not be determinative of whether a product is intended for “diagnosis.”⁹¹ In any event, FDA intends to continue to exercise enforcement discretion for tests intended solely for forensic (law enforcement) purposes, meaning that it generally does not intend to enforce applicable device

⁹¹ See, e.g., *United States v. An Undetermined Number of Unlabeled Cases*, 21 F.3d 1026, 1028-29 (10th Cir. 1994) (finding that containers used to collect urine and saliva specimens for HIV testing for insurance purposes were devices because “[t]he plain meaning of ‘diagnosis’ disregards context and bears no connection to medical treatment”; and “the fact insurance companies rather than health professionals considered [the results] to make business rather than medical decisions does not erase the diagnostic character of...the containers’ use.”).

requirements for such tests. Moreover, FDA would not be able to enforce device requirements for any tests that do not meet the definition of a device.

3. 1976-Type LDTs

(Comment 235) A number of comments supported FDA’s proposal to continue to exercise enforcement discretion for 1976-Type LDTs. However, a few comments stated that while they agreed with the spirit of this proposal, they were concerned that FDA’s focus on 1976-Type LDTs ignores perceived accuracy enhancements from basic automation techniques. Other similar comments stated that FDA’s proposed enforcement discretion policy for 1976-Type LDTs should be expanded to include automated techniques using components legally marketed⁹² for clinical use and interpreted by a pathologist. Some comments pointed to immunohistochemistry automated staining process as an example of such automated techniques, and one comment stated that “the technical aspect of immunohistochemistry is virtually always automated these days, while interpretation is manual.” Another comment indicated that automation was associated with a reduction in human error rate in that particular laboratory.

(Response 235) As described in section V.B.1, FDA intends to exercise enforcement discretion and generally not enforce applicable requirements for 1976-Type LDTs given that the characteristics of these tests--i.e., they involve manual techniques (without automation), are performed by laboratory personnel with specialized expertise, use components legally marketed for clinical use, and are designed, manufactured, and used within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing--mitigate the risks associated with these tests. In particular, and as explained in the NPRM, these characteristics provide the greatest risk mitigation among the characteristics that were commonly associated with LDTs offered in 1976, which resulted in the emergence of FDA’s general enforcement discretion approach for LDTs (88 FR 68006 at 68022). Automation, including

⁹² As used through this rulemaking, a “lawfully marketed” device means a device that is in compliance with FDA requirements, which may include premarket authorization.

automated slide preparation used in immunohistochemistry, can enhance test performance, but automation also introduces new opportunities for error and other risks that, due to the nature of automation, are not easily identifiable. For these reasons, FDA does not believe that expanding the policy for 1976-Type LDTs beyond these characteristics that were commonly associated with LDTs offered in 1976 to include IVDs offered as LDTs with automation is appropriate.

(Comment 236) We received comments requesting clarity on the type of tests that FDA would consider to be 1976-Type LDTs. These comments included requests that FDA define terms such as “automation,” “specialized expertise,” or “manual.” Other comments asked for examples of 1976-Type LDTs.

(Response 236) Examples of tests that might be considered 1976-Type LDTs when done manually and without automation (e.g., without use of software) include: various tests that use staining antibodies and general purpose reagents for cytology, hematology, and bacterial infections; cystic fibrosis sweat tests; certain colorimetric newborn screening tests; certain immunohistochemistry tests; karyotyping tests; and fluorescence in situ hybridization (FISH) tests. We reiterate that the purpose behind this category of continued enforcement discretion is to recognize the tests that have the sort of mitigations in place that resulted in the emergence of FDA’s general enforcement discretion approach for LDTs, and to help focus FDA’s oversight on more complex tests and tests posing higher risks.

FDA understands that commenters requested more information about the terms “automation,” “specialized expertise,” and “manual.” We generally intend for these terms to have their ordinary meaning. To the extent that additional information and examples would be helpful, FDA will consider issuing guidance on this topic as appropriate and in accordance with good guidance practices (§ 10.115).

(Comment 237) A few comments expressed concern that FDA’s continuation of the general enforcement discretion approach for 1976-Type LDTs will encourage laboratories to avoid automation and instead perform manual tests. The comments stated that this will

disincentivize efficiency and improvement, cause laboratories to close, or increase risks to patients because the comments perceived that manual tests have more room for error.

(Response 237) FDA disagrees with these comments. FDA does not anticipate that the final phaseout policy will cause laboratories to avoid automation and instead perform manual tests. Many comments from laboratories described the substantial benefits of automated approaches. These comments stated that automation improves efficiency, because, for example, fewer individuals are needed to perform a test and testing can occur more quickly. Therefore, FDA thinks it is unlikely that laboratories will stop offering automated tests and switch to manual processes so that their tests may be considered 1976-Type LDTs in the future.

FDA also does not believe that IVDs currently on the market are likely to change from an automated to manual methodology because FDA generally intends to exercise enforcement discretion with respect to premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3. Although this enforcement discretion policy pertains only to premarket review and most QS requirements, whereas FDA intends to exercise enforcement discretion and generally not enforce any applicable requirements for 1976-Type LDTs, the costs of compliance with applicable requirements other than premarket review and QS requirements are only a small fraction of the costs of compliance with applicable requirements under the FD&C Act and FDA's regulations (see section II.F of the FRIA (Ref. 10)). Out of the total estimated costs to industry of \$1.17 billion, the estimated costs of compliance with requirements other than premarket review and QS requirements are about \$95.35 million. Therefore, FDA anticipates that laboratories will not drastically change their current practices or cease to use automation for IVDs currently on the market.

Finally, FDA does not agree that 1976-Type LDTs pose more risk to patients than other tests. As previously noted, features like automation can lead to improved performance and efficiency but can also introduce new opportunities for error and other risks.

(Comment 238) A comment supported the concept of FDA continuing its general enforcement discretion approach for 1976-Type LDTs. This comment suggested, however, that FDA instead use certain other factors (instead of the 1976-Type LDT characteristics) such as the risk to the patient posed by incorrect results, availability of laboratory controls to mitigate these risks, qualification required of those performing or interpreting the test, CLIA certification level of the laboratory, the level of integration between the healthcare provider, test provider, and patient, and whether there is an IVD available, to determine if FDA's general enforcement discretion approach should continue to apply--noting that FDA should continue to exercise enforcement discretion only for an LDT where all of these elements are present.

(Response 238) FDA appreciates the support for its approach to 1976-Type LDTs; however FDA does not agree with expanding the policy for 1976-Type LDTs in the manner suggested by the comment. The purpose behind this policy is to recognize the tests that have the sort of mitigations in place that resulted in the emergence of FDA's general enforcement discretion approach for LDTs and to help focus FDA's regulatory oversight on more complex tests and tests posing higher risks. The factors proposed by the comment do not achieve the same purpose. FDA notes, however, that many of the factors identified by the comment have informed FDA's policy for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients (see section V.B.3).

(Comment 239) Comments requested clarification regarding whether adsorption of warm-reactive autoantibodies using allogeneic or autologous red blood cells to prepare samples for further immunohematology testing would be considered a 1976-Type LDT.

(Response 239) Adsorption of warm-reactive autoantibodies using allogeneic or autologous red blood cells to prepare samples for further immunohematology testing generally

involves only manual techniques performed by laboratory personnel with specialized expertise, and therefore would generally be considered a 1976-Type LDT that would fall under the enforcement discretion policy for those tests provided it uses components legally marketed for clinical use and the design, manufacture, and use is all within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing.

4. Low-Risk IVDs Offered as LDTs

(Comment 240) FDA received several comments recommending FDA adopt a different approach for lower risk tests. One comment suggested FDA provide a “tiered risk-based approach and have streamlined submission and approval options for simpler, lower risk LDTs” to help reduce any negative consequences stemming from the phaseout policy. Another comment recommended the Agency “adopt a new premarket review pathway” for laboratories seeking FDA authorization for low- or moderate-risk tests. One comment stated that there should be an enforcement discretion policy for low-risk LDTs so that clinical microbiology laboratories would continue offering infectious disease LDTs to serve vulnerable communities.

(Response 240) FDA does not intend to have a separate policy for low-risk IVDs offered as LDTs. The statutory framework for device regulation is already risk-based and provides different premarket pathways for devices based on their risk, and FDA can neither change the review pathways established by statute nor create new review pathways not authorized by the statute. Most low-risk tests are exempt from premarket review, and moderate-risk tests are reviewed through the 510(k) and De Novo pathways rather than being subject to premarket approval.

With respect to infectious disease tests, FDA disagrees that all such tests are low-risk or that FDA should adopt an enforcement discretion policy for all clinical microbiology laboratories offering infectious disease LDTs. There are over 500 distinct product codes for infectious disease IVDs in FDA’s classification database, and less than half of those are considered low-risk, or class I (most of which are exempt from premarket notification). Infectious disease IVDs pose

risks that are not necessarily mitigated by other safeguards, and these tests have implications both for an individual patient and other members of the public. Therefore, FDA does not agree that it should continue the general enforcement discretion approach for all infectious disease LDTs offered by clinical microbiology laboratories. However, as described in section V.B, FDA generally intends to exercise enforcement discretion with respect to premarket review requirements for certain categories of tests, including currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3, and LDTs that are approved by NYS CLEP. FDA anticipates that these policies will help patients, including those in vulnerable communities, have continued access to existing beneficial tests on which they rely, and minimize undue disruption to the provision of care, while providing FDA with information about test performance through labeling, MDR reporting, and other applicable requirements.

(Comment 241) One comment expressed concern that the proposed phaseout policy could “inadvertently result in millions of Americans abruptly losing access to much needed tests” due to “undue delay” of FDA premarket review and recommended that FDA should continue the general enforcement discretion approach with respect to premarket review and QS requirements for low- and moderate-risk LDTs until FDA has demonstrated its ability to review and “regulate” high-risk LDTs.

(Response 241) Although FDA does not agree that FDA premarket review itself will cause “undue delay,” FDA is concerned that laboratories may stop offering IVDs on which patients are currently relying if FDA expects compliance with premarket review and all QS requirements for currently marketed IVDs offered as LDTs. Therefore, as discussed elsewhere in the preamble, to address concern regarding potential disruption of access to currently marketed IVDs offered as LDTs, FDA generally intends to exercise enforcement discretion with respect to premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the

date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3.

FDA disagrees with the comment's suggested approach for low- and moderate-risk IVDs offered as LDTs as it relates to IVDs introduced on or after the date of issuance of this rule. In general, low-risk devices are not subject to premarket review or the QS design control requirements (the main source of QS costs under the FRIA), so FDA does not consider the proposed enforcement discretion policy fitting with respect to those IVDs. In addition, FDA expects that compliance with premarket review and QS requirements for moderate-risk IVDs offered as LDTs will have substantial public-health benefits going forward. For example, FDA anticipates that oversight will help ensure the safety and effectiveness of tests that predict a person's risk of cancer, are used in newborn screening, provide information on the risk of adverse events from a therapeutic product, aid in the diagnosis of heart disease, aid in the diagnosis of chlamydia and gonorrhea, and aid in the diagnosis of neurodegenerative disease such as Alzheimer's, among others. Overall, IVDs that may be considered low- or moderate-risk still inform decisions by patients and their healthcare providers, and uncertainty about whether IVDs offered as LDTs provide accurate and reliable results can significantly impact public health. To the extent they apply, premarket review and QS requirements are valuable tools that will help to better ensure the safety and effectiveness of IVDs offered as LDTs by laboratories. Therefore, under the final phaseout policy, the general enforcement discretion approach with respect to premarket review requirements for low- and moderate-risk IVDs introduced on or after the date of issuance of this rule will end 4 years after publication of this final rule.

Further, to the extent this comment is suggesting FDA will lack sufficient resources or technical expertise to conduct premarket review of IVDs offered as LDTs in a timely manner, FDA disagrees as explained in sections VI.C.2, VI.C.3, and VI.N.

(Comment 242) One comment from a laboratory stated that results from its "drugs of abuse screening tests" are not used to "diagnose, treat, or prevent any illness" but rather "provide

accountability of patient use of controlled substances and are used as a means to monitor patient progress,” and false positives or negatives are unlikely to result in patient harm. The comment concluded that such tests are low risk, and that low-risk tests should remain under the general enforcement discretion approach.

(Response 242) FDA disagrees with the blanket statement that “drugs of abuse screening tests” are low-risk tests. “Drugs of abuse” tests are used to diagnose a clinical condition (drug intoxication), which informs a state of health, and to monitor patient use of controlled substances or track patient progress with respect to substance use, which FDA does not consider to be low-risk. FDA generally regulates clinical toxicology tests for drugs of abuse as class II devices with special controls. *See, e.g.*, 21 CFR 862.3650 (opiates), 21 CFR 862.3250 (cocaine and metabolites). For additional information about drugs of abuse tests that FDA has cleared for marketing, we recommend consulting decision summaries in FDA’s 510(k) database by searching under the toxicology panel. Although FDA has determined that it is appropriate to exercise enforcement discretion and generally not enforce any applicable requirements for drugs of abuse tests used solely for law enforcement purposes (see comment response 247), FDA does not see a reason to adopt an enforcement discretion policy for other drugs of abuse tests (see comment responses 248 and 249 for additional information).

(Comment 243) One comment urged FDA to establish classification panels that can act quickly to down-classify IVDs to class I or class II based on a risk assessment before enforcing any regulatory requirements related to LDTs. The comment noted that this would decrease regulatory burden on the Agency and laboratories and provide clarity on the number of class III IVDs offered as LDTs that would require premarket approval. As an example, the comment discussed CDx devices, which are generally class III devices. The comment also stated that “it is critical that decisions regarding IVD risk classification be reexamined and that LDT device types be unambiguously assigned well before marketing application submission deadlines.”

(Response 243) Generally, FDA believes that IVDs offered as LDTs and other IVDs for the same indications should be under the same classification, so FDA intends to consider any reclassification efforts for IVDs holistically, rather than separating out IVDs offered as LDTs.

On January 31, 2024, FDA announced its intent to initiate the reclassification process for most IVDs that are currently class III into class II (Ref. 66). The majority of these tests are infectious disease and CDx IVDs. Reclassification would allow manufacturers of certain types of IVDs to seek clearance through the less burdensome 510(k) pathway rather than the PMA pathway, the most stringent type of FDA device review. The reclassification process will include opportunities for public comment and FDA aims to complete the process before stage 4 of the phaseout policy.

For discussion of the use of classification panels in the context of other IVDs offered as LDTs, please see comment response 195. In addition, FDA intends to continue taking a risk-based approach in the initial classification of individual IVDs (including IVDs offered as LDTs) to determine the appropriate level of regulatory controls and whether a new IVD may be classified into class II or class I through De Novo classification (and special controls established), rather than being class III and subject to the PMA pathway. FDA also regularly considers whether there are class II IVDs that can be reclassified to class I and intends to continue to do so.

5. IVDs Offered as LDTs for Rare Diseases/Unmet Needs

(Comment 244) Many comments reported that LDTs address unmet needs for which there are no FDA-authorized alternatives. For example, comments cited various tests for rare diseases, pediatric patients, infectious diseases including STIs, confirmation of drugs of abuse screening test results, candida auris, immunohistochemistry, and chimerism analysis for monitoring bone marrow transplants. Comments stated that in some cases, laboratories modify FDA-authorized IVDs to meet unmet needs, such as when an alternative specimen type must be used for a patient. One patient's parent wrote about their child's multiyear diagnostic journey

that concluded when a whole genome sequencing LDT revealed a pathogenic genetic alteration. Several comments described challenges in rare disease test development, including the lack of potential profit due to low volume use. Comments stated that most patients with rare diseases are treated at AMCs. Comments expressed concern that increased FDA oversight could further disincentivize rare disease test development, noting that the HDE program does not effectively address the issue, including because the 8,000 tests per year limit is too restrictive and the perceived burden of IRB and reporting requirements dissuade use of the program. Some comments recommended that FDA expand the HDE program. In addition, some comments claimed that the shorter turnaround time for results from certain LDTs (e.g., LDTs for inflammatory cytokines and NK cell killing LDTs) compared to sending a sample to a reference laboratory can impact a physician's ability to cure a patient with a rare disease or condition.

(Response 244) FDA recognizes the challenges faced by patients with rare diseases, their families, and their treating physicians. FDA also recognizes that IVDs offered as LDTs play an important role in healthcare and may address various unmet needs including for rare diseases. We believe several of the enforcement discretion policies adopted in the final phaseout policy will help to address the concerns raised in the comments regarding the availability of IVDs for unmet needs and rare diseases. For example, for the reasons discussed in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs, including IVDs for unmet needs and rare diseases, as long as they are not modified following the issuance of this final rule, or are modified as described in section V.B.3. In addition, for the reasons discussed in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. This policy is intended, among other things, to address

situations described in comments where there is no available FDA-authorized IVD for the disease or condition, where a laboratory needs to modify an FDA-authorized IVD to meet a specific patient need, or where the improved turnaround time of an LDT compared to an FDA-authorized IVD may be critical for the patient's care.

Several comments suggested FDA expand the HDE program. It is not clear what the comments meant by such an expansion, but to the extent this was a suggestion to change the criteria necessary for HDE approval, we note that such criteria are established by statute and cannot be expanded by FDA (see 21 U.S.C. 360j(m)).

FDA intends to consider whether issuing additional guidance regarding validation of tests, including those for rare diseases that takes into consideration the challenges in obtaining a robust number of samples for validation, would be helpful, as discussed in section V.B.3. In the event FDA were to issue any such guidance, FDA would do so in accordance with good guidance practices (see § 10.115).

(Comment 245) One comment expressed concern about applying the HUD program to IVDs offered as LDTs due to the program's complexity and constraints. This comment noted that tests for rare diseases are often developed and run at the request of clinicians, do not have an FDA-authorized alternative, and do not have the volume to support an FDA authorization. This comment recommended that tests for rare diseases remain under an enforcement discretion approach if they serve a local community, use a well-characterized standard test, and are offered in small volumes.

(Response 245) FDA acknowledges concerns regarding the constraints of the HUD program. For these and other reasons discussed in section V.B.3, FDA believes that an enforcement discretion policy for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system is appropriate. This policy should help avoid laboratories integrated within healthcare systems from no longer manufacturing LDTs to meet the unique needs of their

patients, such as when there is no available FDA-authorized alternative (often the case for rare diseases).

FDA disagrees that an enforcement discretion policy for tests for rare diseases that serve a local community, use a well-characterized standard test, and are offered in small volumes would be appropriate as FDA has concerns that there would not be sufficient risk mitigations in such circumstances. Further, limiting an enforcement discretion policy for rare diseases to “well-characterized standard tests” would exclude certain LDTs for rare diseases that are critical to patients and that may not be manufactured by laboratories due to the limited market for such LDTs and the perceived costs of compliance with premarket review requirements.

6. IVDs Offered as LDTs Intended Only for Public Health Surveillance

(Comment 246) FDA received comments regarding our proposal that tests exclusively used for public health surveillance remain unaffected by the phaseout policy. Some comments supported this while others suggested oversight of such tests should be considered, regardless of whether results are returned to the patient or provider. One cited an example of a test that monitors for the presence or spread of a microorganism in a healthcare facility, which may not be used “explicitly” for patient management but is “actionable” by the facility and results may be made available to healthcare providers. The comment encouraged FDA to consider whether the phaseout policy should apply to certain surveillance tests, like this example.

(Response 246) FDA continues to believe that tests manufactured and offered for use exclusively for public health surveillance should remain unaffected by the phaseout policy. As described in the NPRM and this preamble, the scope of public health surveillance tests is limited to tests where results are not reported to patients or their healthcare providers (see section V.A.2, 88 FR 68006 at 68023). Where test results are not reported to patients or their healthcare providers, they are not informing the care of that patient, and increased FDA oversight is less critical. As to the comment’s example of tests for microorganisms in a healthcare facility, if

those tests are not on human specimens, they are not IVDs, and are therefore outside the scope of this rulemaking.

7. IVDs Offered as LDTs Intended to Detect the Presence of Drugs of Abuse

(Comment 247) FDA received several comments on “drugs of abuse” tests. Some suggested that FDA continue the general enforcement discretion approach for drugs of abuse IVDs offered as LDTs used in employment and insurance testing as well as for law enforcement purposes.

(Response 247) Drugs of abuse tests intended solely for employment and insurance testing and not for Federal drug testing programs are exempt from premarket review and would continue to be, regardless of whether they are offered as an LDT (see 21 CFR 862.3100, 862.3150, 862.3170, 862.3250, 862.3270, 862.3580, 862.3610, 862.3620, 862,3630, 862.3640, 862.3650, 862.3700, 862.3870, 862.3910; *see also* 84 FR 71794 to 71819, December 30, 2019). With respect to other requirements applicable to drugs of abuse tests used in employment or insurance testing, FDA does not see a reason to treat IVDs offered as LDTs differently from other IVDs going forward; FDA believes it is important, for example, for such IVDs to be listed in FDA’s database, labeled as required under FDA regulations, and manufactured in compliance with QS requirements, given their risks. FDA has not identified any characteristics that are unique to IVDs offered as LDTs intended to detect the presence of drugs of abuse tests that would justify treating them differently from other drugs of abuse tests.

With respect to drugs of abuse tests used solely for law enforcement purposes, FDA has explained elsewhere in this preamble that it is appropriate to exercise enforcement discretion and generally not enforce any applicable requirements for such tests. This reflects current policy, regardless of whether the tests are IVDs offered as LDTs (see sections V.B.1 and VI.L.2 for additional information).

(Comment 248) One comment stated that the general enforcement discretion approach should continue for all IVDs offered as LDTs intended as drugs of abuse tests because

laboratories need to be able to adapt to combat modifications made to illicit drugs to evade detection. The comments stated, for example, that the FDA-cleared test for fentanyl does not detect modified versions of the drug.

(Response 248) FDA disagrees with the comment suggesting FDA continue the general enforcement discretion approach for all IVDs offered as LDTs to test for drugs of abuse. We acknowledge that such drugs may be modified and that tests for drugs of abuse may need to be modified in order to detect the new versions of these substances. However, FDA oversight does not preclude laboratory manufacturers from making such changes. FDA believes this oversight is important due to the risks to patients from false positive and false negative drugs of abuse test results. False positive results may delay treatment for the patient's true condition if that condition involves symptoms that overlap with drug intoxication (for example, missing a critical opportunity to treat cerebral hemorrhage or stroke). False negative results may put the patient at risk--for example, if they were to drive or were to need urgent treatment for overdose. Compliance with quality system requirements, such as design controls, will help assure that these drugs of abuse tests perform as intended, and compliance with premarket review, where applicable, will help assure that the drugs of abuse test's performance is suitable for the test's intended use.

Where a manufacturer may anticipate the types of changes it intends to make, it may consider seeking clearance or approval of a PCCP. Under section 515C of the FD&C Act, a PMA supplement or new 510(k) is not required for a modification to a device that would otherwise be required if the change is consistent with a PCCP previously approved or cleared by FDA. To the extent a PCCP is approved or cleared by FDA for a particular IVD, any changes within the bounds of that PCCP would not necessitate a new submission to FDA.

(Comment 249) Because the FDA-cleared drugs of abuse tests are only for screening, comments suggested that FDA continue the enforcement discretion approach for confirmatory LDTs intended as drugs of abuse tests, given that these tests are addressing an unmet need.

(Response 249) FDA acknowledges that in drugs of abuse testing, most confirmatory diagnostic tests are currently offered as LDTs. However, as discussed in response to comment 248, FDA oversight of drugs of abuse tests is important, including when such tests are confirmatory.

With respect to the comments' concerns, FDA notes that the final phaseout policy includes several new enforcement discretion policies that may help address those concerns. As explained in section V.B.3, FDA generally intends to exercise enforcement discretion with respect to premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule, including drugs of abuse IVDs offered as LDTs, and that are not modified, or that are modified as described in section V.B.3. In addition, going forward, LDTs may fall within the enforcement discretion policy for unmet needs when they are manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system (see section V.B.3).

8. Genetic IVDs Offered as LDTs/Next Generation Sequencing

(Comment 250) Comments asserted that the phaseout policy is problematic for genetic tests because if such tests are expected to comply with FDA requirements, that will hamper innovation and compromise patient care. One comment claimed that FDA's validation requirements for each variant are unmanageable for LDTs that analyze tens of thousands of variants from multiple sample types. The comment asserted that FDA requires 20 unique wildtype samples and 3-20 unique positive samples per variant per sample type. Other comments asserted that oversight is needed for genetic tests. One comment suggested FDA hire genetic counselors to facilitate decision-making focused on the risk of harm for genetic tests. Another expressed particular concern with pharmacogenomic tests making false claims.

(Response 250) FDA agrees with comments expressing the need for oversight of genetic tests. As illustrated by the pharmacogenomic example cited by comments, FDA is concerned that

test offerings are outpacing the science that supports them. Technological advances have made it possible to sequence DNA in large volumes quickly, but there is not always evidence of clinical validity for the variants reported and used for clinical decision-making. FDA oversight will help ensure appropriate clinical validation. FDA's office that oversees in vitro diagnostics employs individuals with a wide range of expertise in genetics, currently including molecular pathologists, a genetic counselor, and PhD trained scientists.

With respect to NGS tests for the detection of human genetic variants, FDA does not agree that its premarket expectations are unmanageable, and we do not necessarily require 20 unique positive samples for each variant for each specimen type. During premarket review, FDA considers prevalence when considering the number of samples necessary to validate an NGS assay and generally considers a representative approach to validation across variant types. For example, such an approach is described in FDA's final guidance document entitled "Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases" (Ref. 223). This is feasible to do as demonstrated by the many NGS tests, including IVDs manufactured by laboratories, that have received premarket authorization from FDA (see, e.g., information available in FDA's PMA database (Ref. 165) for PMA numbers P210011, P160018, P190032, P200011, and P190014; information available in FDA's De Novo database (Ref. 166) for De Novo numbers DEN170058 and DEN200059; and information available in FDA's 510(k) database (Ref. 224) for 510(k) numbers K210017, K202304, K192063, and K190661).

9. Antimicrobial Susceptibility Tests (ASTs)

(Comment 251) Comments asserted that susceptibility test panels for bacteria, fungi, Nocardia, and mycobacteria are mostly LDTs, as the few FDA-authorized panels have substantial limitations and there is a lack of FDA authorization for less common pathogens. Comments further asserted that there are no FDA breakpoints for susceptibility tests for many of

the pathogens listed by CDC as urgent and serious antibiotic resistance threats, including, for example: *Candida auris*, drug resistant *N. gonorrhoeae*, and carbapenem-resistant *Acinetobacter baumannii*. Comments claimed that it would be unlikely that a laboratory would be able to get FDA authorization for a test that applies non-FDA interpretive breakpoints (CLSI or European Committee on Antimicrobial Susceptibility Testing (EUCAST)), which creates a “catch-22” situation given the Agency’s role in breakpoint approval. The comment stated that laboratories will have to default to the breakpoints for which the assays received FDA approval, which are also out of sync with many of the CLSI updated breakpoints.

(Response 251) FDA recognizes the importance of using updated susceptibility test interpretive criteria (STIC), also referred to as breakpoints, when using antimicrobial susceptibility test (AST) systems. FDA’s Center for Drug Evaluation and Research (CDER) maintains a website with the most up-to-date STIC for antibacterial and antifungal drugs, including FDA’s recognition of STIC established by standards development organizations (SDOs) (Ref. 225). FDA has cleared hundreds of ASTs (addressing hundreds of individual organism/drug combinations) and has worked to ensure that the most up to date STIC are used, including having cleared more than 60 ASTs with breakpoint change protocols, allowing for the rapid adoption of updated breakpoints without further FDA review. To help address the importance of adopting updated breakpoints quickly, FDA recently issued a final guidance entitled “Antimicrobial Susceptibility Test (AST) System Devices--Updating Breakpoints in Device Labeling,” which describes least burdensome approaches for AST manufacturers to update their device labeling with the updated breakpoints listed on the FDA’s STIC Website (see Refs. 225 and 226). This final guidance provides FDA’s recommendations for submission of PCCPs for new AST systems, describes a policy regarding device manufacturers applying certain change protocols submitted to FDA in a separate 510(k) to implement breakpoint updates for the sponsor’s legacy AST system device without a new 510(k) submission to FDA, and clarifies the process for incorporating by reference a cleared PCCP or breakpoint change

protocol into a new submission. FDA believes these approaches will facilitate more timely adoption of updated breakpoints for numerous marketed devices with out-of-date breakpoints and streamline the process for future updated breakpoints to be incorporated quickly on an ongoing basis.

FDA disagrees that “there are no FDA breakpoints for susceptibility tests for many of the pathogens listed as CDC urgent and serious antibiotic resistance threats (including *Candida auris*, drug resistant *N. gonorrhoeae*, carbapenem-resistant *Acinetobacter baumannii*, and more)” as stated in the comment. The CDC list often includes qualifiers such as noting resistance to a particular drug. Generally, breakpoints are established for organism groups without resistance qualifiers, with notable exceptions like methicillin-resistant *S. aureus* and vancomycin-resistant Enterococci for which there is specific and significant data to support inclusion of the qualifiers. For other organisms, the same breakpoint is used regardless of the isolates. For example, there are FDA recognized breakpoints for *Acinetobacter* with many drugs; however, there are no separate breakpoints identified for drug-resistant *Acinetobacter* as the differentiation between drug-resistant and non-drug resistant *Acinetobacter* isolates has not been established in terms of breakpoint determination. It is important to note that CLSI and EUCAST similarly do not often have different breakpoints identified for drug-resistant and non-drug resistant isolates.

FDA also disagrees that “[s]usceptibility test panels...are mostly LDTs” and with the characterization that there are only a “few FDA cleared panels.” As noted, FDA has cleared ASTs addressing hundreds of organism/drug combinations and continues working towards assuring the breakpoints are updated expeditiously once recognized. In addition, referring to Table 2 in Simner *et al*, 2022, FDA notes that between 95.3 percent and 98.8 percent of surveyed CAP-accredited U.S. laboratories use automated AST devices (described in the paper as one of three commercial AST systems) (see Ref. 227). While some of these may be LDTs if the laboratory is modifying the original FDA-authorized AST device to use a different breakpoint or a non-cleared organism, the same study noted that between 37.9 percent and 70.5 percent of U.S.

laboratories reported using out-of-date breakpoints for the antimicrobials that were queried. Therefore, this publication does not support the claim that the majority of ASTs are LDTs. This data supports the need for these tests to be updated with current breakpoints but does not support the claim that the majority of FDA-authorized AST devices are being modified and offered as LDTs in order to use updated breakpoints.

FDA notes in response to the statement that “there is a lack of FDA clearance for less common pathogens,” that there are FDA-authorized tests and FDA-recognized breakpoints for organism groups corresponding to commonly encountered pathogens described in CLSI M100 Table 1, “Antimicrobial Agents That Should Be Considered for Testing and Reporting.” While there are some drug/organism combinations that lack FDA-recognized breakpoints, this is due to the lack of adequate data (clinical, pharmacological, in vitro, etc.) to support the establishment of breakpoints. In most of these cases, as well as the above discussed cases of drug-resistant isolates, there are no breakpoints established by CLSI or EUCAST, either. It is important to note that any stakeholder, including a test manufacturer, also has the ability to submit a request to FDA requesting recognition of a particular breakpoint. This process is described in the docket to which these requests can be made (Ref. 228).

10. IVDs Offered as LDTs for Emergency Use

(Comment 252) Some comments stated that enforcement of premarket review requirements for emergency use tests is not appropriate while others stated it is necessary. Those opposed to such enforcement cited concerns with the ability of public health and AMC laboratories to respond to an outbreak quickly and the corresponding impact on patient access. Some also expressed concern about the impact of the phaseout policy on the availability of tests for emergent situations that do not rise to the level of a declared public health emergency.

(Response 252) FDA agrees with comments that oversight of IVDs for emergency use is important. In this context, the potential for false results can have serious implications for disease transmission and public health decision-making, in addition to the individual patient’s care. For

these reasons, after all previous declarations under section 564(b) of the FD&C Act, FDA's general enforcement discretion approach generally has not applied to LDTs, and FDA is not changing its existing approach to tests for emergency use in this final rule (see section V.A.2). FDA issued EUAs to 116 IVDs from laboratories for COVID-19 and 1 IVD from a laboratory for Mpox.

We note that after a declaration is made under section 564 of the FD&C Act, FDA may issue EUAs to products that fall within the declaration and that meet certain statutory criteria. Notably, the statutory standard for EUAs is different than traditional premarket authorization. As discussed in FDA's final guidance entitled "Emergency Use Authorization of Medical Products and Related Authorities" (Ref. 229), "the 'may be effective' standard for EUAs provides for a lower level of evidence than the 'effectiveness' standard that FDA uses for product approvals." This final guidance includes information on how to request an EUA.

FDA appreciates the need for immediate response to emergent situations (e.g., harmful exposures or outbreaks) during the time between detection of the exposure or outbreak and either resolution of that exposure/outbreak or issuance of a declaration under section 564 of the FD&C Act. Accordingly, in parallel to this rulemaking, FDA is issuing draft guidance for an "Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564." This draft guidance includes an enforcement discretion policy that is limited to certain tests needed for immediate response and limited to certain laboratories, such as those that are USG laboratories, State or local public health laboratories, or other laboratories that have agreements with the USG.

FDA also appreciates that different emergency situations may present unique circumstances for which additional enforcement discretion policies should be considered. FDA has issued a draft guidance document describing "Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency," which describes factors FDA intends to

consider in determining whether to issue an enforcement discretion policy during an emergency declared under section 564 for certain tests.

11. IVDs Offered as LDTs by Public Health Laboratories

(Comment 253) We received several comments that expressed concerns regarding the phaseout of FDA's general enforcement discretion approach with respect to IVDs offered as LDTs by public health laboratories. Comments stated that public health laboratories develop tests for unmet needs for: infectious diseases (e.g., STIs, biological and chemical threat agents), foodborne diseases, newborn screening, toxicology (e.g., blood lead), drugs of abuse testing, and low volume tests for rare diseases. Multiple state public health laboratories expressed concern with increased oversight of IVDs offered as LDTs for newborn screening. They stated that they use LDTs because there is no FDA-authorized IVD for some disorders on the Recommended Uniform Screening Panel and, in other cases, their LDTs are less costly or provide faster turnaround times compared to available FDA-authorized IVDs. Comments also discussed the significant financial burden associated with premarket submissions to FDA and expressed concern regarding the impact of the phaseout policy on public health laboratories that develop LDTs that are not for profit. Various proposals were provided, including continuing the general enforcement discretion approach for existing public health laboratories' LDTs, making the FDA review and authorization processes similar to that of NYS CLEP or relying on that program, streamlining the regulatory process when a public health laboratory modifies an FDA-authorized IVD, FDA offering fee waivers or exemptions, and FDA providing additional guidance, templates, or other resources to facilitate compliance.

(Response 253) FDA appreciates the important role public health laboratories play in our healthcare system. As discussed further in section V.B, FDA is adopting various enforcement discretion policies that should address some of the concerns raised in these comments. For example, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for

currently marketed IVDs offered as LDTs that are not modified or that are modified as described in section V.B.3 (including those manufactured by public health laboratories) and generally not enforce premarket review requirements for LDTs approved by NYS CLEP (including those manufactured by public health laboratories).

We acknowledge that public health laboratories may manufacture LDTs for unmet needs and that compliance with premarket review and other requirements will impose compliance costs on those laboratories. As discussed further in section V.B.3, we are adopting a policy for unmet needs LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. We believe that in such circumstances there are important risk mitigations present, particularly in the case of unmet need LDTs. We understand that this policy does not apply to most public health laboratories (as they are not integrated into a healthcare system and their public health mandate is to serve patients beyond the hospital system). We think it would be inappropriate to extend the policy to unmet needs LDTs developed and performed by public health laboratories, or other laboratories that are not integrated within a healthcare system, as there are not the same risk mitigations present for such LDTs that would help address and avoid the use of problematic LDTs.

FDA disagrees with comments suggesting a streamlined process for when a public health laboratory modifies an FDA-authorized IVD. FDA does not think modifications by a public health laboratory to an FDA-authorized IVD merit a different approach or policy, and the comments did not explain why the considerations raised in the comments are unique to public health laboratories. We note, however, that FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements when a laboratory, including a public health laboratory, certified under CLIA and meeting the regulatory requirements under CLIA to perform high complexity testing modifies another manufacturer's lawfully marketed test that is not a PMA-approved or BLA-licensed test, in a manner that could not significantly affect the

safety or effectiveness of the test or its intended use, as described in sections V.C.4 and V.C.5. Further, FDA intends to develop appropriately targeted enforcement discretion policies for certain common changes to IVDs (including those manufactured and offered by public health laboratories), such as extension of specimen stability and certain alternative specimen types, following good guidance practices.

Regarding comments about fee waivers or exemptions, please refer to the response to comment 190 describing when payment of a user fee is required under the current MDUFA authorization. Exceptions from the requirement to pay a user fee are established by statute (see sections 738(a)(2)(B) and 738(a)(3)(B) of the FD&C Act). The statute also provides authority for FDA to waive some user fees for certain small businesses (see sections 738(a)(3)(B) and 738(d)(1) of the FD&C Act). More information about MDUFA fees, user fee exceptions, and how to request a fee waiver are available on FDA's website (Ref. 183).

Finally, FDA intends to consider making additional resources available over the course of the phaseout period, which could potentially include guidance documents and templates to facilitate compliance.

12. IVDs Offered as LDTs for Research Use Only

(Comment 254) FDA received multiple comments requesting that FDA establish reasonable requirements to incentivize companies to seek FDA authorization for RUO IVD reagents or test kits. One asserted that the majority of LDTs performed in clinical laboratories use test kits distributed by large companies and labeled for RUO. Another comment stated it is common practice for laboratories to modify FDA-authorized IVDs to use RUO instruments or reagents rather than the specified instruments or reagents in the FDA-authorized IVD instructions for use. This comment stated that, in the event a laboratory makes an LDT from RUO components, only the final LDT should be required to comply with regulatory requirements.

(Response 254) FDA has issued a final guidance document that addresses RUO products (see Ref. 176). As explained in the final guidance, the RUO labeling is meant to serve as a warning to prevent such products from being used in clinical diagnosis, patient management, or an investigation that is not exempt from part 812. In general, IVD products that are intended for clinical diagnosis or patient management must be labeled “For In Vitro Diagnostic Use” (§ 809.10(a)(4)) and be in compliance with all applicable requirements for in vitro diagnostic devices. In other words, if an IVD is intended for clinical diagnostic use, it should not be labeled RUO. RUO products are generally not manufactured under the QS requirements, and therefore, are not expected to have the quality controls necessary for clinical use. A manufacturer that labels their product RUO but intends it for clinical diagnostic use would be in violation of the FD&C Act, including misbranding the product under section 502(a) of the FD&C Act due to the labeling being false or misleading.

If a laboratory chooses to use one or more RUO components in its IVDs offered as LDTs, then the laboratory is responsible for qualifying such components in its IVDs. For those IVDs offered as LDTs for which the phaseout policy with respect to the QS requirements would apply, as long as the laboratory has implemented a quality system that meets the QS requirements, as applicable, and is able to appropriately manage the quality of these components under that quality system, then the components may be incorporated as part of an IVD offered as an LDT (see section V.C.3 for a discussion of when FDA generally expects compliance with the QS requirements for IVDs offered as LDTs). The RUO-labeled component(s) will be reviewed in the premarket submission for the IVD offered as an LDT, if applicable.

13. IVDs Offered as LDTs for Sexually Transmitted Infections

(Comment 255) Comments expressed concern that FDA’s proposed phaseout of enforcement discretion would negatively affect access to STI tests currently in use. Multiple comments asserted that LDTs are “the only or most appropriate, and most timely tests available” for HIV and other STIs, and that the proposed phaseout policy would “make it substantially more

difficult to adopt new tests or modify existing tests to meet urgent and emerging public health needs.” A comment also expressed that home-testing programs implemented by public health departments and community-based organizations “provide critical access to HIV, viral hepatitis, and STI testing” that includes testing associated with pre-exposure prophylaxis (PrEP).

(Response 255) FDA disagrees with comments predicting that phasing out the general enforcement discretion approach for LDTs will have negative impact on access to STI tests to meet “urgent and emerging public health needs.” As discussed in section VI.L.10 (IVDs Offered as LDTs for Emergency Use) and VI.L.11 (IVDs Offered as LDTs by Public Health Laboratories), FDA anticipates that several of the enforcement discretion policies adopted in the final phaseout policy will help to address the specific concerns raised in the comments regarding the availability of IVDs for emerging public health threats by facilitating timely access to STI IVDs.

FDA also disagrees with the comment that “the most appropriate tests” for HIV and other STIs are currently offered as LDTs. We acknowledge the critical importance of access to safe and effective HIV tests, including tests that may inform decisions about beginning or continuing use of antiretroviral medications for PrEP. However, FDA-authorized HIV diagnostic and supplemental tests and HIV viral load monitoring tests are available to provide such access. We note that there is an FDA-approved OTC HIV test that individuals may use to test themselves at home or in a private location (Ref. 221). FDA also acknowledges the importance of access to safe and effective tests for other STIs, such as chlamydia, gonorrhea, mycoplasma genitalium, and syphilis, for which FDA-authorized tests are also widely available (see, e.g., Refs. 230 to 233). This includes STI tests for use with self-collected samples in clinical settings and one STI test with at-home sample collection for chlamydia and gonorrhea (see, e.g., Ref. 222). As described in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs, including STI tests, that were first

marketed prior to the date of issuance of this rule. FDA anticipates that this policy will help address the concerns expressed in the comments regarding the impact of the proposed phaseout policy on access to STI tests currently in use. However, for the reasons described in the NPRM and in section V.A.2, we note that FDA's general enforcement discretion approach for LDTs has not applied to direct-to-consumer tests, including direct-to-consumer HIV and other STI tests, and they are not included in this enforcement discretion policy (88 FR 68006 at 68022).

14. IVDs Offered as LDTs Conducted by and Within Blood Establishments, Transfusion Services, and Cell and Gene Therapy Laboratories

(Comment 256) Several comments requested that FDA "exempt" all tests conducted by and within blood establishments, hospitals' transfusion services, and accredited cell and gene therapy laboratories and services from FDA's proposed phaseout of the general enforcement discretion approach. In support of this request, a comment asserted that "the existing regulatory framework ensures that [these entities] provide high quality, safe, and effective care," noting that these entities offer LDTs in CLIA certified laboratories that are part of Federal, State, or locally licensed facilities. The comment also noted that "[e]xtensive FDA regulatory requirements" apply to such laboratories such as registration, licensure of donor screening tests, and premarket review (PMA, 510(k), or New Drug Application (NDA)) requirements for certain products, and that some of these laboratories are also subject to heightened State regulation, such as the NYS CLEP. Some comments expressed concerns that FDA's proposal could negatively affect laboratories' abilities to perform compatibility testing for patients in need of blood or testing that supports safe use of cell and gene therapies. Some comments also requested that FDA exclude immunohematology reference laboratories from the scope of the final phaseout policy as their LDTs involve "highly educated and highly trained technologists perform[ing] specialized testing using manual techniques on select, complex samples" and without which accurate and complete antibody identification would not be possible, resulting in "missed antibodies leading to

increased transfusion reactions, strains to the blood supply due to unnecessary phenomatching of Red Cells and many other issues.”

(Response 256) FDA disagrees with adopting an enforcement discretion policy for all tests used in blood establishments, transfusion services, and accredited cell and gene therapy (CGT) laboratories, and for all immunohematology reference laboratories. In the NPRM, FDA identified categories of tests that have not been part of the general enforcement discretion approach for LDTs. These categories of tests include those that are intended to screen donors of blood and HCT/Ps for infectious diseases under §§ 610.40 and 1271.80(c), or for determination of blood group and Rh factors required under § 640.5 (88 FR 68006 at 68021-22). Such tests may be conducted in blood establishments, transfusion services and/or CGT laboratories. Under the cited regulations, a blood or HCT/P establishment must not use a test for the purposes described in the regulation unless the test is authorized by FDA for such use, and in our experience, establishments have been generally complying with these requirements. Therefore, for these tests, we would not expect the phaseout policy to negatively affect the ability to perform blood compatibility testing or testing to determine HCT/P donor eligibility that supports safe use of HCT/Ps, such as cellular therapies. As described in section V.A.2, these tests are not subject to any enforcement discretion policies included in the phaseout policy.

For other tests conducted by blood establishments, transfusion services, or CGT laboratories (i.e., those not subject to the requirements under §§ 610.40, 640.5, or 1271.80(c)), we disagree with the comment’s assertion that enforcement discretion is appropriate because such tests are developed by laboratories that are CLIA certified and part of Federal, State, or locally licensed facilities. For discussion of why CLIA does not provide sufficient assurances of safety and effectiveness for IVDs offered as LDTs, see our responses to comments in section VI.C.2. While the comment did not provide details regarding which Federal, State, and local facility licensure requirements would be relevant, as a general matter, we note that the requirements against which a *facility* is assessed do not necessarily address the analytical and

clinical validity of (or other issues affecting the safety and effectiveness of) IVDs offered as LDTs by a laboratory within that facility.

With respect to the argument that FDA should exercise enforcement discretion for all LDTs conducted by blood establishments, transfusion services, or CGT laboratories because these entities already comply with FDA requirements for certain other products, such entities should already have familiarity with FDA's requirements and thus be better positioned to transition to compliance in accordance with the phaseout policy. Regarding the comment that some blood establishment and CGT laboratories are subject to State requirements like NYS CLEP, FDA considered comments received regarding NYS CLEP and intends to exercise enforcement discretion and generally not enforce premarket review requirements (but intends to phase out enforcement discretion with respect to other requirements) for LDTs that are approved by NYS CLEP. For further discussion of this policy and other comments received related to NYS CLEP see sections V.B.2 and VI.F.5. The comment did not mention other, specific state programs.

Although we disagree with the comments' request for a broad enforcement discretion policy for all LDTs conducted by or within blood establishments or CGT laboratories and for all immunohematology reference laboratories' LDTs, we note that several of the targeted enforcement discretion policies described in section V may encompass some of these tests and help address the concerns raised in the comments. For example, as proposed in the NPRM and described in section V.B.1 of this preamble, FDA intends to exercise enforcement discretion and generally not enforce any applicable requirements for 1976-Type LDTs (88 FR 68006 at 68022). This includes some tests cited in the comments that are used in blood establishments and immunohematology laboratories such as adsorbing warm-reactive autoantibodies using allogeneic or autologous red blood cells, the Donath-Landsteiner test for aiding in the diagnosis of paroxysmal cold hemoglobinuria, Ham's test to aid in the diagnosis of paroxysmal nocturnal hemoglobinuria, tests to evaluate drug-induced hemolysis or interference in compatibility testing,

monocyte-monolayer test to assess possible clinical significance of RBC alloantibodies, modified Kleihauer-Bethke, and SDa antigen neutralization with urine.

In addition, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3. As noted above, FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP, and to exercise enforcement discretion with respect to premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

Finally, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for non-molecular antisera LDTs for rare RBC antigens when such tests are manufactured and performed in blood establishments, including transfusion services and immunohematology laboratories, and when there is no alternative available to meet the patient's need for a compatible blood transfusion as described in section V.B.3. This enforcement policy is based, in part, on FDA's recognition that there are occasions where licensed IVDs are not available for rare RBC antigens but testing for such rare antigens is necessary to help ensure that patients receive a compatible blood transfusion and avoid potentially life-threatening reactions. We believe that this policy, in addition to some of the other enforcement discretion policies described above, helps mitigate the concern raised by one comment that a phaseout of enforcement discretion for immunohematology laboratories' LDTs will result in "missed antibodies leading to increased transfusion reactions."

15. IVDs Offered as LDTs Used in Manufacturing and Development of Cell or Gene Therapy Products

(Comment 257) One comment recommended enforcement discretion for tests used as part of cell therapy product manufacturing. Another comment recommended enforcement discretion for tests on banked cord blood.

(Response 257) We do not agree that it is appropriate to exercise enforcement discretion for all tests used as part of cell therapy product manufacturing or tests on banked cord blood. For example, as discussed in the NPRM, the general enforcement discretion approach for LDTs has not applied to HCT/P donor screening tests required for infectious disease testing under § 1271.80(c), including screening tests for banked cord blood (88 FR 68006 at 68021-22); FDA is not changing this approach in the final phaseout policy. Under the cited regulation, HCT/P establishments must not use a test for the purposes listed in that regulation unless the test is authorized by FDA for such use. With respect to other tests used as part of cell therapy product manufacturing or performed on banked cord blood, we note that this would span a wide variety of tests depending on the particular product and nature of the manufacturing process, including tests that do not meet the definition of an IVD under § 809.3 and are therefore outside the scope of this rulemaking and the phaseout policy. We note that FDA has mechanisms in place, such as “Section 513(g) Requests for Information,” for manufacturers to obtain information regarding the regulatory requirements applicable to a specific product under the FD&C Act (Ref. 65).

To the extent tests about which the comments are concerned would fall within the definition of an IVD, we note that several targeted enforcement discretion policies are included in the final phaseout policy, as described in section V.B. These policies may help address the comments’ concerns. For example, to help address harms that could result from widespread loss of access to IVDs currently on the market, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed

prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3.

(Comment 258) A comment suggested we should continue the general enforcement discretion approach for premarket review and QS requirements for tests used in cell and gene therapy product development, particularly when screening for clinical trial eligibility and monitoring participant response to investigational treatments, since these tests are typically conducted in low volumes and reviewed in connection with therapeutic product sponsor INDs and NDAs. The comment stated that additional regulatory requirements would create additional burdens without countervailing benefits to trial participants and patients.

(Response 258) FDA recognizes that some clinical investigations of therapeutic products (including cell and gene therapy products) use investigational IVDs to guide the management of participants, such as to determine eligibility or monitor response of participants to the investigational therapeutic product. However, the comment appears to suggest that because of the phaseout policy described in the NPRM, premarket review requirements would apply to and be enforced for all such IVDs when used in clinical investigations. Devices intended for use in clinical investigations, including IVDs offered as LDTs, are exempt from most regulatory requirements applicable to devices, including premarket review, as long as the investigation complies with applicable requirements under part 812. As discussed in more detail in response to comment 175, FDA's regulations do not necessarily require submission of an IDE application to FDA for use of a device in a clinical investigation. To the extent submission of an IDE application is required for use of an investigational IVD in a clinical investigation of a drug or biological product, there are steps that sponsors can take to help simplify the process. For example, IDE and IND applications may cross-reference each other through a letter of authorization. While we disagree that it is appropriate to exercise enforcement discretion with respect to applicable QS requirements for all IVDs used in CGT product development, we note that an investigational device with an approved IDE application (or deemed to have an approved

IDE under § 812.2(b)) is generally exempt from most QS requirements issued under section 520(f) of the FD&C Act (see § 812.1). As described in section V.C, FDA intends to phase out the general enforcement discretion approach with respect to QS requirements during stage 3, including, as applicable, QS requirements for investigational devices.

In all cases, FDA is committed to advancing CGT product development while protecting the safety of trial participants. Compliance with applicable investigational use requirements is important for the protection of participants. Under the phaseout policy described in section V.C, FDA expects compliance with applicable IDE requirements and other applicable requirements, such as parts 50 and 56, for investigations that involve investigational IVDs offered as LDTs 2 years after publication of this final rule. The Agency has resources available that may help sponsors designing trials of therapeutic products that involve the use of investigational IVDs, which are discussed further in our response to comment 175. Sponsors can also engage with FDA under the Q-Submission Program to address questions related to IVD risk, study design, and regulatory requirements.

16. Histocompatibility

(Comment 259) FDA received multiple comments regarding HLA tests. Many comments supported FDA's proposed approach to HLA tests for transplantation. Multiple comments that supported this approach indicated that the extensive and multilayer national system of regulatory oversight provided through United Network for Organ Sharing, OPTN, the Scientific Registry of Transplant Recipients, NMDP, FACT, and the Center for International Blood and Marrow Transplant Research for histocompatibility laboratories has ensured analytical and clinical validity and patient safety for decades. One comment noted that these tests often need to be "customized" to the needs of the patient, and that requiring premarket approval, or even notification, could prevent testing that is critical for patient care. One comment requested that FDA include HLA tests used for blood transfusion in its enforcement discretion approach. Another comment proposed that FDA broaden the scope of its continued enforcement discretion

for HLA tests for transplantation to all histocompatibility tests. Another comment suggested that other tests beyond HLA tests are “generally performed in urgent, life-saving situations for the patient” and therefore should be treated similarly.

(Response 259) FDA agrees with the comments to the extent that they support the Agency’s proposed approach related to HLA tests for transplantation. As discussed in the NPRM, and consistent with the 2014 draft guidance document on oversight of LDTs (Ref. 38), FDA intends to exercise enforcement discretion and generally not enforce any applicable requirements for HLA tests for transplantation used in histocompatibility laboratories that meet the regulatory requirements under CLIA to perform high complexity histocompatibility testing, when used in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing, for HLA antibody screening and monitoring, or for conducting real and “virtual” HLA crossmatch tests (88 FR 68006 at 68022). While other tests may be performed in urgent and life-threatening situations, we note that HLA tests for transplantation are often modified rapidly in response to urgent situations and individualized within each medical facility based on local HLA polymorphisms and patient demographics. Further, we do not agree to exercise enforcement discretion with respect to all applicable requirements for HLA tests for blood transfusion. As described in the NPRM, and in contrast to HLA tests for transplantation, HLA tests for blood transfusion are highly standardized across institutions (88 FR 68006 at 68022). In addition, as noted by some of the comments and explained in more detail in section V.B.1, in the context of HLA tests for transplantation, there are other Federal oversight mechanisms (such as OPTN and NMDP requirements for histocompatibility laboratories and HLA testing) that help mitigate risks of inaccurate results.

17. Antisera Used to Test for Rare Red Blood Cell Antigens

(Comment 260) Several comments recommended FDA continue to exercise enforcement discretion for unlicensed antisera that are used to test for rare RBC antigens. A comment also asserted that FDA’s guidance document entitled “Labeling of Red Blood Cell Units with

Historical Antigen Typing Results” recognizes that blood establishments use unlicensed reagents or unapproved molecular tests for RBC antigen typing and that such tests did not appear to be included in the categories of tests for which FDA proposed to continue to apply its current general enforcement discretion approach going forward.

(Response 260) FDA recognizes there are occasions where licensed IVDs are not available for rare RBC antigens but testing for such rare antigens is necessary to help ensure that patients receive a compatible blood transfusion. While there are molecular tests approved for use in genotyping RBC antigens, there may not be an available approved molecular test to use as an alternative for all rare antigens. After considering the comments on this issue, as discussed in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for non-molecular antisera LDTs for rare RBC antigens when such tests are manufactured and performed in blood establishments, including transfusion services and immunohematology laboratories, and when there is no alternative available to meet the patient’s need for a compatible blood transfusion. However, for the reasons discussed in section V.B.3, FDA does not intend to extend this enforcement discretion policy to molecular tests used for genotyping red blood cell antigens.

M. IVD Modifications

(Comment 261) FDA received comments about modifications to IVDs in different scenarios. Some referred to modifications laboratories make to their own IVDs offered as LDTs for various reasons, including to improve their IVDs. Some stated that laboratories often make modifications to other manufacturers’ FDA-authorized tests to accommodate different specimen types, different patient populations, various storage conditions, additional variants for genetic tests, and many other factors. Comments stated that laboratories cannot afford the expense or significant administrative burden associated with seeking FDA review for each such modification. One comment detailed the flexibilities under the VALID Act for CLIA-certified

high-complexity laboratories to make certain modifications to approved in vitro clinical tests without seeking independent premarket review and suggested FDA adopt a similarly flexible policy for modifications through amendments to the FD&C Act and CLIA regulations or through continued enforcement discretion. The comment noted that a flexible modifications policy should extend to “grandfathered tests” because failure to do so would make a “grandfathering” policy “obsolete as modifications are routinely made to improve performance and adjust to changing circumstances.”

(Response 261) As discussed below, we believe the existing requirements and policies and the enforcement discretion policies described in section V above generally address laboratory modifications of IVDs.

FDA’s regulations describe when manufacturers must submit a premarket submission for a modification to their own device. Specifically, premarket review is required when: an approved device is modified in a way that changes the safety or effectiveness of the device, with certain exceptions (pursuant to § 814.39(a)); a cleared device, or a device classified through the De Novo process and subject to 510(k) requirements, is modified in a way that could significantly affect the safety or effectiveness of the device (pursuant to § 807.81(a)(3))⁹³; or a 510(k)-exempt device is modified outside the scope of the 510(k) exemption. In the context of IVDs, these standards have generally been interpreted to include changes to the operating principle, intended use and other changes that impact performance (see, e.g., Refs. 224 and 61). Post-approval changes to a licensed device must be submitted in accordance with § 601.12. Where the manufacturer may anticipate the types of changes they intend to make, they may consider seeking clearance or approval of a PCCP. Under section 515C of the FD&C Act, a PMA supplement or new 510(k) is not required for a modification to a device that would otherwise require such a submission if the change is consistent with a PCCP previously approved or

⁹³ FDA has published several guidance documents to help stakeholders navigate this process, including “Deciding When to Submit a 510(k) for a Change to an Existing Device” and “Deciding When to Submit a 510(k) for a Software Change to an Existing Device” (Refs. 61 and 211).

cleared by FDA. To the extent a PCCP is approved or cleared by FDA for a particular IVD, any changes within the bounds of that PCCP would not necessitate a new submission to FDA.

In the final phaseout policy described in this preamble, FDA is also including several policies under which FDA generally does not intend to enforce the premarket review requirements for certain modified IVDs offered as LDTs. For example, if an IVD offered as an LDT was first marketed prior to the date of issuance of this rule, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements when the IVD is modified in certain limited ways as described in section V.B.3. As described in response to comment 124, this policy is intended to preserve access to beneficial IVDs on which patients and the healthcare community currently rely, including versions of that IVD with minor changes. In addition, the final phaseout policy described in this preamble includes an enforcement discretion policy under which FDA generally does not intend to enforce premarket review requirements for certain LDTs for unmet needs, which may consist of a laboratory modification to an LDT or to another manufacturer's legally marketed test to meet an unmet need for use by a laboratory integrated within a healthcare system (see section V.B.3). Third, as described in sections V.C.4 and V.C.5, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements when a laboratory makes certain changes to another manufacturer's lawfully marketed 510(k) cleared or De Novo authorized test.

FDA also intends to develop appropriately targeted enforcement discretion policies for certain common changes, such as extension of specimen stability and certain alternative specimen types, following good guidance practices. Although FDA does not anticipate that such enforcement discretion policies will be analogous to certain provisions in the VALID Act, FDA nonetheless anticipates that such enforcement discretion policies will further help to address concerns regarding modifications as described in comments submitted to the docket. Moreover, the custom device exemption in the FD&C Act (21 U.S.C. 360j(b)), or enforcement discretion

decisions for individual manufacturers, IVDs, or IVD modifications, may be appropriate to address unique patient needs or unforeseen circumstances.

(Comment 262) FDA received comments discussing the use of PCCPs as an option in complying with FDA requirements addressed in the phaseout policy. One comment inquired as to whether the PCCP process would extend to all assays or if it would be specific to sequencing assays, and whether FDA would issue a document explaining the PCCP process, including the type of change that would still require submission to FDA.

(Response 262) The use of PCCPs is not limited to certain types of devices, such as sequencing assays. FDA intends to issue draft guidance for stakeholders on Predetermined Change Control Plans for Medical Devices, as noted in the list of proposed guidances for fiscal year 2024 prepared by CDRH (Ref. 234).

(Comment 263) Another comment stated that PCCPs would not alleviate the need for new 510(k)s and PMA supplements for modifications because it would apply only to changes that a manufacturer makes to its own device and would not allow laboratories to adapt cleared or approved tests from other manufacturers to meet evolving clinical needs; and further, it would apply only to changes that the manufacturer can anticipate at the time of submission and does not enable laboratories to modify tests in response to other changing circumstances like reagent shortages or unique patient needs.

(Response 263) FDA agrees that the use of a PCCP would not be applicable in all circumstances in which a laboratory modifies an IVD. Inclusion of a PCCP in the clearance or approval of a device is based on FDA's review of the manufacturer's approach for validating certain types of modifications and associated acceptance criteria. While PCCPs are necessarily limited to the types of modifications the manufacturer can anticipate for a device that is under premarket review, use of the PCCP is just one approach to support the iterative improvement of a manufacturer's own devices. In addition, FDA has adopted or intends to adopt other enforcement discretion policies that may be relevant to the modifications described by the comments, which

are described in the previous comment response. Otherwise, FDA believes premarket review of modifications as described in response to comment 261 is appropriate, consistent with the overall goal of this rulemaking to better assure the safety and effectiveness of IVDs offered as LDTs.

(Comment 264) FDA received a few comments that questioned the extent to which PCCPs would alleviate regulatory burdens for industry and how well they would function. One comment stated that, from experience with the current PCCP process, reaching agreement has been burdensome and lengthy, which limits the utility of PCCPs. Other comments stated that it is premature for FDA to assume that PCCPs will help laboratories as the program is still very new and it is unclear how well it will work for various categories of devices; and further, that it is unreasonable to expect laboratories that previously were generally not expected to comply with FDA requirements to leverage tools that still challenge more seasoned manufacturers.

(Response 264) FDA recognizes that efforts around PCCPs are relatively new and not all manufacturers may utilize PCCPs when making IVD modifications. In order to provide additional information to stakeholders on this topic, FDA has announced that it intends to issue draft guidance on PCCPs in fiscal year 2024 (Ref. 234). In addition, by the time of stages 4 and 5 of the final phaseout policy, FDA anticipates that it will have more experience with PCCPs, including in the context of IVDs, in order to facilitate manufacturer use of this tool. FDA may also provide additional guidance and educational opportunities for stakeholders, as appropriate. In any event, whether laboratories choose to use the PCCP process does not affect the public-health need for this rulemaking.

(Comment 265) FDA received comments expressing concern that premarket review requirements will cause disruption in access to tests and requesting the Agency take a more flexible approach or provide simplified submission requirements for specific types of assay modifications. Some comments suggested that FDA create a new submission pathway whereby low-risk modifications are reviewed on an expedited 45-day timeline and use this pathway when a PCCP may not be possible or available for low-risk modifications (i.e., those that do not

change the intended use, indications for use, or adversely affect the approved analytical or clinical performance) so that test manufacturers may implement low-risk modifications more expeditiously and ensure patient access to cutting-edge technology.

(Response 265) At the outset, FDA notes that compliance with premarket review requirements protects and promotes public health by helping assure that devices are safe and effective. In addition, not all modifications require premarket review. For modifications requiring premarket review, FDA will use the well-established premarket pathways set forth in the statute and regulations. With respect to the 45-day review period proposed by the comments, FDA declines to adopt a new policy expediting review of these modifications, which would divert resources from other priorities. However, for certain modifications that require premarket submission, FDA anticipates that the established expedited premarket pathways, such as the Special 510(k) program for moderate-risk devices with a 30-day timeline and the Real Time PMA program for high-risk devices with a 90-day timeline (see Refs. 235 and 236), will help laboratories implement these modifications in a timely manner. In addition, FDA has adopted or intends to adopt other enforcement discretion policies that may be relevant to such modifications. See the discussion in comment response 261.

(Comment 266) One comment proposed a continued enforcement discretion approach for modifications of certain FDA-approved (third-party) IVDs by appropriately trained and “certified” clinical scientists/pathologists at certain clinical laboratories, such as laboratories with high sample volume, reference laboratories, and laboratories serving ethnically diverse patient populations. This comment further proposed that qualified laboratory personnel would develop, review, and validate the modifications and submit a final report to FDA “for information only,” which would be used to facilitate FDA’s review of the test characteristics when a submission for the modified IVD is submitted by the initial third-party manufacturer. The comment proposed that this approach should be limited to modifications of an FDA approved assay adapted for the local clinical need.

(Response 266) FDA does not agree that it should adopt the approach proposed in the comment. By “FDA-approved” IVD, we assume that the comment is referring to an IVD that is approved under a PMA. Such IVDs are class III devices that are considered high risk. When an IVD is high risk, changes to that IVD pose corresponding increased risks. Therefore, although FDA has adopted an enforcement discretion policy for certain laboratory changes to another manufacturer’s lawfully marketed 510(k) cleared or De Novo authorized test (see sections V.C.4 and V.C.5), this policy does not apply to IVDs approved under a PMA.

However, FDA is adopting several other enforcement discretion policies that may be relevant to the comment’s concern. As described in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)), for: (1) IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule, including versions of those IVDs with minor changes and (2) LDTs manufactured and performed by a laboratory integrated within a healthcare system to address an unmet need of patients receiving care within the same healthcare system.

(Comment 267) With respect to laboratory modifications to another manufacturer’s FDA-authorized test, another comment suggested that FDA “clarify through special controls what laboratories are expected to do when performing such validations and the extent to which the modified test’s performance can change from the originally authorized version.” The comment stated that it would be more practical for FDA to expect a premarket submission from a laboratory only when the modification is to another manufacturer’s already cleared or approved device and a “significant change” has been made, as defined in FDA’s guidance document entitled “Deciding When to Submit a 510(k) for a Change to an Existing Device” (Ref. 61).

(Response 267) FDA agrees with this comment in that FDA intends to exercise enforcement discretion with respect to the premarket review requirements for certain modifications to certain lawfully marketed tests. Specifically, as described in sections V.C.4 and

V.C.5, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements when a laboratory certified under CLIA and meeting the regulatory requirements under CLIA to perform high complexity testing modifies another manufacturer's lawfully marketed 510(k) cleared or De Novo authorized test, following design controls and other quality system requirements for which FDA expects compliance as described in section V.C.3, in a manner that could not significantly affect the safety or effectiveness of the test and does not constitute a major change or modification in intended use, and where the modified test is performed only in the laboratory making the modification. The guidance document mentioned in the comment applies to a manufacturer's modification of its own legally marketed device that is subject to 510(k) requirements. However, its description of changes that could significantly affect the safety or effectiveness of a test or constitute a major change or modification in intended use would be helpful and relevant for purposes of the enforcement discretion policy described in this paragraph.

Further, FDA intends to develop appropriately targeted enforcement discretion policies for certain common changes, such as extension of specimen stability and certain alternative specimen types, following good guidance practices.

In addition, to the extent the comment suggested that FDA should not expect premarket submissions from laboratories when a modification is made to a laboratory's own IVD, we disagree. Even if a laboratory is making a change to its own IVD, certain of those changes warrant premarket review in order to protect and promote public health. For example, for a 510(k)-cleared device, premarket review is expected when a change could significantly affect the safety or effectiveness of the device.

If a manufacturer needs assistance in understanding FDA's expectations for validation for a particular test, whether the test is designed initially by the laboratory manufacturer or whether the laboratory manufacturer is modifying another manufacturer's test, it may seek information through FDA's Pre-Submission program, which is further explained in FDA's guidance

document entitled “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program” (Ref. 65). Validation expectations may also be included in device-specific special controls, guidance documents, decision summaries, and recognized standards, all of which can be found on FDA’s website. Further, FDA plans to consider what other resources may be helpful for laboratory manufacturers that modify another manufacturer’s FDA-authorized test. Any future such resources will also be made available on FDA’s website.

(Comment 268) FDA received several comments regarding test modifications in various areas of medicine, such as genetic testing, STI tests, and others that would be impacted by the phaseout policy. One comment asserted that the ability to rapidly update tests has improved the accuracy of genetic testing and provides improved sensitivity and specificity of testing across diverse populations in the United States. Another comment stated that increased oversight of LDTs would have significant implications for ongoing improvements using real-world evidence and continuous feedback loops, which allows for iterative enhancements to tests that greatly benefit patients. Another comment discussed the modifications to another manufacturer’s FDA-authorized tests that are used in the pediatric population, where information in the labeling, such as intended use statements, are restrictive regarding patient population and specimen collection.

(Response 268) FDA agrees that test modifications, including those implemented based on real-world evidence information and to expand the indications for use of another manufacturer’s FDA-authorized test to include pediatrics, can greatly benefit patients when the modified test remains safe and effective. FDA has seen modifications to tests that were intended to improve the test but did not actually do so; once the modified test underwent validation testing, the performance of the test was worse than the unmodified test and the test was no longer safe and effective for its intended purpose. FDA has also seen modifications to tests that have not been supported by valid scientific evidence--for example, when there has been a lack of valid scientific evidence demonstrating the clinical validity of the modified test. FDA does not agree with the underlying implication of these comments that being able to modify IVDs without

premarket review, regardless of the type of modification, best serves public health. FDA premarket review of modifications that could affect a test's safety and effectiveness helps ensure that modified IVDs are safe and effective. For example, FDA premarket review helps ensure appropriate clinical validation for modifications, among other things, including for genetic and STI tests, which were specifically raised by one comment.

(Comment 269) One comment expressed concern regarding the “potential rigidity” of the device regulatory scheme and its impact on the ability to “routinely adjust DNA/RNA extraction processes to obtain more quality material for testing based on improving technology.” The comment went on to propose FDA adopt an “improved technology verification protocol” that will allow a party to submit the reasons for modifications with a justification of improvements and demonstration that QC measures are being maintained.

(Response 269) The comment proposed a new regulatory approach to device modifications based on an “improved technology verification protocol.” Even assuming such an approach were within FDA's statutory authority, creating a new regulatory approach for all device or IVD modifications is not within the scope of this rulemaking, which is focused on phasing out the general enforcement discretion approach for LDTs. FDA notes that it may be appropriate to include certain changes, such as the modification to DNA/RNA extraction methods mentioned in the comment, in a PCCP in a premarket submission to FDA. For a more detailed discussion of PCCPs, see comment responses 262-264.

(Comment 270) Several comments discussed antimicrobial breakpoints and whether updates to breakpoints of ASTs should fall within the phaseout policy. One comment asserted that FDA's policy for requiring manufacturers of automated AST devices to wait for FDA to recognize updated breakpoints forces laboratories “to choose between FDA's outdated breakpoints...or performing internal validation of CLSI's updated breakpoints.” Another comment asserted that manufacturers of “FDA-cleared or approved automated devices are not required to update breakpoints, and therefore modified FDA-cleared/approved (LDT) testing

must be used” and further asserted that their laboratory would not have the necessary staffing and financial resources to submit premarket submissions for revised breakpoints.

(Response 270) FDA disagrees with the premise that FDA’s recognized breakpoints are outdated. Section 3044 of the Cures Act created a system to expedite the recognition of breakpoints, referred to in the Act as antimicrobial STIC (section 511A of the FD&C Act, 21 U.S.C. 360a-2). Since implementation of this statutory provision, FDA posts information online about FDA’s recognition, or withdrawal from recognition, in whole or in part, of STIC established by an SDO and lists of exceptions or additions to the recognized STIC that the SDO established (Ref. 225). These online references are updated regularly. This approach allows FDA to more quickly communicate updated STIC than would be possible through updating and re-updating drug labeling. FDA has also created corresponding processes for rapid updates of breakpoints in AST devices. For example, FDA works with manufacturers to include PCCPs in their premarket submissions so that they can update their devices to address updated breakpoints without premarket review. In 2023, FDA issued a final guidance document, “Antimicrobial Susceptibility Test (AST) System Devices--Updating Breakpoints in Device Labeling” (Ref. 226), in which FDA describes least burdensome approaches for AST system device manufacturers to update their device labeling with the updated breakpoints listed on FDA’s STIC website (Refs. 225 and 226). Generally, updating the STIC could significantly affect the safety and effectiveness of the AST system device and would therefore require a 510(k) submission prior to updating the device labeling. However, the final guidance provides recommendations on the marketing submission content for PCCPs for new AST system devices, describes an enforcement policy regarding applying such updates to “legacy” AST system devices (AST system devices that were reviewed and cleared by FDA and did not include a breakpoint change protocol), and clarifies the process for incorporating by reference a cleared PCCP or breakpoint change protocol into a new 510(k) submission for an AST system device. FDA anticipates that this final guidance will facilitate timely adoption of updated breakpoints in AST system devices,

which helps to maintain device safety and effectiveness. This should also reduce the burden on laboratories regarding the need to modify automated devices or submit premarket submissions where the manufacturers of the automated devices are using these streamlined approaches to quickly adopt updated breakpoints.

Additionally, for laboratories that are already offering AST devices as LDTs, as discussed in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule, and for certain modifications to such currently marketed IVDs offered as LDTs. In general, future updates to breakpoints of currently marketed ASTs offered as LDTs are within the scope of this enforcement policy, provided that such update is validated, does not change the indications for use of the AST, does not alter the operating principle of the AST, does not include significantly different technology, and does not adversely change the performance or safety specifications of the AST. For a modification to the breakpoint to an IVD currently offered as an LDT to be considered clinically validated, FDA expects the updated breakpoint to reflect that identified on the STIC website.

(Comment 271) Some comments stated that enforcing premarket review requirements for manufacturing changes will hamper process innovation, which will disincentivize changes that may improve laboratory operations and costs to patients, such as updating software, adding automation, and adjusting workflow to accommodate throughput needs of the institution.

(Response 271) As an initial matter, FDA notes that updating software, adding automation, and adjusting workflow to accommodate throughput could be examples of manufacturing process changes or changes to the design of an IVD, depending on how the change applies. For example, an update to the software used by a test would generally be considered a design change. For additional information regarding modifications to IVDs offered as LDTs, including design modifications, see the responses to comments 261 through 270. To

the extent the comments are specific to changes made to the manufacturing process, FDA requirements for premarket review of manufacturing process changes are calibrated to the significance of the change and risk of the device, such that premarket review (to the extent required) of minor changes is more streamlined than for major manufacturing changes. We believe this framework helps address some of the comments' concerns.

For example, for devices approved under a PMA or licensed under a BLA, FDA regulations require the submission of a supplement or a 30-day notice for certain manufacturing changes (see §§ 814.39 and 601.12). The appropriate type of submission varies with the nature of the change, as discussed in FDA's final guidance, "Modifications to Devices Subject to Premarket Approval (PMA)--The PMA Supplement Decision-Making Process" (Ref. 185) (see also § 601.12(b)-(c)). In some cases, which generally involve minor changes, manufacturing changes may be noted in a PMA or BLA annual report after they have been implemented (see §§ 814.39(b) and (e) and 601.12(e)). We also note that FDA estimates that premarket approval or licensure requirements will apply to only a small percentage of IVDs offered as LDTs (see Appendix A of the FRIA (Ref. 10)).

For devices subject to premarket notification, which are generally lower risk than those subject to PMA or BLA requirements, a change in the device manufacturing process would require a new 510(k) only if the change was one that could significantly affect the safety or effectiveness of the device (see § 807.81(a)(3)). Although, the need for premarket review of a manufacturing process change for an IVD is typically a case-specific evaluation, many changes implemented to improve laboratory operations may not trigger the requirement for a new 510(k) submission under FDA regulations. As discussed in FDA final guidance, manufacturers should consider the impact of manufacturing changes on device labeling, technology, engineering, performance, and/or materials to determine if a new 510(k) submission is required (Ref. 61).

In our experience, FDA premarket review of certain manufacturing changes is important to prevent adverse effects on device safety and effectiveness. For example, if a new

manufacturing line is introduced that significantly alters the specificity of an antibody used for colon cancer screening, hundreds of individuals may receive false negative cancer screening results and miss critical early detection of colon cancer. In this example, even if introduction of the new manufacturing line was intended to improve operations, the change could have a significant, unintended adverse impact on the device's safety and effectiveness and, ultimately, on patients.

Moreover, as discussed in response to comment 261, FDA is issuing several policies under which FDA generally does not intend to enforce the premarket review requirements for certain modifications to IVDs offered as LDTs. The Agency anticipates these enforcement discretion policies will also help alleviate some of the concerns expressed in these comments.

(Comment 272) One comment stated that FDA should “differentiate permitted off-label use from actions that create a ‘new’ or ‘modified’ test such that FDA would have jurisdiction” and that FDA should “ensure that it protects the legitimate (and statutorily protected) right of a healthcare professional to utilize a legally marketed test for an unapproved use.”

(Response 272) Section 1006 of the FD&C Act sets forth what conduct falls outside FDA's statutory authority as the “practice of medicine,” 21 U.S.C. 396, meaning Congress has already “differentiate[d]” in the manner suggested by the comment. For further discussion of the practice of medicine, see sections VI.D.6 and VI.D.7 of this preamble.

(Comment 273) One comment requested guidance “on the use of specific IVD Cleared reagents and the conditions under which an LDT status is assigned.”

(Response 273) To the extent this comment is requesting clarification on whether the use of 510(k)-cleared reagents to develop a new test system would be considered manufacture of an IVD offered as an LDT, the answer is that it would. A test system is itself a device subject to applicable device requirements, regardless of whether the components of the system comply with FDA requirements.

(Comment 274) Some comments expressed concerns that FDA would not have sufficient resources to conduct timely premarket review of IVDs offered as LDTs to meet the public health needs. Some recommended that FDA modify the phaseout policy to prolong the period of time prior to phasing out the general enforcement discretion approach with respect to premarket review requirements, and/or continue to apply the general enforcement discretion approach with respect to premarket review requirements for certain LDTs, to reduce the FDA resource needs.

(Response 274) FDA has considered Agency resources in developing the final phaseout policy (see section II.G of the FRIA (Ref. 10)). FDA disagrees that the Agency will lack sufficient resources to conduct premarket review of IVDs offered as LDTs in a timely manner.

First, FDA does not intend to phase out the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs offered as LDTs until 3½ years after publication of this final rule (stage 4 of the phaseout policy), and for moderate- and low-risk IVDs offered as LDTs (that require premarket submissions), until 4 years after publication of this final rule (stage 5 of the phaseout policy). This timeline aligns with the next reauthorization of MDUFA. This alignment will provide an opportunity for FDA and industry to negotiate regarding user fees and performance goals with the knowledge that laboratory manufacturers will be expected to comply with applicable premarket review requirements. Additional discussion regarding FDA's implementation of the phaseout policy is provided in response to comment 291. As discussed further in that response and in section V.C, for IVDs offered as LDTs for which a complete PMA, HDE application, 510(k) submission, BLA, or De Novo request has been received by the beginning of stage 4 or stage 5 of the phaseout policy (as applicable), FDA generally does not intend to enforce premarket review requirements until FDA completes its review of the application/submission. Thus, the timeliness of review of these submissions generally should not impact patient access.

Second, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M

(Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3. FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP, and to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. These aspects of the phaseout policy are discussed further in section V.B of this preamble, and collectively will significantly reduce the number of premarket submissions for IVDs offered as LDTs, as compared to the estimates in the PRIA. In particular, the total estimated number of affected tests has been reduced from 88,176 (see Ref. 60) to 7,606 (Ref. 10).

Third, FDA will gain more visibility into the universe of IVDs offered as LDTs through registration and listing in stage 2, which should help the Agency facilitate the efficient allocation of premarket review resources for those IVDs. As explained in the NPRM and discussed in the FRIA, FDA's device authorities require premarket review only for certain IVDs (88 FR 68006 at 68013). FDA estimates that approximately 50 percent of IVDs offered as LDTs will not require premarket review (see section II.F.2 of the FRIA (Ref. 10)). However, there are uncertainties surrounding the estimate of total numbers of IVDs offered as LDTs on the market because FDA generally has not enforced the registration and listing requirements for LDTs under section 510 of the FD&C Act and parts 607 and 807 (excluding subpart E). By 2 years after publication of this final rule, during stage 2 of the phaseout policy, FDA will obtain registration and listing information from laboratory manufacturers offering IVDs as LDTs. This information will help FDA assess and plan for the resources needed for premarket review of those IVDs before stages 4 and 5 of the phaseout policy. In addition, on January 31, 2024, FDA announced its intent to initiate the reclassification process for most IVDs that are currently class III into class II (Ref.

66). The majority of these tests are infectious disease and CDx IVDs. FDA aims to complete this reclassification process before stage 4 of the phaseout policy. Reclassification would allow manufacturers of certain types of tests to seek marketing clearance through the less burdensome 510(k) pathway rather than the PMA pathway, the most stringent type of FDA medical device review. FDA also intends to continue taking a risk-based approach in the initial classification of individual IVDs to determine the appropriate level of regulatory controls and whether a new test may be classified into class II through De Novo classification (and special controls established), rather than being class III and subject to the PMA pathway. Based on our experience, we believe that special controls could be developed, along with general controls, that could provide a reasonable assurance of safety and effectiveness for most future CDx and infectious disease IVDs. We therefore anticipate the percent of IVDs, including LDTs, eligible for 510(k) review to increase.

Fourth, other aspects of FDA's phaseout policy and related FDA actions will help to reduce premarket review resource needs. For example, FDA is currently working to enhance its Third Party review program to handle the review of low- and moderate-risk devices by 3P510k Review Organizations. This will free up Agency staff time to review more complex, innovative, high-risk devices. FDA estimates that half of the IVDs offered as LDTs subject to 510(k) requirements will be reviewed under the Third Party review program.

Fifth, FDA anticipates that laboratories may utilize PCCPs, and as discussed in response to comment 261, for certain common changes (like extension of reagent stability and certain alternative specimen types), FDA intends to develop appropriately targeted enforcement discretion policies, following good guidance practices. See additional discussion regarding test modifications in our responses to comments in section VI.M. FDA believes that PCCPs and targeted enforcement discretion policies will minimize the number of premarket submissions for modifications to IVDs offered as LDTs.

(Comment 275) Some comments questioned whether FDA would have adequate capacity to provide timely review of LDT applications/submissions because many EUA requests were not reviewed due to resource limitations during the COVID-19 pandemic. At least one comment cited FDA's review of a particular EUA request for an LDT during the COVID-19 pandemic, in which FDA's review of the request did not conclude until after the subject LDT had been removed from the market, as proof that FDA does not have adequate resources to conduct premarket review of LDTs.

(Response 275) FDA disagrees that its review of any one particular EUA request submitted for an LDT during the COVID-19 pandemic is indicative of how FDA will review premarket applications/submissions for IVDs offered as LDTs generally. FDA also disagrees that decision timelines on EUA requests, in general, are a good indicator to predict FDA's timelines for review of premarket applications/submissions for IVDs offered as LDTs.

First, EUAs differ substantially from standard premarket review pathways. FDA's authority to issue EUAs for LDTs is under a different statutory provision (section 564 of the FD&C Act) than traditional premarket reviews. Moreover, FDA is not required to review individual EUA requests submitted to FDA or review them on a specific timeline, or to authorize the emergency use of a medical product even if it meets the relevant criteria for an EUA, giving FDA flexibility to determine how to prioritize its efforts in emergencies to protect and promote public health. Second, during the COVID-19 pandemic, FDA received a large influx of submissions that had not been anticipated. In the context of the phaseout policy, FDA has estimated the number and type of premarket submissions we can expect in stages 4 and 5, and annually thereafter, and can prepare for those submissions.

Third, as noted in an FDA memorandum to file that was part of the record for this rulemaking (Ref. 18), FDA identified many issues with EUA requests from laboratories. When data are not presented clearly or data are inadequate to support authorization, FDA works with the submitter to address these issues and, in most cases, achieve authorization. This process

extends review times. FDA anticipates that phasing out the general enforcement discretion approach for LDTs, combined with additional education or guidance, will ultimately lead to better submissions from laboratory manufacturers once they become familiar with FDA's expectations.

(Comment 276) Some comments referenced FDA's MDUFA IV performance report from FY2020 to 2022 (during the COVID-19 pandemic) and predicted that the increased volume of submissions from laboratory manufacturers that would result from the phaseout policy would affect FDA's overall ability to review premarket submission for all IVDs, meet its MDUFA performance goals, and conduct other essential work, including policy and post-market activities.

(Response 276) MDUFA performance goals include shared outcome goals agreed to by both FDA and representatives of the industry. FDA and applicants share the responsibility for achieving the Total Time to Decision objectives. Since premarket review of IVDs offered as LDTs is based on significant interaction between the Agency and applicants, high quality submissions will generally help reduce FDA's review time. FDA anticipates providing more targeted guidance on various topics, such as validation, and making additional resources available on the topic of premarket review of IVDs offered as LDTs over the course of the phaseout period. Further, as noted in response to comment 274, the phaseout of enforcement discretion for premarket review requirements aligns with the next reauthorization of MDUFA, providing an opportunity for FDA and industry to negotiate regarding user fees and performance goals with the knowledge that laboratory manufacturers will be expected to comply with applicable premarket review requirements.

(Comment 277) Another comment referenced FDA's "prolonged review" of a particular consensus standard and suggested that "such an extended review period raises concerns about the FDA's capacity to regulate and approve essential LDTs in a timely manner."

(Response 277) FDA disagrees that our standards recognition process has any bearing on our ability to conduct timely premarket reviews, including reviews of LDTs. The premarket

review process and the standards recognition process are independent and have different timelines and prioritization. Further, FDA's participation in standards writing committees does not automatically signal that FDA intends to recognize the standard. As these are consensus standards with many participants, FDA may or may not agree with the final published content and has a formal process for considering recognition.

(Comment 278) Some comments expressed concerns that a substantial increase in FDA staff and review capacity will be required to implement the phaseout policy, and workforce shortages will make it difficult to recruit and retain adequate numbers of qualified reviewers who are trained in laboratory diagnostics. Some comments stated that FDA lacks the personnel with relevant knowledge and expertise in laboratory medicine to effectively oversee molecular genetic IVDs offered as LDTs. One comment concluded that FDA had not kept up with the state-of-the-art methods for evaluating whole genome sequences, based on the fact that FDA declined to accept the Average Nucleotide Identity (ANI) results offered to correct the FDA-ARGOS database because the ANI results had not yet been standardized through the National Center for Biotechnology Information (NCBI).

(Response 278) FDA disagrees that the Agency lacks the knowledge and expertise to oversee IVDs offered as LDTs in the field of molecular genetics or in other fields. FDA has regulated IVDs under the comprehensive device authorities of the FD&C Act for almost 50 years, and it has the expertise and experience to regulate these tests, as discussed in response to comments 10 and 92. Specifically, OHT7 is staffed with scientific and medical experts who specialize in IVDs. OHT7 is responsible for overseeing total product lifecycle activities for IVDs. As noted previously, FDA also plans to utilize resources outside the Agency to support the implementation of the phaseout policy via the Third Party review program, and intends to exercise enforcement discretion and generally not enforce certain requirements for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3; LDTs approved by

NYS CLEP; LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system; and LDTs manufactured and performed within VHA and DoD. Additional discussion can be found in response to comments in sections VI.F.5, VI.O, and VI.P of this preamble.

FDA also disagrees that its decision to follow the established quality control procedures for inclusion of genome sequences in the FDA-ARGOS database suggests that FDA's regulatory science in this area is outdated. Rather, the ongoing FDA-ARGOS project demonstrates FDA's investment in tools to support innovation of emerging technologies and commitment to regulatory science. The public FDA dAtabase for Reference Grade MicrObial Sequences (FDA-ARGOS) was established in 2014 and is a collaboration between FDA and DoD, the Institute for Genome Sciences at the University of Maryland, and NCBI (Ref. 237). FDA-ARGOS contains quality controlled and curated genomic sequence data to support research and regulatory decisions (Ref. 238). This is an evolving database that can be used as a tool for in-silico (computer simulation) performance validation and potentially reduce the testing burden on manufacturers of infectious disease NGS devices. There are ongoing projects focused on expanding the FDA-ARGOS database (Ref. 239). To maintain quality control of FDA-ARGOS as a reliable genome reference database, established quality metrics must be met and any updates to the quality control process are appropriately considered and vetted.

(Comment 279) Some comments expressed concerns related to whether FDA has sufficient resources to enforce compliance with requirements during stages 1 through 3 of the phaseout policy, which will occur before the next MDUFA reauthorization. Some of these comments stated that FDA would require additional resources before the next MDUFA reauthorization to support a significant increase in Pre-Submissions from laboratory manufacturers in anticipation of the phaseout of premarket review requirements for new and modified IVDs offered as LDTs. The comments suggested that FDA would need to hire more staff to review Pre-Submissions seeking FDA's input on the potential risk classification of many

IVDs offered as LDTs for which there are no predicate devices. According to the comments, this increase in Pre-Submissions would not be addressed by issuing guidance documents, unless FDA issued those guidance documents expeditiously.

(Response 279) FDA believes that there will be adequate resources available from user fees (as permissible) and budget authority in stages 1 through 3 of the phaseout policy to provide advice, guidance, and education on premarket review and other regulatory requirements applicable to IVDs offered as LDTs. Also, during stages 1 through 3, FDA is phasing out the general enforcement discretion approach with respect to various requirements (e.g., MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files) in stage 1; registration and listing, labeling, and investigational use requirements in stage 2; and QS requirements in stage 3 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1)) and we believe information FDA receives as a result of compliance with those requirements will help FDA's allocation of anticipated available resources. FDA's estimate of the resources associated with stages 1 through 3 can be found in section II.G of the FRIA (Ref. 10).

FDA's projections do not presume a disproportionate increase in Pre-Submissions for IVDs offered as LDTs during stages 1 through 3 of the phaseout period in light of the enforcement discretion policies relating to premarket review described in section V.B, including for currently marketed IVDs offered as LDTs; LDTs approved by NYS CLEP; and LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

For all of the foregoing reasons, FDA believes that the resources authorized under MDUFA V, combined with budget authority, are sufficient to fund the activities necessary for the review of voluntary Pre-Submissions received during stages 1 through 3 of the phaseout policy.

(Comment 280) Some comments predicted that FDA’s phaseout of the general enforcement discretion approach for LDTs will face challenges similar to those experienced in Europe in connection with the implementation of the In Vitro Diagnostic Medical Device Regulation, 2017/746 (IVDR). The IVDR was reported to cause significant delays in drug clinical trials by creating a bottleneck with respect to IVD approvals, as well as the discontinuation of certain rare disease diagnostics.

(Response 280) FDA disagrees that the phaseout policy will likely result in significant delays in clinical trials or disruption in patient access to LDTs for unmet needs, including tests for rare diseases, akin to what the comment claims has been observed during the implementation of the IVDR in Europe.

First, FDA intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for currently marketed IVDs offered as LDTs, and thus does not anticipate disruption of patient access to such tests, including those for certain rare diseases, due to the phaseout policy. Going forward, FDA also intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. FDA anticipates this policy will support continued innovation of new tests for rare diseases. For additional discussion regarding IVDs for unmet needs and IVDs for rare diseases, see our responses to comments in section VI.L.5.

With respect to use of IVDs offered as LDTs in clinical investigations of drugs, FDA does not anticipate that compliance with IDE requirements will meaningfully delay drug or IVD development activities, as described in response to comment 175. To the extent the comments are concerned about a potential review bottleneck due to resources, FDA disagrees that this will be the case for implementation of this rule, as described in response to comment 274.

(Comment 281) FDA received several comments supporting the use of FDA's Third Party review program to review 510(k) submissions for IVDs offered as LDTs. These comments stated that Third Party review will help to avoid strains on FDA's review capacity, streamline the timeline for review, limit redundancy with CLIA accreditation, and/or avoid detracting from other components of FDA's mission.

(Response 281) FDA agrees that use of the Third Party review program to review IVDs offered as LDTs could provide significant benefits to both industry and FDA, including by potentially reducing demand on FDA resources and facilitating timely review of 510(k) submissions. Under the MDUFA V commitment letter, FDA is currently working to enhance the Third Party review program, and the Agency anticipates interest in the Third Party review program among laboratories that manufacture IVDs offered as LDTs. As discussed in section II.G of the FRIA, FDA estimates that half of the IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the Third Party review program. FDA also recognizes that if CLIA accreditation organizations seek accreditation under FDA's Third Party review program, there may be certain efficiencies or other advantages because the two programs are complementary, as described in response to comment 7.

(Comment 282) Some comments questioned the likelihood that a significant percentage of laboratories that manufacture IVDs offered as LDTs that require a 510(k) submission will use FDA's Third Party review program, based on historical utilization of the program. Comments suggested that the Third Party review program currently includes only a small number of Third Party reviewers, who review only a small subset of types of IVDs that require a 510(k) submission, and that laboratories may choose not to utilize the Third Party review program given that use of the program is voluntary.

(Response 282) Under the MDUFA V agreement, FDA committed to undertake several activities intended to enhance the Third Party review program with the objective of eliminating FDA's routine re-review of Third Party reviews. These activities include providing training to

Third Parties seeking accreditation, auditing 3P510k Review Organizations, providing tailored retraining to 3P510k Review Organizations (based on the results of audits), and other activities (Ref. 240).

In addition, FDA has heard from entities interested in potentially serving as 3P510k Review Organizations for 510(k)s submitted for IVDs. Some of these entities are CLIA accreditation organizations with whom laboratories may already be familiar. We anticipate that when a laboratory already has a relationship with an organization, the laboratory may be inclined to work with that organization through the Third Party review program.

FDA anticipates that improving the Third Party review program, including through continued efforts to eliminate routine re-review of 510(k)s that have already been reviewed by a 3P510k Review Organization, as well as potential accreditation of organizations with whom laboratories may already be familiar, will increase use of the Third Party review program (as noted in response to comment 281 and discussed in section II.G of the FRIA, FDA estimates that half of the IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the Third Party review program). FDA intends to continue efforts to enhance and facilitate greater use of the Third Party review program during implementation of the phaseout policy, including in advance of stage 5 of the phaseout policy.

FDA nonetheless acknowledges that participation in the Third Party review program is voluntary. Although FDA anticipates increased participation in the Third Party review program, as discussed in FDA's response to comment 284, FDA also anticipates that it will have sufficient resources to review 510(k) submissions for IVDs offered as LDTs even if participation in the Third Party review program is lower than estimated.

We also note that, as stated in FDA's final guidance document regarding the Third Party review program, "[m]ost in vitro diagnostic (IVD) devices are eligible for [Third Party] review," provided they meet certain factors described in the final guidance (Ref. 56). About 75 percent of product codes for IVDs that are subject to 510(k) requirements (i.e., ~750 out of

1,000 product codes) are currently eligible for submission to a 3P510k Review Organization, and FDA anticipates that this list may continue to grow as more IVDs are classified into class II (i.e., through reclassification or De Novo classification) and as FDA gains experience with newer types of class II devices that are subject to 510(k) requirements.

(Comment 283) One comment noted that many devices do not qualify for Third Party review. Another comment noted that the Third Party review program does not extend to PMAs or De Novo submissions. These comments asserted that based in part on these factors, the Third Party review program does not sufficiently address concerns regarding the potential high volume of premarket submissions that may be submitted by laboratories as a result of the phaseout policy.

(Response 283) FDA agrees that PMA and De Novo submissions are not eligible for Third Party review under the Third Party review program as currently authorized under section 523 of the FD&C Act (21 U.S.C. 360m). In the FRIA, FDA has estimated the potential impact of the Third Party review program on costs and transfers associated with 510(k) submissions, but has not anticipated any impact from the program on costs or transfers associated with PMA or De Novo submissions (see sections II.G and II.H of the FRIA (Ref. 10)). FDA also recognizes that some devices that require a 510(k) submission are not eligible for Third Party review (see 21 U.S.C. 360m(a)(3)). However, as discussed in response to comment 282, about 75 percent of product codes for IVDs that are subject to 510(k) requirements (i.e., ~ 750 out of 1,000 product codes) are currently eligible for submission to a 3P510k Review Organization, and FDA anticipates that this list may continue to grow as more IVDs are classified into class II (i.e., through reclassification or De Novo classification) and as FDA gains experience with newer types of class II devices that are subject to 510(k) requirements. In addition, as discussed in response to comment 274, the Agency anticipates that certain enforcement discretion policies with respect to premarket review requirements, among other requirements, described in section

V.B will also help to address concerns regarding the potential high volume of premarket submissions that may be submitted by laboratories as a result of the phaseout policy.

Further, as previously announced, FDA intends to initiate the reclassification process for most IVDs that have been previously classified in class III to class II (Ref. 66). FDA aims to complete this reclassification process before stage 4 of the phaseout policy. In addition, FDA intends to continue taking a risk-based approach in the initial classification of IVDs to determine the appropriate level of regulatory controls and whether a new test may be classified into class II through De Novo classification (and special controls established), rather than being class III and subject to the PMA pathway. Based on our experience, we believe that special controls could be developed that, along with general controls, could provide a reasonable assurance of safety and effectiveness for most future CDx and infectious disease IVDs, such that they could be regulated as class II devices. We therefore anticipate the percent of IVDs, including IVDs offered as LDTs, reviewed in a 510(k) submission to increase, and that the number of IVDs eligible for review by a 3P510k Review Organization may also increase. As shown in Table A.5 of the FRIA, the estimated numbers of PMAs and PMA supplements are lower after potential reclassification, while the estimated numbers of 510(k) submissions and De Novo requests are higher after potential reclassification.

(Comment 284) FDA received comments stating that a high rate of re-review of 510(k)s that have already been reviewed by a 3P510k Review Organization may extend premarket review times, and one comment stated that Third Party review should not be a substantial part of FDA's plans for managing the anticipated workload associated with premarket submissions for IVDs offered as LDTs until FDA has eliminated routine re-review of 510(k)s that have already been reviewed by a 3P510k Review Organization. One comment stated that if FDA intends to utilize the Third Party review program as a critical part of FDA's plans to manage the Agency's anticipated workload, FDA should not phase out the general enforcement discretion approach with respect to premarket submissions until FDA has demonstrated in a pilot program that

3P510k Review Organizations can apply FDA's requirements in a least burdensome manner. In addition, one comment suggested that FDA conduct a study to better understand the historical lack of utilization of the Third Party review program before making the program a core part of FDA's plans for managing the Agency's anticipated workload associated with premarket submissions for IVDs offered as LDTs.

(Response 284) FDA disagrees with the comments indicating that it is premature for the Agency to incorporate use of the Third Party review program into its plans for managing review of 510(k)s for IVDs offered as LDTs. FDA also disagrees that it should delay the phase out of enforcement discretion with respect to premarket review requirements prior to conducting a pilot to demonstrate application of least burdensome principles in the Third Party review program. As discussed in response to comment 282, under the MDUFA V agreement, FDA committed to undertake several activities intended to enhance the Third Party review program with the objective of eliminating FDA's routine re-review of Third Party reviews. These activities include providing training to Third Parties seeking accreditation, auditing 3P510k Review Organizations, and providing tailored re-training to 3P510k Review Organizations. FDA anticipates that these activities will advance FDA's efforts to eliminate routine re-review of 510(k)s that have already been reviewed by a 3P510k Review Organization and does not expect that there will be a "high rate of re-review" of 510(k)s submitted for IVDs offered as LDTs as some comments suggest. We also expect that these activities will facilitate 3P510k Review Organizations' consistent application of FDA's requirements for 510(k) review in a least burdensome manner. Further, we note that FDA provides training materials on its "least burdensome" approach to medical device regulation as part of its training curriculum for 3P510k Review Organizations (Ref. 241).

As discussed in response to comment 282, FDA anticipates that improving the Third Party review program will increase the program's use and estimates that approximately half of IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the Third Party review program (see section II.G of the FRIA (Ref. 10)). However, even if the majority of

submitters do not choose to use the Third Party review program, FDA anticipates that the Agency will be able to effectively manage review of 510(k) submissions for IVDs offered as LDTs. As described in section V.B.3, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs. FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs that are approved by NYS CLEP, and to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. Collectively, these policies significantly reduce the estimated number of premarket submissions for IVDs offered as LDTs, as compared to the preliminary estimates in the PRIA (see sections II.F and II.G of the FRIA (Ref. 10)). In addition, as noted in our response to comment 274, FDA does not intend to phase out enforcement discretion with respect to premarket review requirements for moderate- and low-risk IVDs offered as LDTs that require 510(k) submissions until after the next reauthorization of MDUFA. This will provide an opportunity for FDA and industry to negotiate regarding user fees taking into consideration FDA's anticipated resource needs to review 510(k) and other submissions for IVDs offered as LDTs.

(Comment 285) Some comments stated that the Third Party review program should utilize 3P510k Review Organizations that are accustomed to CLIA, or that FDA should encourage laboratory accreditation bodies to become 3P510k Review Organizations, to facilitate integration of the two programs, ensure the involvement of expert reviewers, and be less burdensome for laboratories.

(Response 285) As discussed in section V.C, FDA recognizes that a laboratory may be particularly inclined to use the Third Party review program when the laboratory is already

familiar with a 3P510K Review Organization. FDA is aware of certain CLIA accreditation organizations that may be interested in becoming 3P510k Review Organizations, and the Agency encourages such organizations to continue exploring potential participation in the Third Party review program. To the extent the comments advocating for “integration” of CLIA accreditation and FDA’s Third Party review programs were suggesting that CLIA accreditation and review of a 510(k) overlap, we note that, while there may be certain efficiencies or other advantages associated with CLIA accreditation organizations also serving as 3P510k Review Organizations, these are separate programs with complementary but distinct purposes (see, e.g., response to comment 7).

(Comment 286) Several comments raised concerns about potential conflicts of interest among 3P510k Review Organizations, given that 3P510k Review Organizations are paid by the laboratories whose submissions they review. One comment asserted that the potential conflicts of interest among 3P510k Review Organizations may be particularly significant when the 3P510k Review Organization is also a CLIA accrediting organization.

(Response 286) FDA recognizes that avoiding conflicts of interest among 3P510k Review Organizations is critical to the success of the Third Party review program. With respect to the fact that laboratories would pay 3P510k Review Organizations to review 510(k)s for their IVDs offered as LDTs, we note that section 523(b)(5) of the FD&C Act (21 U.S.C. 360m(b)(5)) specifically provides that compensation for 3P510k Review Organizations to review a 510(k) “shall be paid by the person who engages such services.” However, the FD&C Act also contains provisions related to conflicts of interest for 3P510k Review Organizations, including provisions concerning the minimum qualifications for 3P510k Review Organizations and certain recordkeeping requirements (see sections 523 and 704(f) of the FD&C Act). In addition, FDA’s final guidance document entitled “510(k) Third Party Review Program” addresses safeguards against potential conflicts of interest among 3P510k Review Organizations. As explained in FDA’s final guidance document, “FDA expects 3P510k

Review Organizations to be impartial and free from any commercial, financial, and other pressures that might present a conflict of interest or an appearance of a conflict of interest. Therefore, FDA will consider whether the potential 3P510k Review Organization has established, documented, and executed policies and procedures to prevent any individual or organizational conflict of interest or the appearance of a conflict of interest, including conflicts of interests pertaining to their external Technical Experts” (Ref. 56). FDA’s final guidance document also explains, among other things, that “conflict of interest policies for a 3P510k Review Organization should be fully implemented and there should be an attestation that those policies have been implemented that is signed by the most responsible individual at the organization before any 510(k) is accepted for review.” While FDA appreciates that concerns regarding potential conflicts of interest may be heightened when a 3P510k Review Organization is also a CLIA accreditation organization, the statutory provisions regarding the Third Party review program and FDA’s implementation thereof already take potential conflicts of interest into account.

(Comment 287) One comment stated that FDA’s discussion in the NPRM regarding use of the Third Party review program was vague. Another comment stated that with respect to Third Party review, FDA should provide “better clarity and more information as to the participating entities, their capacities, throughput and turnaround time to review submissions by such entities.” A third comment stated that FDA should “formally withdraw inconsistent and outdated guidance,” in particular FDA’s draft guidance document regarding in vitro diagnostic multivariate index assays (IVDMIA), as such guidance documents will create confusion among 3P510k Review Organizations and others if not withdrawn.

(Response 287) In the NPRM, FDA’s discussion of the Third Party review program: (1) provided a general description of the program; (2) stated that FDA anticipated interest in the Third Party review program among test manufacturers and new 3P510k Review Organizations; and (3) explained the basis for anticipating that interest (see 88 FR 68006 at 68027). FDA does

not agree that these statements were vague. However, to the extent stakeholders seek additional information regarding the Third Party review program, stakeholders may consult FDA's "510(k) Third Party Review Program" final guidance document (Ref. 56), which was cited as a reference in the NPRM (see 88 FR 68006 at 68027), as well as information available on FDA's website regarding the Third Party review program (Ref. 67). This includes information regarding current 3P510k Review Organizations and the devices they may review (Ref. 242). FDA publishes quarterly reports on the performance of 3P510k Review Organizations (Ref. 243). These reports include, among other things, data on the total number of submissions, review times, and decisions. FDA notes that 3P510k Review Organizations are best situated to address specific questions from potential submitters regarding their capacity and turnaround time for review of 510(k) submissions.

FDA agrees that inconsistent or outdated guidance documents may cause confusion among stakeholders. The Agency strives to maintain consistency across its final guidance documents and to update those documents when appropriate, consistent with good guidance practices (§ 10.115). We note that the specific guidance mentioned in the comment is a draft guidance. Draft guidance documents are not for implementation and explicitly state (on their title pages) that they are distributed for comment purposes only. Thus, the draft guidance mentioned in the comment should not cause confusion among stakeholders. With respect to final guidance documents, the Agency undertakes retrospective review of previously issued final guidance documents (21 CFR 10.115(k)) and is interested in receiving external feedback about final guidance documents that should be revised or withdrawn (see § 10.115(f)(4)). Stakeholders can submit comments on any guidance document at any time (§ 10.115(g)(5)).

(Comment 288) One comment stated that the ISO 15189 standard should be considered a viable alternative for quality management system requirements for laboratories that manufacture IVDs, and suggested that for specific provisions of the ISO 13485 standard that

may not be covered in ISO 15189, FDA should include the provisions as a requirement (or through guidance) as part of the Third Party review program.

(Response 288) FDA does not agree that ISO 15189 is a viable alternative for quality management system requirements for laboratories that manufacture IVDs offered as LDTs, or that the Third Party review program is an appropriate mechanism to address any differences between the ISO 13485⁹⁴ and ISO 15189 standards. For additional discussion of the ISO 15189 standard, see our response to comment 183. Further, the Third Party review program addresses 510(k) premarket review by accredited persons (see section 523 of the FD&C Act). It is not a mechanism to add or change the requirements that apply to a device manufacturer's quality system.

(Comment 289) FDA received a comment stating that FDA “should leverage device performance reviews or external quality assessments of LDTs conducted by certified and creditable third parties” as an alternative to premarket review by FDA for LDTs offered by AMCs.

(Response 289) The comment did not provide additional detail on what would constitute a “certified and creditable” third party that could provide such assessments. However, we note that FDA intends to continue supporting the use of its Third Party review program authorized under section 523 of the FD&C Act, as described in our responses to comments 281 through 288. The statute authorizes FDA to recognize Third Parties to review 510(k) submissions for certain types of devices and imposes various requirements on those organizations. We also note that FDA discusses comments received related to LDTs manufactured and performed by AMCs, including an enforcement discretion policy that may apply to certain LDTs manufactured and performed by AMC laboratories, in section VI.F.4 (see also section V.B.3).

⁹⁴ As noted elsewhere in this preamble, FDA recently finalized amendments to part 820, which take effect in February 2026. These amended QS requirements incorporate by reference the 2016 edition of ISO 13485 (see 89 FR 7496).

P. Implementation

(Comment 290) FDA received comments suggesting that the Agency provide additional information regarding how FDA will be implementing the final phaseout policy. One comment recommended that the phaseout policy include timelines and “criteria” for transitioning from the general enforcement discretion approach for LDTs.

(Response 290) FDA agrees with the comment suggesting that FDA include timelines for transitioning from the general enforcement discretion approach for LDTs, and notes that section V.C of this preamble addresses this issue. As set forth more fully in that section:

- Stage 1: beginning 1 year after the publication date of this final rule, FDA will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files) for IVDs offered as LDTs;
- Stage 2: beginning 2 years after the publication date of this final rule, FDA will expect compliance with requirements not covered during other stages of the phaseout policy, including registration and listing requirements, labeling requirements, and investigational use requirements, for IVDs offered as LDTs;
- Stage 3: beginning 3 years after the publication date of this final rule, FDA will expect compliance with QS requirements (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1) for IVDs offered as LDTs;
- Stage 4: beginning 3½ years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for high-risk IVDs offered as LDTs, unless a premarket submission has been received by the beginning of this stage in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review; and
- Stage 5: beginning 4 years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs (that require premarket submissions), unless a premarket submission has

been received by the beginning of this stage in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review.

(Comment 291) Comments requested that FDA publish clear guidance document(s), including regarding: practical instructions, examples, and case studies; definitions of and other information regarding LDT risk categories; guidance on how laboratories can tailor their validation processes based on the complexity and potential impact of their LDTs; scenarios addressing how the phaseout policy affects specialized LDTs, such as those for rare diseases; and other topics. Comments requested that stakeholders be offered the opportunity to participate in guidance document development. FDA also received questions regarding the content and format for premarket submissions.

(Response 291) FDA agrees with comments that recommended that FDA provide additional resources on specific topics that may be useful as laboratories come into compliance with applicable requirements. FDA anticipates issuing a small entity compliance guide and/or making additional resources available on topics such as applicable labeling requirements over the course of the phaseout period. FDA also anticipates offering robust educational resources, potentially including but not limited to a webinar, a Town Hall meeting, Frequently Asked Questions webpages, and other materials designed to guide laboratories and other stakeholders. FDA also intends to consider issuing additional guidance during the phaseout period as appropriate, and would do so in accordance with good guidance practice regulations, which set forth the processes for participating in the development and issuance of guidance documents (§ 10.115).

In response to the comments seeking information regarding how laboratories can determine the risk categories of their IVDs offered as LDTs, we note that this rule does not change the statutory framework under which FDA regulates medical devices, including the risk-based classification of devices. FDA has previously provided multiple resources intended to help manufacturers determine the classification of their devices, including on FDA's webpage entitled

“Classify Your Medical Device” (Ref. 201), and in FDA’s classification database (Ref. 200). In addition, laboratory manufacturers may request feedback from FDA regarding the potential regulatory pathway for a device through a Pre-Submission, described in FDA’s final guidance document entitled “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program” (Ref. 65). Laboratory manufacturers may also consider submitting a request for information regarding the class in which a device is classified or the requirements applicable to a device under section 513(g) of the FD&C Act, the process for which is further described in FDA’s final guidance document entitled “FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act” (Ref. 244). For further information, you may view the training module available on FDA’s website, entitled “513(g) Requests for Information” (Ref. 245).

In response to comments seeking information regarding the content and format for premarket submissions, FDA offers Device Advice on Premarket Submissions: Selecting and Preparing the Correct Submission on FDA’s webpage (Ref. 246).

As discussed in section V.C, for IVDs offered as LDTs for which a complete PMA, HDE application, 510(k), BLA, or De Novo request has been received by the beginning of stage 4 or stage 5 of the phaseout policy (as applicable), FDA generally does not intend to enforce premarket review requirements until FDA completes its review of the submission.

(Comment 292) A comment stated that hospital and health system laboratories cannot currently assess how each part of the device regulations would apply to their LDTs under the phaseout policy. The comment noted that the uncertainty is problematic and underscores the need for continued enforcement discretion, most particularly in certain areas, such as for low- and moderate-risk tests.

(Response 292) As discussed further in the response to comment 162, FDA believes the information included in the phaseout policy, including the timeline for the various stages in the phaseout policy and information regarding enforcement discretion policies described in this

preamble, provides clear expectations for laboratories that offer IVDs as LDTs. FDA appreciates that additional guidance regarding implementation of the phaseout policy may facilitate efforts by laboratories to comply with applicable requirements.

We note that FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. For further discussion of this policy, refer to section V.B.3. As discussed further in the responses to comments in section VI.L.4, FDA is not adopting an enforcement discretion policy in the final phaseout policy for low- and moderate-risk tests.

Notably, and as set forth more fully in response to comment 291, FDA is not changing the statutory framework under which FDA regulates medical devices. In this rule, FDA has made explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory. IVDs, as defined in § 809.3, are devices intended for human use and are subject to the FD&C Act. They include class I, class II, and class III devices, as well as both preamendments and postamendments devices. Like other devices, IVDs are subject to general controls, including premarket notification, reporting requirements regarding adverse events and corrections and removals, IDE requirements (though some investigations of IVDs are exempt from most provisions of the IDE regulation), and other applicable requirements under the FD&C Act and FDA's regulations. IVDs are also subject to specific labeling requirements in part 809. FDA has made numerous resources available to assist device manufacturers, including laboratories, in understanding device requirements.

(Comment 293) A comment stated that the phaseout policy does not provide enough guidance for laboratories to determine what data laboratories must submit for premarket review of existing or new LDTs.

(Response 293) Where premarket review is expected, the particular data required may vary based on the type of test at issue. There are multiple resources available to help IVD manufacturers, including laboratories, understand the type of data and information that is included in support of premarket submissions for IVDs. For example, FDA posts on its website the decision summaries for each IVD authorized (see Refs. 66, 166, 224, 247, and 248). These decision summaries describe the data and information that was provided to support the authorization and can be used as a model for manufacturers of the same types of tests. FDA also has issued general and device specific final guidance documents that describe recommendations for the data and information to be submitted in premarket submissions (see, e.g., Refs. 234, 165, 190, and 249 to 253)), and has partially or fully recognized 110 CLSI consensus standards for In Vitro Diagnostics (Ref. 254). Many of these FDA recognized consensus standards describe recommendations for validation study designs. Manufacturers may also submit a Pre-Submission for specific feedback on individual tests (Ref. 65).

We note that FDA intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for currently marketed IVDs offered as LDTs that were first marketed as of the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3. Thus, FDA generally does not expect laboratories to submit data for existing LDTs in a premarket review submission. FDA has also included several other enforcement discretion policies with respect to premarket review for certain LDTs as described in section V.B.

Further, we note that as more fully described elsewhere in this preamble, under FDA's device authorities, FDA premarket review is required only for certain IVDs (generally those classified into class II or class III), and FDA estimates that approximately 50 percent of IVDs offered as LDTs would not require premarket review.

In addition, when tests are modified, premarket review is required only in certain circumstances, as discussed elsewhere in this preamble (see response to comments 215 and 261).

(Comment 294) A number of comments suggested that FDA should assess the LDT marketplace to determine which LDTs present the “highest risk,” and implement the phaseout policy by risk category.

(Response 294) As described in section V.C, FDA’s phaseout policy prioritizes the review of applications for high-risk IVDs offered as LDTs (stage 4) over those for moderate- and low-risk IVDs offered as LDTs that require premarket review (stage 5). For the reasons set forth in our response to comment 155, we do not believe the other stages of the phaseout should be ordered or dictated by the level of risk of an IVD offered as an LDT.

(Comment 295) FDA received a comment inquiring whether facilities that manufacture LDTs will be inspected in the same manner as other devices.

(Response 295) All domestic and foreign device establishments, including those that manufacture IVDs offered as LDTs, are subject to inspection. Section 704(a) of the FD&C Act provides FDA authority for inspections, specifically providing authority for duly designated officers or employees of FDA to enter, at reasonable times, and inspect, at reasonable times and within reasonable limits and in a reasonable manner, facilities subject to regulation under the FD&C Act.

FDA uses a risk-based evaluation to select device manufacturing facilities for inspection. *See* section 510(h)(2) of the FD&C Act (stating that the Secretary “shall inspect establishments...that are engaged in the manufacture, propagation, compounding, or processing of a device or devices...in accordance with a risk-based schedule established by the Secretary.”). The Agency prioritizes device surveillance inspections deemed high-risk based on a variety of specific criteria, such as: (1) facility type, such as manufacturer, control laboratory; (2) the facility’s compliance history, including whether it has been inspected in the last 4 years; (3) hazard signals, including the record of signals, history and nature of product recalls linked to the facility; and (4) inherent risks of the device manufactured at a facility (Ref. 255). FDA does not

intend to have a different approach for selecting laboratory manufacturing facilities for inspection.

(Comment 296) We received several comments that FDA should include industry experts and solicit outside expertise at various points during the implementation of the phaseout policy and in the regulation of IVDs offered as LDTs going forward. Comments suggested FDA solicit input on test classifications on an ongoing basis, convene expert panels to recommend risk categories and advise on specific types of technology and tests, and allow experts to participate in reviewing and approving premarket submissions in the areas of their expertise, and to “have a seat at the table during the implementation of the FDA regulations, as well as long-term monitoring/approval” of IVDs offered as LDTs.

(Response 296) To the extent the comments recommended that FDA seek input from stakeholders and outside experts, we agree that such input is important, and in fact required, in certain circumstances. For device classification, FDA follows the procedures required under section 513 of the FD&C Act and outlined in part 860. When classifying a preamendments device for the first time, for example, FDA provides a public process as required under section 513(d) of the FD&C Act. This process involves a public meeting of the appropriate advisory committee panel and notice and comment rulemaking.

More generally, FDA uses panels of the Medical Devices Advisory Committee (MDAC) to provide advice and recommendations to FDA on various regulatory issues. This may include advice on particular submissions, general issues, and device type classifications, among other things. The MDAC consists of 18 panels, including the following panels with established rosters reflecting expertise regarding IVDs, including LDTs: Clinical Chemistry and Clinical Toxicology Devices Panel (Ref. 256), Hematology and Pathology Devices Panel (Ref. 257), Immunology Devices Panel (Ref. 258), Microbiology Devices Panel (Ref. 259), and Molecular and Clinical Genetics Panel (Ref. 260). The rosters, calendars, and materials from past meetings are available on FDA’s website as noted in the references above. For example, in September

2023, FDA convened the Microbiology Devices Panel to seek preliminary input on potential reclassification of certain types of IVDs for hepatitis B virus, human parvovirus B19, and M. tuberculosis from class III to class II with special controls (Ref. 261). In another recent example, FDA convened the Molecular and Clinical Genetics Panel in November 2023 to discuss and make recommendations on the design of multicancer detection in vitro diagnostic devices (tests) as well as potential study designs and study outcomes of interest that could inform the assessment of the probable benefits and risks of such tests (Ref. 262). The committee's discussion and recommendations from these meetings will help inform future Agency regulatory efforts for these tests.

FDA can also seek external expertise through its Network of Experts program, which is a vetted network of partner organizations and their members, scientists, clinicians, and engineers who can provide FDA rapid access to expertise when it is needed to supplement existing knowledge and expertise within CDRH (Ref. 263). There are multiple organizations within the Network of Experts with expertise relevant to IVDs. As has been FDA's practice, and when appropriate, FDA will continue to engage with experts and stakeholders through conferences, meetings, industry roundtables, town halls, and through collaborative communities in which we participate.

We note that FDA has long solicited and considered input from stakeholders regarding the Agency's oversight of LDTs. In 2010, FDA held a public meeting and requested comments on the "Oversight of Laboratory Developed Tests" (75 FR 34463, June 17, 2010). In 2014, FDA issued and requested comments on two draft guidance documents entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" (Ref. 38) and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)" (Ref. 112), and subsequently held and requested comments on a 2015 Public Meeting regarding the Agency's proposed oversight framework (Ref. 116). In 2017 we issued the 2017 Discussion Paper synthesizing the feedback that had been provided to the Agency (Ref. 57).

Furthermore, our Q-Submission program, in addition to providing IVD manufacturers with an opportunity to provide input to and request feedback from FDA on specific devices or submissions, also includes an opportunity to request an Informational Meeting to share with FDA information, among other purposes, to familiarize the FDA review team with new device(s) with significant differences in technology from currently available devices and provide an overview of ongoing or upcoming device development (see FDA’s final guidance document entitled “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program” (Ref. 65)).

We note, however, that industry participation in certain activities referenced in the comments, such as the review and authorization of premarket submissions, would raise issues related to confidentiality and conflicts of interest (e.g., if IVD manufacturers, including those who may be developing similar or competitor products, review or influence the outcome of other IVD manufacturers’ premarket submissions). FDA has obligations to maintain confidentiality of certain aspects of premarket submissions and to make decisions about whether to authorize devices without undue influence.

Q. Interplay with Oncology Drug Products Used with Certain In Vitro Diagnostic Tests Pilot Program

(Comment 297) Several comments addressed FDA’s ongoing pilot described in the final guidance document entitled “Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program” (Ref. 264). Most comments indicated support for the pilot; one did not. Supporters thought the model described in the pilot is valuable and should be considered in other disease areas, including rare diseases. Another comment suggested that the pilot’s model should be used for tests used as part of cell and gene therapy product development. One suggested that FDA delay finalizing the rule until the pilot is completed and expanded.

(Response 297) FDA agrees that the concept of establishing performance expectations is valuable for test development generally, including for tests for rare disease. Such goals could be developed by the community and used to support premarket review submissions.

We note that the pilot program was initiated as one step that may be helpful in reducing the risks associated with LDTs used for oncology drug treatment decisions (then under the general enforcement discretion approach for LDTs), while the Agency continued to work on a broader approach for LDTs, including moving forward with this rulemaking. As discussed further in the response to comment 298, the phasing out of the general enforcement discretion approach for LDTs means that FDA generally will expect compliance with applicable requirements for IVDs offered as LDTs, including those IVDs described in the oncology pilot program.

(Comment 298) Some comments asked for clarification regarding the impact of the phaseout policy on the pilot. One comment suggested pilot participants should be “exempt” from the phaseout. One comment asked if an unapproved clinical trial assay could be used upon approval of the therapeutic with a postmarket commitment to obtain approval of a CDx.

(Response 298) FDA disagrees with the suggestion to “exempt” unapproved assays used in the pilot from the phaseout policy. The types of LDTs discussed in the pilot program may provide information that is essential for the safe and effective use of a corresponding therapeutic product. As described in the NPRM, we have seen variability in performance among LDTs offered for a use that is the same as a CDx such that, in some cases, selection of a treatment for a given patient can be impacted by which test is used (see 88 FR 68006 at 680209-10). For example, the same patient may receive a particular therapeutic if they are tested with one LDT and not receive the therapeutic if they are tested with another LDT due to differences in test performance. For these reasons, the phaseout of the general enforcement discretion approach generally applies to LDTs offered for a use that is the same as a CDx, including the types of LDTs discussed in the pilot program.

(Comment 299) One comment asserted that the pilot program will amplify risks to patients by encouraging the use of tests that are not clinically validated.

(Response 299) The pilot program was initiated as one step that may be helpful in reducing the risks associated with using LDTs for oncology drug treatment decisions while the Agency continued to work on a broader approach for LDTs, including moving forward with this rulemaking. For the reasons in this preamble, FDA is phasing out the general enforcement discretion approach for LDTs, including the types of LDTs discussed in the pilot program final guidance.

(Comment 300) One comment suggested that FDA's general approach to CDx approvals is a barrier to innovation in that it requires clinical concordance studies to other PMA-approved devices or clinical trials in partnership with drug companies. The comment explained that there is no incentive for a drug company to conduct additional clinical trials to support diagnostic approvals and no incentive for the laboratory with the approved CDx to conduct clinical concordance studies with additional laboratories to support other diagnostic approvals. This comment expressed concern that increased oversight of LDTs is likely to put significant constraints on CDx availability, where doctors and patients would be forced to send samples to specific laboratories.

(Response 300) As discussed in response to comment 298, FDA has seen variability in performance among LDTs offered for a use that is the same as a CDx such that, in some cases, selection of a treatment for a given patient can be impacted by which test is used. For this reason, and for the reasons further discussed throughout this preamble, FDA believes that increased oversight for these and others IVDs offered as LDTs is generally necessary and appropriate. FDA understands the current system presents challenges for development of additional tests to select patients for a drug once one CDx is authorized. FDA seeks to engage with the community on additional efforts to create standardization, such as through reference

materials, so that clinical validity can be extrapolated to other tests of the same type in more cases.

R. Miscellaneous

(Comment 301) We received many comments regarding the impacts that FDA's proposal would have on the medical education of those training in pathology. Comments noted that the increased financial and regulatory burdens on smaller teaching laboratories would reduce the number of tests available at those laboratories, which would eliminate, significantly delay, or make less attractive the opportunities for training clinical pathologists and additionally fewer laboratories would be able to meet the criteria for training programs prescribed by ACGME. Comments additionally stated that without robust opportunities to learn pathology principles and the skills needed to pass the pathology board certification exam, fewer trainees may be able to pass.

Comments stated that fewer learning opportunities would, in turn, exacerbate existing pathologist workforce burnout and shortages, and lead to fewer and less qualified and competent pathologists, which would lead to a decline in the practice of pathology that would reduce the quality and timeliness of patient care, and potentially the ability for healthcare to address advanced or new disease altogether. Additional comments noted that for-profit reference laboratories are not obligated to train pathology residents and fellows and that the pipeline of medical students who train at small laboratories is also an important pool of talent for IVD manufacturers, other clinical laboratory affiliated industries, and regulatory agencies, which will be similarly negatively affected.

Some comments stated that reduced medical training opportunities would particularly affect genetic and genomic medicine, an area of increasing demand and worsening workforce shortages, because it relies so heavily on LDTs. Another comment noted that if data available from LDTs was limited, then genomics and genetics biomedical research training at the Ph.D.

graduate and postgraduate levels that depend on that data would also suffer and ultimately affect the health of the U.S. population and the competitiveness of the U.S. research enterprise.

(Response 301) As set forth in section V.B, FDA is adopting several enforcement discretion policies in the phaseout policy that reflects a balancing of the important public health considerations at issue in the rule (see further discussion of these considerations in section III.B). We anticipate the impact of these policies will address some of the concerns expressed in comments related to the impact on medical education, insofar as the financial burdens on laboratories will be reduced, resulting in fewer laboratories scaling back operations, exiting the market, or otherwise limiting educational opportunities. As a result of these policies and other adjustments, the FRIA estimates a 78 percent reduction in cost to industry compared to the PRIA. Specifically, the FRIA estimates a \$1,166M 20-year annualized cost to industry--a reduction of \$4,170M.

(Comment 302) A comment requested clarity about how FDA considers its potential enforcement actions or remedies when the Agency identifies a violation of the law. In particular, the comment was interested in whether enforcement actions apply to the laboratory activity, revenue, and operations or only the manufacturing of the test.

(Response 302) This comment was not entirely clear; we have interpreted this comment as seeking more information about FDA's approach to device enforcement. Such enforcement by FDA is taken on a case-by-case basis and the specifics of each enforcement action depend on the specific facts at issue. FDA generally seeks to work with device manufacturers to address issues where the manufacturer or device is in noncompliance with requirements. FDA may issue a warning letter or take other advisory actions where appropriate. Administrative and enforcement actions authorized under the FD&C Act include: seizure of adulterated or misbranded devices (see section 304 of the FD&C Act); injunction against a manufacturer (see section 302 of the FD&C Act); and civil monetary penalties (see section 303 of the FD&C Act).

(Comment 303) One comment stated that FDA’s characterization of LDTs as simple devices was incorrect, because all tests require professional interpretation given that test results should be interpreted in the context of a patient’s overall clinical status and the specifics of a particular test. The comment stated that two tests assessing the same parameter may measure different things (i.e., hot spot testing vs. sequencing of the entire coding region of a gene), while the same result may mean different things in different patients.

(Response 303) FDA is not clear what the comment is referencing when it states that FDA characterized LDTs as “simple.” FDA did not include such a description in the NPRM. Rather, FDA noted in the NPRM that many LDTs rely on high-tech or complex instrumentation and software to generate results and clinical interpretations (88 FR 68006 at 68008). Nevertheless, FDA agrees that test results should be interpreted in the context of overall clinical status and the specifics of a particular test. This is one reason why it is important that IVDs have appropriate assurance of safety and effective for their specific intended uses.

(Comment 304) FDA received comments discussing part 11 (21 CFR part 11). One comment asked whether IVDs offered as LDTs would be subject to part 11 and, if so, what type of documentation would be required for software associated with an IVD offered as an LDT, and requested guidance on how to treat software that analyzes results for automatic release or that analyzes sequencing data to identify mutations or other targets of interest.

(Response 304) This rule does not change the framework under which FDA regulates devices, including the scope and application of electronic records and electronic signatures regulations found at part 11.

The comment that asked about the applicability of part 11 and requested guidance does not appear to be speaking for or against any aspect of this rulemaking, or presenting any matter which is relevant to this rulemaking. FDA notes nevertheless that it has issued final guidance on part 11. For example, FDA’s final guidance document entitled “Part 11, Electronic Records; Electronic Signatures--Scope and Application” (Ref. 265) provides guidance to persons who, in

fulfillment of a requirement in a statute or another part of FDA's regulations to maintain records or submit information to FDA, have chosen to maintain the records or submit designated information electronically and, as a result, have become subject to part 11. People can comment on that final guidance document or any other at any time, and FDA will revise guidance documents in response to comments when appropriate (§ 10.115(g)(5)). FDA also periodically reviews existing final guidance documents to determine among other things whether they need to be changed (§ 10.115(k)(1)).

(Comment 305) One comment stated that it could be overly burdensome to meet the requirements of part 11 for systems that were designed to be used for clinical care but would now be used as the system of record for data that is included in a premarket submission.

(Response 305) It is not clear what particular submission requirements are being referred to by the comment that said it could be overly burdensome to comply, or what legal or policy changes, if any, this comment would recommend. While this comment talked about the requirements of part 11, FDA notes that submission requirements might arise under the FD&C Act, the PHS Act, and FDA regulations other than part 11, and that FDA's policies regarding part 11 would not affect such requirements. And, of course, this rulemaking does not change part 11.

In any event, in the "Part 11, Electronic Records; Electronic Signatures--Scope and Application" final guidance, FDA observed that some broad interpretations of the scope of part 11 "could lead to unnecessary controls and costs and could discourage innovation and technological advances without providing added benefit to the public health." Accordingly, in that final guidance document, FDA stated that it "intends to interpret the scope of part 11 narrowly." Moreover, FDA currently exercises enforcement discretion with respect to certain part 11 requirements. In particular, and as described in that final guidance, FDA currently does "not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11 as explained in this guidance" and

does “not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems) under the circumstances described in section III.C.3 of this guidance.” FDA believes that its interpretation of and enforcement policies regarding part 11 strike an appropriate balance between public health and innovation, without being overly burdensome. Nevertheless, and consistent with the “Part 11, Electronic Records; Electronic Signatures--Scope and Application” final guidance, as a result of its re-examination of part 11, FDA anticipates initiating rulemaking to change part 11 as appropriate.

(Comment 306) One comment asked if FDA will establish a fund to compensate physicians who face malpractice lawsuits that may result from misdiagnoses as a result of phasing out the general enforcement discretion approach for LDTs.

(Response 306) Malpractice lawsuits are outside the scope of this rulemaking.

(Comment 307) Some comments stated that FDA should work with Congress to advance new legislation regarding the regulation of IVDs more broadly, such as the VALID Act. These comments generally acknowledged that FDA has a role to play in the oversight of LDTs, but suggested that legislation could better balance a variety of considerations and objectives--such as promoting patient safety, ensuring flexibilities, facilitating innovation, and supporting patient access--as compared to what is possible with FDA’s existing authorities. One comment suggested that legislation could better take into consideration unique characteristics of the diagnostics industry and the “multitude of stakeholders” affected by the regulation thereof, while other comments stated that new legislation could provide “unequivocal” statutory authority, as well as the resources necessary to effectively oversee diagnostics.

(Response 307) These comments are outside the scope of this rulemaking. The ability to enact new legislation rests with Congress. This rulemaking is focused on FDA’s oversight of devices under the current statutory authorities set forth in the FD&C Act. Based on the evidence currently available to the Agency, FDA has determined that there is a public health need to better

assure the safety and effectiveness of IVDs offered as LDTs, and FDA has determined to address that need consistent with our existing authorities by amending our regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory, and by phasing out the general enforcement discretion approach for LDTs.

FDA recognizes that the Agency's current statutory authorities could be amended or supplemented to establish a different regulatory framework for IVDs than the one that currently exists. FDA notes that this rulemaking does not prevent Congress from enacting new legislation.

VII. Effective Date

This rule is effective [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

VIII. Economic Analysis of Impacts

We have examined the impacts of the final rule under EO 12866, EO 13563, EO 14094, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

EOs 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers of available regulatory alternatives and to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Rules are "significant" under EO 12866 Section 3(f)(1) (as amended by EO 14094) if they "have an annual effect on the economy of \$200 million or more (adjusted every 3 years by the Administrator of OIRA for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities." OIRA has determined that this final rule is a significant regulatory action under EO 12866 Section 3(f)(1).

Because this rule is likely to result in an annual effect on the economy of \$100 million or more or meets other criteria specified in the Congressional Review Act/Small Business

Regulatory Enforcement Fairness Act, OIRA has determined that this rule falls within the scope of 5 U.S.C. 804(2).

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because most facilities that will be affected by this rule are defined as small businesses and the final rule is likely to impose a substantial burden on the affected small entities, we find that the rule will have a significant economic impact on a substantial number of small entities.

We prepared an analysis consistent with the Unfunded Mandates Reform Act of 1995 (section 202(a)), which requires the preparation of a written statement that includes estimates of anticipated impacts before issuing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$177 million, using the most current (2022) Implicit Price Deflator for the Gross Domestic Product. This final rule will result in an expenditure in at least one year that meets or exceeds this amount.

This final rule amends FDA’s regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory. As discussed in section V of the preamble to the final rule, FDA is phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs.

We anticipate that the benefits of phasing out FDA’s general enforcement discretion approach for LDTs includes a reduction in healthcare costs associated with unsafe or ineffective IVDs offered as LDTs (generally referred to in this document as “problematic IVDs”), including IVDs offered as LDTs that are promoted with false or misleading claims, and from therapeutic decisions based on unreliable results of those tests. Quantified benefits are the annualized sum of both health and non-health benefits. Unquantified benefits include the reduction in costs from

lawsuits. We discuss the benefits of the phaseout of FDA's general enforcement discretion approach for IVDs offered as LDTs in section II.E of the FRIA.

This phaseout policy will result in compliance costs for laboratories that are ensuring their IVDs offered as LDTs are compliant with statutory and regulatory requirements, as described in section V. We discuss the costs of the phaseout policy in section II.F of the FRIA. These costs overlap somewhat with effects associated with this phaseout policy in the form of user fees, including annual registration fees, fees for premarket applications/submissions, and annual fees for periodic reporting concerning PMA-approved devices, which are paid from laboratories to FDA. These fees are paid by laboratories but are revenue for FDA; the approach to estimating fee effects is distinct from the approaches for either benefits or costs, so they will be presented as transfers. We discuss transfers in section II.H of the FRIA.

Table 1 summarizes the annualized benefits, costs, and transfers of the phaseout policy. At a 7 percent discount rate, 20-year annualized benefits range from about \$0.99 billion to \$11.1 billion, with a primary estimate of \$3.51 billion per year. At a 3 percent discount rate, 20-year annualized benefits range from \$1.24 billion to \$13.62 billion, with a primary estimate of \$4.34 billion per year. At a 7 percent discount rate, 20-year annualized costs range from about \$566 million to \$3.56 billion, with a primary estimate of \$1.29 billion per year. At a 3 percent discount rate, annualized costs range from about \$603 million to \$3.79 billion, with a primary estimate of \$1.37 billion per year. At a 7 percent discount rate, 20-year annualized transfers range from \$20 million to \$81 million, with a primary estimate of \$41 million per year. At a 3 percent discount rate, 20-year annualized transfers range from \$29 million to \$115 million, with a primary estimate of \$58 million per year. These estimates do not include anticipated offsets from user fees. At a 7 percent discount rate, 20-year annualized costs to FDA range from \$61 million to \$243 million, with a primary estimate of \$121 million per year. At a 3 percent discount rate, 20-year annualized costs to FDA range from \$65 million to \$259 million, with a primary estimate of \$129 million per year. Factoring in offsets from user fees at current levels,

estimated costs to FDA are reduced to \$40 million to \$162 million at a 7 percent discount rate, with a primary estimate of \$81 million, and to \$36 million to \$144 million at a 3 percent discount rate, with a primary estimate of \$72 million, covering approximately 30 to 40 percent of the estimated costs to FDA.

Table 1.--Summary of Benefits, Costs and Transfers of the Final Rule (millions of 2022 U.S. dollars)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized (\$m/year)	\$3,509	\$988	\$11,096	2022	7%	20 years	Major sources of benefits will be the avoidance of harms to patients from use of problematic IVDs offered as LDTs and the avoidance of spending on such IVDs.
		\$4,341	\$1,244	\$13,619	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
Qualitative								
Costs	Annualized Monetized (\$m/year)	\$1,287	\$566	\$3,559	2022	7%	20 years	A portion of foreign costs will be passed on to domestic consumers. We estimate that up to \$147 million in annualized costs (7%, 20 years) to foreign facilities could be passed on to domestic consumers.
		\$1,372	\$603	\$3,789	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
Qualitative								
Transfers	Federal Annualized Monetized (\$m/year)	\$41	\$20	\$81	2022	7%	20 years	The main portion of transfers will be user fees for premarket submissions.
		\$58	\$29	\$115	2022	3%	20 years	
	From: Device Industry			To: FDA				
	Other Annualized Monetized (\$m/year)					7%		
						3%		
From:		To:						
Effects	State, Local, or Tribal Government: No significant effects Small Business: The phaseout policy will have a significant economic impact on a substantial number of small laboratories that manufacture IVDs offered as LDTs. Wages: N/A Growth: N/A							

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the phaseout policy. The full analysis of economic impacts is available in the docket for this phaseout policy (Ref. 10) and at <https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria>.

IX. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

X. Paperwork Reduction Act of 1995

FDA concludes that this rule contains no new collections of information. However, we expect that the phaseout of our general enforcement discretion approach for LDTs will necessitate adjustment to the burden estimates for several approved information collections, before the relevant phaseout stage begins. Such adjustments will account for an anticipated increase in the number of responses due to the expected compliance of laboratory manufacturers with applicable requirements for which FDA previously exercised enforcement discretion under the general enforcement discretion approach. Such adjustments will be submitted for review and clearance by OMB under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521).

In section II.D.1 of the FRIA for this rulemaking, we estimate a range of 590 to 2,362 affected laboratories and 47 to 189 new affected laboratories entering the market per year. We intend to adjust the applicable information collection burden estimates to reflect additional responses to correspond with the phaseout policy.

As discussed in section V.C of this preamble, FDA has determined to gradually phase out its current general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs. This

phaseout policy includes targeted enforcement discretion policies for specific categories of IVDs manufactured by a laboratory, including currently marketed IVDs offered as LDTs and LDTs for unmet needs, as described in section V.B of this preamble. FDA has structured the phaseout policy to contain five key stages. In the following paragraphs, we include a brief description of the stages and the OMB control numbers under which the related information collections (corresponding to the requirements for which FDA will expect compliance in each stage) are approved.

In stage 1, beginning 1 year after the publication date of this final rule, FDA generally will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files). Information collections associated with the MDR requirements under 21 U.S.C. 360i(a) through (c) and part 803 are approved under OMB control number 0910-0437. Information collections associated with correction and removal reporting requirements under 21 U.S.C. 360i(g) and part 806 are approved under OMB control number 0910-0359. Information collections associated with QS requirements under part 820, including § 820.198 (complaint files), are approved under OMB control number 0910-0073. Costs associated with stage 1 are discussed in section II.F.1 of the FRIA.

In stage 2, beginning 2 years after the publication date of this final rule, FDA generally will expect compliance with requirements not covered during other stages of the phaseout policy. These other requirements include registration and listing requirements under 21 U.S.C. 360 and parts 607 and 807 (excluding subpart E) (related information collections are approved under OMB control numbers 0910-0052, and 0910-0625, respectively); labeling requirements under 21 U.S.C. 352 and parts 801 and 809, subpart B (related information collections are approved under OMB control number 0910-0485); investigational use requirements under 21 U.S.C. 360j(g) and part 812 (related information collections are approved under OMB control number 0910-0078); and, for certain devices that are biological products, investigational use

requirements under 42 U.S.C. 262 and 21 CFR part 312 (related information collections are approved under OMB control number 0910-0014). Costs associated with stage 2 are discussed in section II.F.2 of the FRIA.

Additionally, for questions that are specific to a particular IVD, laboratory manufacturers may request feedback from FDA through a Pre-Submission, which is further explained in FDA's final guidance document entitled "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" (Ref. 65) (related information collections are approved under OMB control number 0910-0756).

In stage 3, beginning 3 years after the publication date of this final rule, FDA generally will expect compliance with QS requirements under part 820 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1). Information collections associated with QS requirements under part 820 are approved under OMB control number 0910-0073. Costs associated with stage 3 are discussed in section II.F.3 of the FRIA.

In stage 4, beginning 3½ years after the publication date of this final rule, FDA generally will expect compliance with premarket review requirements for high-risk IVDs. The premarket review requirements for PMAs are set forth in 21 U.S.C. 360e and part 814 (related information collections are approved under OMB control number 0910-0231). Premarket review requirements specific to HDE applications are set forth in 21 U.S.C. 360j(m) and part 814, subpart H (related information collections are approved under OMB control number 0910-0332). Licensure requirements are set forth in 42 U.S.C. 262 and 21 CFR part 601 (related information collections are approved under OMB control number 0910-0338). Costs associated with stage 4 are discussed in section II.F.4 of the FRIA.

In stage 5, beginning 4 years after the publication date of this final rule, FDA generally will expect compliance with premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs (that require premarket submissions). These premarket submissions include 510(k) submissions, the requirements for which are set forth at 21 U.S.C. 360(k),

360c(i), and part 807, subpart E (related information collections are approved under OMB control number 0910-0120). These submissions also include De Novo requests, which laboratories may submit for IVDs offered as LDTs for which there is no legally marketed device upon which to base a determination of substantial equivalence, and for which the laboratory seeks classification into class I or class II. These requirements are set forth at 21 U.S.C. 360c(f)(2) and part 860, subpart D (related information collections are approved under OMB control number 0910-0844). Costs associated with stage 5 are discussed in section II.F.4 of the FRIA.

FDA also anticipates that laboratories may seek to utilize FDA's Third Party review program. FDA currently operates a Third Party review program for medical devices, and multiple organizations are accredited to conduct reviews of 510(k) submissions for certain IVDs (see Ref. 67). We anticipate interest in the Third Party review program among laboratory manufacturers, as well as potential new 3P510k Review Organizations. Information collections associated with the Third Party review program are approved under OMB control number 0910-0375.

XI. Federalism

We have analyzed this final rule in accordance with the principles set forth in EO 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the EO and, consequently, a federalism summary impact statement is not required.

One comment stated that FDA failed to conduct the required federalism analysis under EO 13132 and that the Agency erroneously stated in the NPRM that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among

the various levels of government. Another comment stated that the conclusions in the NPRM regarding federalism “do not reflect the impact on practice of medicine” given that, in the comment’s view, FDA’s proposal conflicts with certain state medical practice acts as well as NYS CLEP, which currently permits the review, approval, and use of LDTs.

As discussed in response to comment 101, the requirement for a federalism summary impact statement applies to the proposed amendment to § 809.3 (and not the phaseout policy), and because the proposed regulation would not establish any new requirements, it would not have any federalism implications under EO 13132. Moreover, even if the requirement for a federalism summary impact statement were to apply to the phaseout policy, the policy does not have federalism implications because it is not establishing any new requirements. For further discussion on the relationship between this rule and state medical practice acts and NYS CLEP, as raised in the comments summarized above, see comments 76 and 101 and the responses to those comments.

XII. Consultation and Coordination With Indian Tribal Governments

We have analyzed this rule in accordance with the principles set forth in EO 13175. We have determined that the rule does not contain policies that have substantial direct effects on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. FDA received one comment on the NPRM that expressed concern that the rule, if implemented, would have significant tribal implications, resulting from loss of access to IVDs offered as LDTs that address special needs of the Native American population. As discussed in response to comment 223 (section VI.K), FDA does not anticipate that the Native American population will lose access to such IVDs offered as LDTs based on the final phaseout policy. We conclude that the rule does not contain policies that have tribal implications as defined in the EO and, consequently, a tribal summary impact statement is not required.

XIII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

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List of Subjects in 21 CFR Part 809

Labeling, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 809 is amended as follows:

PART 809—IN VITRO DIAGNOSTIC PRODUCTS FOR HUMAN USE

1. The authority citation for part 809 is revised to read as follows:

Authority: 21 U.S.C. 321(h)(1), 331, 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 371, 372, 374, 381, and 42 U.S.C. 262.

2. In § 809.3, revise the last sentence of paragraph (a) to read as follows:

§ 809.3 Definitions.

(a) * * * These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act, including when the manufacturer of these products is a laboratory.

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Dated: April 22, 2024.

Robert M. Califf,

Commissioner of Food and Drugs.