4164-01-P

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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing 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, FDA is proposing a policy under which FDA intends to phase out its general enforcement discretion approach for laboratory developed tests (LDTs) so that IVDs manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs. FDA is proposing this phaseout to better protect the public health by helping to assure the safety and effectiveness of LDTs. If finalized, this phaseout may also foster the manufacturing of innovative IVDs for which FDA has determined there is a reasonable assurance of safety and effectiveness.

DATES: Either electronic or written comments on the proposed rule must be submitted by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by

mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2023-N-

2177 for "Medical Devices; Laboratory Developed Tests." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, 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.

FOR FURTHER INFORMATION CONTACT: Toby Lowe, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301-796-6512, LDTProposedRule@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to amend 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 would reflect that the device definition in the FD&C Act does not differentiate between entities manufacturing the device, and would provide further clarity, including for stakeholders affected by the accompanying changes to FDA's general enforcement discretion approach for LDTs. In connection with amending the regulation, FDA intends to phase out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs. 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 generally 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 general 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 section III.B, today's LDTs are generally, 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 been under this general enforcement discretion approach. Given these changes, and for the additional reasons discussed in section III.B, phasing out the general enforcement discretion approach for LDTs is important to protect the public health. The phaseout of FDA's general enforcement discretion approach for LDTs is intended to help assure the safety and effectiveness of LDTs, and may also foster the manufacturing of innovative IVDs for which FDA has determined there is a reasonable assurance of safety and effectiveness.

B. Summary of the Major Provisions of the Proposed Rule

This rulemaking would amend the definition of "in vitro diagnostic products" in FDA 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 also proposing a policy under which FDA intends to phase out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs. Additional details regarding the proposed phaseout policy are discussed further in section VI.

C. Legal Authority

FDA is proposing to issue 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).

D. Costs and Benefits

We quantify benefits to patients from averted health losses due to problematic IVDs offered as LDTs.[1] Due to limitations in the data, we quantify health benefits only with respect to IVDs for certain diseases and conditions; however, we would expect additional health benefits

[1] See discussion of "IVDs offered as LDTs" in section VI.A below.

associated with averted health losses for other diseases and conditions. We estimate that the annualized benefits over 20 years would range from $2.67 billion to $86.01 billion at a 7 percent discount rate, with a primary estimate of $31.41 billion, and from $1.81 billion to $61.41 billion at a 3 percent discount rate, with a primary estimate of $22.33 billion. Additional benefits would include averted non-health losses from the quantified reduction in costs of problematic IVDs offered as LDTs and unquantified reduction in costs from lawsuits and costs to healthcare systems. We quantify costs to affected laboratories for complying with applicable statutory and regulatory requirements. Additional costs would include some costs to FDA, which we include in our estimates. The annualized costs would range from $2.52 billion to $19.45 billion at a 7 percent discount rate, with a primary estimate of $5.87 billion, and from $2.39 billion to $18.55 billion at a 3 percent discount rate, with a primary estimate of $5.60 billion. The annualized transfers[2] would range from $100 million to $452 million at a 7 percent discount rate, with a primary estimate of $226 million, and from $121 million to $538 million at a 3 percent discount rate, with a primary estimate of $269 million. The annualized costs to FDA would range from $265 million to $1.06 billion at a 7 percent discount rate, with a primary estimate of $530 million, and from $251 million to $1.00 billion at a 3 percent discount rate, with a primary estimate of $501 million. These estimates do not include anticipated offsets from user fees. Factoring in offsets from user fees at current levels, estimated costs to FDA are reduced to $165 million to $607 million at a 7 percent discount rate, with a primary estimate of $304 million, and to $103 million to $465 million at a 7 percent discount rate, with a primary estimate of $233 million, covering approximately half of the estimated costs to FDA.

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

[2] This proposed rule would result in compliance costs for laboratories that are ensuring their IVDs offered as LDTs are compliant with applicable statutory and regulatory requirements. These costs overlap somewhat with effects associated with this rule in the form of user fees including annual registration fees, fees for premarket submissions, and annual fees for periodic PMA reporting, which are paid from laboratories to FDA. These fees are paid by laboratories but are considered 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.

Abbreviation/Acronym	What It Means
510(k)	Premarket Notification
AMC	Academic Medical Center
ASR	Analyte Specific Reagent
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CLIA	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare & Medicaid Services
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
HCT/Ps	Human Cells, Tissues, and Cellular and Tissue-Based Products
HLA	Human Leukocyte Antigen
IDE	Investigational Device Exemption
IVD	In Vitro Diagnostic Product
IVDMIA	In Vitro Diagnostic Multivariate Index Assay
LDT	Laboratory Developed Test
MDA	Medical Device Amendments of 1976
MDR	Medical Device Report
MDUFA	Medical Device User Fee Amendments
NIPS	Non-Invasive Prenatal Screening
PMA	Premarket Approval Application
QS	Quality System

III. Background

A. Introduction

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 performed on 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 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. Section V.B sets forth the legal reasoning for FDA's position that IVDs manufactured by laboratories, including LDTs, are devices.

However, in implementing the MDA, FDA generally has exercised enforcement discretion such that it generally has not enforced applicable requirements with respect to most LDTs. 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 tests. They also tended to employ manual techniques (and did not use automation) 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 regulatory requirements. Due to these and other factors, FDA generally 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 rely on high-tech or complex instrumentation and software to generate results and clinical interpretations. They are often used in laboratories outside of the patient's healthcare setting and are often manufactured in high volume for large and diverse populations. Many LDTs are

[3] Although FDA's general enforcement discretion approach continues today, it does not apply to LDTs in all contexts; for example, it does not apply 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).

manufactured by laboratory corporations that market the tests 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 heart disease.[4] The risks associated with most modern LDTs are therefore much greater today 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, because they are not actually designed, manufactured, and used within a single laboratory (see, e.g., Refs. 4 and 5).

As a result of this evolution 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 set forth in the "History of the Rulemaking" section below (section III.D). Over the past few years, FDA has accumulated even more information supporting the need for a change, as discussed below. In light of these developments, FDA is proposing to amend 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 proposing a policy under which FDA intends to phase out FDA's general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs.

B. Need for the Rule

[4] See, e.g., Refs. 1 to 3. 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 developing and running LDTs.
[5] As discussed further in section V, FDA is also proposing to amend 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 (21 U.S.C. 321(h)(1)).

FDA is proposing a policy under which FDA intends to phase out the general enforcement discretion approach for LDTs because that approach has led to an oversight scheme that does not best serve the public health. LDTs that are under the general enforcement discretion approach are treated differently from other IVDs. However, there is no longer a sound basis for this distinction. In FDA's experience, including with COVID-19 tests and IVDs that are offered as LDTs after FDA's approval of a comparable companion diagnostic, many test systems made by laboratories today are functionally the same as those made by other manufacturers of IVDs. They involve the same materials and technologies, are intended for the same or similar purposes, are developed by and for individuals with similar expertise, and are marketed to the same patients, sometimes on a national scale. For these reasons, tests made by laboratories are often used interchangeably by healthcare providers and patients with tests made by other manufacturers. In fact, today, the testing industry has come to view FDA's general enforcement discretion approach as an alternative pathway to market for test systems, such that test systems are often "launched as LDTs" with no assurance that they meet requirements under the FD&C Act and its implementing regulations (see, e.g., Refs. 6 and 7).[6] These tests lack the characteristics and institutional safeguards that originally justified FDA's general enforcement discretion approach, as discussed above, and may directly compete with FDA-authorized kit-based test systems. FDA views this bifurcated system of oversight as untenable and inconsistent with FDA's public health mission.

The proposed phaseout of FDA's general enforcement discretion approach is designed to redress the imbalance in oversight and protect the public health. Diagnostic testing is a cornerstone of modern medicine; CDC estimates that 70 percent of medical decisions are based on laboratory test results (Ref. 8). IVDs offered as LDTs are a growing sector of that market (Ref. 1). Moreover, these tests are proliferating in some of the most complicated and sensitive

[6] The references cited are examples of the described practice. Their inclusion does not represent FDA support for or approval of the activities described.

areas of medical practice, where the presence of a valid test can be most important.

As the testing landscape has evolved, information about these tests in the scientific literature, news articles, and anecdotal reports submitted to the Agency, among other sources, has exposed evidence of problems associated with these tests. This evidence is discussed in more detail below. Particularly over the last few years, this evidence has been growing and likely does not reflect the full scale of the problems. (Until FDA systematically collects information on these tests, such as adverse event reports, it will not be able to assess more fully the extent of the risks to patients in the manner it does for other devices.) Based on current safety signals, FDA is proposing to phase out the general enforcement discretion approach to help assure that patients are receiving accurate and reliable diagnostic test results regardless of where the tests are made.

1. IVDs Offered as LDTs Have a Significant Impact on Modern Medical Care

Today, IVDs offered as LDTs are ubiquitous, and are intended to diagnose a broad range of diseases and conditions (see Ref. 2). In many cases, these IVDs are meant for use in complex areas of medicine involving life-threatening diseases, such as cancer, neurological diseases, cardiovascular illness, infectious diseases, and rare diseases. They can proliferate in areas where diagnosis is difficult, and the healthcare community has few points of reference for determining test validity. Sometimes, they use complex algorithms to calculate "scores" for diagnosis with little transparency to the user about the basis for these algorithms. Increasingly, these IVDs are intended to inform drug treatment, directing physicians to choose certain drugs based on a patient's genetic or other information. FDA has witnessed an explosion in the volume, complexity, and scope of IVDs offered as LDTs for use in determining cancer treatments,[7] and as discussed below, news coverage, including as recently as this year, has drawn attention to the use of IVDs offered as LDTs for non-invasive prenatal screening (NIPS), which evaluate fetal DNA circulating in a pregnant individual's blood. In general, IVDs offered as LDTs are

[7] FDA has initiated a pilot program for certain oncology diagnostics as one step that may be helpful in reducing the risks associated with using certain LDTs to identify cancer biomarkers (see 88 FR 40273 (June 21, 2023)).

occupying a growing share of the testing market and are used in some of the most complex areas of medicine (see, e.g., Refs. 1 and 2).

Given the role these IVDs play in modern medical care, their validity has a significant impact on the public health. False positive test results, which erroneously indicate that a patient has a certain disease or condition, can delay diagnosis and treatment of the true disease or condition, lead to unwarranted interventions, and cause needless distress. Interventions may involve medication with serious side effects or risky medical procedures. False negative results can lead to progression of disease, in some cases without the opportunity for life-saving treatment, and the spread of infectious disease. The harms to patients from false positive and negative results can be significant. For example, the application of an ineffective oncology treatment due to a false positive for a patient already weakened from disease, or the failure to receive a life-saving medication due to a false negative, can be fatal. These false results 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. Flaws in a test's algorithm can mean the difference in whether a patient with cancer receives a beneficial immunotherapy. Pregnant people may use screening tests to make decisions without obtaining appropriate confirmatory testing. In 2016, FDA learned of a false positive result from a genetic test for long QT syndrome (a heart signaling disorder) that led to the erroneous implantation of a defibrillator in a healthy individual. In addition to the risks associated with the implantation procedure, the defibrillator delivered inappropriate shocks to the patient, which posed the risk of sudden cardiac death (Refs. 9 and 10). These are just a few examples of how diagnostic tests can and do have significant long-term consequences for patients.

2. Current Information Raises Serious Questions About Whether Patients Can Rely on IVDs Offered as LDTs

FDA has highlighted the risks associated with IVDs offered as LDTs for decades, and our concerns have grown in recent years. As described in the "History of the Rulemaking" section,

we first took steps to address the issue in the late 1990s, followed by a series of different proposed strategies for increasing oversight. In 2015, the Agency published a report of 20 case studies involving inaccurate, unsafe, ineffective, or poor quality LDTs that caused or may have caused patient harm ("2015 Report") (Ref. 11). More recent evidence suggests that the situation is getting worse. This evidence 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. Overall, the evidence points to fundamental uncertainty in the marketplace about whether IVDs offered as LDTs provide accurate and reliable results.

Scientific literature is one source of evidence. Over time, FDA has become aware of various publications that describe problems with IVDs offered as LDTs. In the past 3 years, four different studies have documented high variability in performance among these IVDs (Refs. 12 to 15). In one study, 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 (Ref. 12). For almost half of the tests studied, analytical accuracy was significantly lower than that of the parallel test approved by FDA. In another study, researchers sent identical samples to two different laboratories to detect tumor mutations and found over 70 percent discordance in the results from their tests (Ref. 13). A study by Friends of Cancer Research found substantial variability among tumor mutational burden (TMB) tests manufactured by laboratories and used to identify patients with cancer most likely to benefit from immunotherapy (Ref. 14). A fourth study highlighted validity concerns specific to early cancer detection tests, including one IVD offered as an LDT that delivered nine false positive results for every true cancer diagnosis (Ref. 15). An article published earlier this year detailed an oncologist's experience with false results from an unapproved blood-based multi-cancer early detection IVD offered as an LDT and intended to screen for more than 50 types of cancer (Ref. 16). A 2016 study published in the *New England Journal of Medicine* reported false positive results from genetic IVDs offered as

LDTs for hypertrophic cardiomyopathy in multiple patients of African American descent (Ref. 17). These studies do not mean that every laboratory is manufacturing bad tests or that no patient can rely on IVDs offered as LDTs. Instead, they reflect a level of variability, including the potential for inaccurate or incomplete results, that highlights the need for changes to the basic oversight scheme.

FDA's own experience has reinforced concerns regarding IVDs offered as LDTs. FDA has gathered information about IVDs offered as LDTs through its review of submissions. Although the Agency generally has not enforced requirements for LDTs, it has received premarket submissions from some laboratories seeking authorization for their tests. We have received numerous submissions for such tests, including premarket review submissions,[8] Q-submissions,[9] and investigational use submissions for IVDs offered as LDTs, as well as many emergency use authorization (EUA) requests from laboratories (which are discussed further below). FDA's review of these submissions has provided insight into laboratory test development and, in some cases, revealed significant concerns. For example, FDA has observed that many laboratories fail to perform appropriate or adequate validation studies, have data demonstrating their test does not work as intended but offer the test anyway, or use instruments and other components that are not adequately controlled for clinical use. The tests described in these submissions have been intended for a range of diseases or conditions, some of which are very serious. FDA has received submissions for IVDs offered as LDTs to diagnose Alzheimer's disease, predict heart disease risk, diagnose Fabry disease (a rare neurological disorder), and inform treatment considerations for a rare blood cancer, all of which lacked adequate validation to support authorization.

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[8] These submissions have been for a wide variety of indications, including tests intended to detect nucleic acids from viruses associated with head and neck cancers; to identify patients with obesity due to rare genetic conditions to inform treatment eligibility; to aid in the management of therapy for patients taking certain anticoagulants; and tests for breast cancer prognosis, tumor profiling, and treatment selection, for patients with cancer.

[9] For discussion of FDA's Q-submission program, see FDA's guidance document issued on June 2, 2023, entitled "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submissions Program," available at https://www.fda.gov/media/114034/download.

In addition, given that FDA's general enforcement discretion approach for LDTs has not applied to IVDs for emergency use (though FDA has issued enforcement policies for such IVDs during specific emergencies, as explained elsewhere in this preamble), FDA has received EUA requests for tests from laboratories, including many for COVID-19 diagnostics. Of the first 125 EUA requests for COVID-19 molecular diagnostic tests submitted from laboratories, 82 showed test design or validation problems (Ref. 18). In one case, the approach to validation was so poor that when redone correctly, there was a 400-fold difference in performance, leading the laboratory to take the test off the market. In another example, an academic medical center (AMC) laboratory purported to validate its test with only 12 positive samples, showing perfect performance. FDA requested evaluation of additional specimens to confirm. When an additional 12 samples were evaluated, the cumulative performance revealed an unacceptably high false negative rate, where the test identified only 71 percent of known positive specimens as positive and falsely identified 29 percent of known positive samples as negative, and the EUA request was withdrawn. In addition, multiple laboratories that offered their tests as described in FDA's COVID-19 test guidance (see discussion in Ref. 19) did not provide any analytical and/or clinical validation data in the EUA requests that they submitted after the tests were in use. This experience provided a window into the approach that many laboratories may take to test validation, and not only confirmed but increased FDA's concerns about the validation of IVDs offered as LDTs. The experience also showed that even tests involving relatively well-understood techniques (here, the polymerase chain reaction, or PCR, technique) may not perform well. In all, test performance seen in this subset of submissions from laboratories was far worse than we expected. To the extent that this sample represents larger trends in the performance of IVDs offered as LDTs, it underscores the need for greater FDA oversight.

FDA has also received multiple complaints, adverse event reports, and other allegations identifying problems with IVDs offered as LDTs.[10] One complaint alleged that an IVD offered

[10] FDA has not confirmed the veracity of the allegations or facts in every complaint, report, and allegation.

as an LDT to diagnose autism had insufficient clinical validation to support this use. In another complaint, an informant alleged that a laboratory was forging results when its liquid biopsy test did not work. Additionally, FDA has received multiple voluntary medical device reports (primarily from patients) of inaccurate NIPS test results, as well as inaccurate results from an oncology IVD offered as an LDT that predicts risk of breast cancer recurrence and informs the decision to pursue chemotherapy, both of which can pose serious, irreversible harm to patients. Another report described a false negative result from a BRCA test marketed to predict one's risk of breast cancer. The patient was later diagnosed with breast cancer and found to be BRCA1 positive by another test. A separate report from a healthcare provider described a different patient that received discrepant results from testing with this BRCA test and with another IVD offered as an LDT for hereditary cancer risk prediction. In yet another report, a patient described a false positive breast cancer result from an oncology blood IVD offered as an LDT and that led to invasive followup procedures, emotional anguish, and unnecessary monetary expenses. FDA also received a report regarding a blood-based test for lung cancer that underestimated cancer in about 40 percent of patients. Additionally, FDA has received medical device reports regarding infectious disease genetic IVDs offered as LDTs without validation, from which inaccurate results could lead to limb loss or women's health issues, and regarding inaccurate results from an IVD offered as an LDT to assess medication adherence. As noted above, collectively, this information, though anecdotal, points to potential problems among IVDs offered as LDTs, the scope and scale of which FDA cannot fully assess or address without phasing out the general enforcement discretion approach for applicable requirements (such as adverse event reporting).

Aside from the scientific community and FDA, the general public is coming to recognize concerns with the current scheme, in which most LDTs are generally not overseen by FDA. General news sources and other outlets have reported on such concerns (see, e.g., Refs. 20 to 26). For example, the *New York Times* recently conducted an indepth investigation into NIPS tests

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Nevertheless, collectively this information points to potential problems among IVDs offered as LDTs.

and found that positive results from the tests are incorrect about 85 percent of the time (Ref. 22). NIPS tests are screening tests, so they should be followed up with confirmatory diagnostic testing, but the *New York Times* article reported that patients and healthcare providers are making healthcare decisions based on results from these screening tests alone due to manufacturers' marketing claims. A device whose labeling is false or misleading in any particular manner is misbranded under the FD&C Act; however, under the general enforcement discretion approach, FDA generally has not enforced this proscription for IVDs offered as LDTs. As another example, *ProPublica* reported on a COVID-19 test offered by a laboratory under contract with a university without EUA authorization from FDA, which, according to the report, missed 96 percent of the positive cases from the university campus, and routinely sent people infected with COVID-19 back into the community (Ref. 26). In addition, consumers, shareholders, and investors are filing lawsuits against laboratory manufacturers for false and misleading statements about test efficacy, including lawsuits related to pharmacogenetic tests (genetic tests intended to inform drug selection) and NIPS (see, e.g., Complaint, *In re Myriad Genetics, Inc. Sec. Litig*., No. 2:19-cv-00707-PMW (D. Utah 2019); Complaint, *Hickok* v. *Capone*, No. 2021-0686 (Del. Ch. 2021); Complaint, *Davis* v. *Natera, Inc*., No. 3:22–cv-00985 (N.D. Cal. 2022); Complaint, *Carroll* v. *Myriad Genetics Inc.*, No. 4:22-CV-00739 (N.D. Cal. 2022); *Biesterfeld* v. *Ariosa Diagnostics, Inc.*, No. 1:21--CV-03085, 2022 WL 972281 (N.D. Ill. 2022); and Complaint, *Kogus* v. *Capone*, No. 2022-0047-SG (Del. Ch. 2022)). The overall picture presented by this evidence indicates that a change in oversight is needed to better assure the safety and effectiveness of IVDs offered as LDTs.

3. Greater FDA Oversight is Needed to Protect the Public Health

As described above, the evidence FDA has collected points to flaws in laboratory manufacturing of tests that need to be addressed to protect the public. Greater oversight by FDA would help address these flaws.

In the past, FDA has communicated with the public when it is particularly concerned

about a type of IVD offered as an LDT. For example, in addition to the 2015 Report, FDA has issued safety communications about pharmacogenetic tests, NIPS tests, ovarian cancer screening tests, nipple aspirate tests, and instruments used in the design of many different LDTs (Refs. 27 to 31). FDA has also taken compliance action in some circumstances, such as issuing a warning letter to a laboratory manufacturing a pharmacogenetic test in April 2019 (Ref. 32). However, more structural change is needed. FDA's general enforcement discretion approach emerged at a time when the typical IVD offered as an LDT looked very different from how it looks today. FDA has made a preliminary determination that this approach has become outdated, and the proposed steps to end this approach in this rulemaking would better protect the public health.

Increased oversight would help to ensure the safety and effectiveness of IVDs offered as LDTs. More accurate diagnoses would lead to better care, which would advance public health overall. Through increased oversight, the public, including patients and healthcare professionals, could have more confidence that the test results they rely on are accurate. Greater FDA oversight of IVDs offered as LDTs has become particularly important as more and more novel treatments require use of a specialized test to identify patients likely to benefit from them. This, in turn, has led to increased development of tests used as the primary driver for therapeutic decisions. These include tests to determine whether to administer a therapeutic, which therapeutic to administer, and at what dose to administer the therapeutic. For example, recent approvals of drug products to treat diseases in their early stages, such as for early-stage Alzheimer's patients, make accurate and early diagnosis of these diseases more critical today than ever before. As another example, gene therapy is an emerging field with incredible potential to treat many diseases or conditions. Testing is required to identify patients with the defective gene targeted by the treatment and, in some cases, to assess whether the patient has antibodies to the vector delivering the treatment that would prevent it from working. In these and other cases, accurate and reliable test results are essential for safe and effective use of a therapeutic.

Increased oversight would also address business strategies that take advantage of the current bifurcated system. For example, in a number of cases, laboratories that have submitted premarket submissions for their tests, but whose tests did not meet applicable requirements for authorization, have still offered these IVDs as "LDTs." Some of these tests, such as a test intended to diagnose Alzheimer's disease, had inadequate validation data to support authorization (see Ref. 33). A genotyping test purported to predict heart disease risk, but FDA found that there was no association between the genetic information the test identified (*KIF6*) and heart disease. A third test, intended to diagnose Fabry disease, showed a high level of false negatives. The public health is not served by a scheme in which tests that have these types of problems are still offered to patients simply because the manufacturer is a laboratory. FDA is also aware that some industry players have created business models that claim a connection to laboratories and offer IVDs as LDTs. The increase in firms using these business models, as well as their substantial magnitude of reach, underscores the need for more oversight.

In addition, FDA anticipates that consistent oversight would bring 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 aware of arguments that better assuring the safety and effectiveness of LDTs would foster test innovation. FDA is also aware of arguments that IVD manufacturers that are not laboratories 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 their tests without complying with FDA requirements. We anticipate that applying the same oversight approach to laboratories and non-laboratories that manufacture IVDs would better assure the safety and effectiveness of LDTs, and would remove a disincentive for non-laboratory manufacturers to develop novel tests, thereby spurring innovation and access to IVDs for which there is a reasonable assurance of safety and effectiveness. As a result, we anticipate that phasing out the general enforcement discretion approach for LDTs would advance

responsible innovation by both laboratory and non-laboratory IVD manufacturers alike, rather than discouraging it.

FDA is aware of other arguments that ending the general enforcement discretion approach for LDTs would interfere with test innovation and patient access due to the potential need for premarket review of new tests. However, under FDA's device authorities, FDA premarket review is only required for certain tests (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 (see section II.F.4 of the Preliminary Economic Analysis of Impacts (Ref. 34)). In addition, FDA review is only required for device modifications in certain circumstances. For devices that are subject to PMA requirements, a PMA supplement is required only for changes that affect the safety or effectiveness of the device, and in some cases the change may be made prior to FDA approval (see 21 CFR 814.39(d)); may be made 30 days after a supplement has been filed, unless FDA takes certain action (see 21 CFR 814.39(e)); or may be made 30 days after FDA receives a notice describing the change (in lieu of a supplement), unless FDA takes certain action (see 21 CFR 814.39(f)). For devices that are subject to 510(k) requirements, a new 510(k) is only required for a significant change or modification in design, components, method of manufacture, or intended use, where a significant change or modification is one that could significantly affect the safety or effectiveness of the device or that is a major change or modification in the device's intended use (21 CFR 807.81(a)). FDA has published several guidance documents to help stakeholders determine whether a certain change or modification may require a PMA supplement, new 510(k), or other submission to FDA, and FDA has several mechanisms available through which manufacturers may seek FDA assistance in making this determination. In addition, under section 515C of the FD&C Act (21 U.S.C. 360e-4), a PMA supplement or new 510(k) is not required for a change to a device that would otherwise require a supplement or new 510(k) if the change is consistent with a predetermined change control plan previously approved or cleared by FDA. We also note that as described in

section VI.B, FDA is proposing to phase out the general enforcement discretion approach for LDTs with respect to premarket review requirements on a date that aligns with or follows the beginning of a new user fee cycle, such that FDA's review timelines and goals would be reflected in commitments newly negotiated with industry. For all of these reasons, FDA does not anticipate that ending the general enforcement discretion approach for LDTs would unduly impair test innovation and patient access.

Furthermore, FDA's approach was never intended to selectively foster laboratory innovation at a cost to public health. Rather, the approach arose based on certain test characteristics and institutional safeguards that at the time adequately protected patients. In general, those characteristics and safeguards are no longer present, putting public health at risk. Further, FDA is aware that this scheme is in some cases fostering unfounded claims of innovation rather than responsible innovation. These claims are concerning to FDA because they can mislead the public, undermine legitimate competition, and disincentivize responsible, science-based innovation.

Finally, increased oversight may help to advance health equity. FDA is aware of concerns that IVDs offered as LDTs may exacerbate health inequities due to higher rates of inaccurate results among underrepresented patient populations, particularly racial and ethnic minorities undergoing genetic testing (see, e.g., Refs. 17 and 35 to 38). Some IVDs offered as LDTs have not been validated for use in all patient populations within a disease state, meaning that it is unknown how well the test may perform across diverse patient populations expected to use the test and the test may be less accurate in underrepresented patient populations, potentially contributing to health disparities (see, e.g., Ref. 39). Increased FDA oversight may help to ensure that information is available pertaining to device safety and effectiveness for specific demographic characteristics if performance differs within the target population, through the enforcement of applicable labeling requirements. In addition, when FDA conducts premarket review of a device, FDA may ask that sponsors provide data for different intended patient

populations, and with new authorities under the Food and Drug Omnibus Reform Act of 2022 (FDORA), sponsors generally are required to submit diversity action plans to FDA, including the sponsor's goals for enrollment in device clinical studies. In contrast, with limited oversight over these tests, FDA does not know whether diverse patient populations are being included in validation studies for these IVDs. FDA has made a preliminary determination that increased oversight for these IVDs would help ensure adequate representation of the intended use population in validation studies and transparency regarding potential differential performance, helping to advance health equity. FDA also recognizes that IVDs offered as LDTs may serve communities in rural, medically underserved areas with disparities in access to diagnostic tests. However, the benefits of test access directly depend on the ability of tests to work as intended. Thus, to the extent that access to IVDs offered as LDTs may benefit patients in rural, medically underserved communities, the harms of unsafe or ineffective IVDs offered as LDTs may also be realized among these underserved patient populations. By increasing its oversight, FDA may better prevent and mitigate such harms, thereby better protecting the health of these underserved populations.

We are aware of arguments that other mechanisms--such as the medical expertise of laboratorians or requirements under CLIA--already provide adequate oversight of IVDs offered as LDTs. However, our review of the evidence indicates otherwise. Evidence suggests that under the current scheme, the healthcare community lacks adequate assurances about the safety and effectiveness of IVDs offered as LDTs. Although laboratories that offer LDTs are also subject to CLIA, which is primarily administered by the Centers for Medicare & Medicaid Services (CMS), CLIA is not a substitute for FDA oversight. CLIA establishes requirements for laboratories and laboratory personnel pertaining to operations, inspections, and certification, with a focus on the proficiency with which laboratories perform clinical testing (see 42 U.S.C. 263a and 42 CFR part 493). Among other requirements, clinical laboratories generally must have a CLIA certificate that corresponds to the complexity of tests performed prior to accepting human

samples for testing. However, under 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 patients who participate in test clinical research trials; and does not require adverse event reporting. As such, CMS has described the FDA and CMS "regulatory schemes" as "different in focus, scope and purpose, but they are intended to be complementary" (Ref. 40). Where CLIA does play a role (as discussed further below, compliance with CLIA may provide certain assurances relating to quality system (QS) requirements), FDA has tailored its proposed phaseout policy accordingly.[11]

We are also aware of arguments that any additional oversight of LDTs should be accomplished by granting new statutory authorities to CMS. However, this would cause a problematic split in oversight, with the same types of tests being reviewed by different Agencies depending on where the test was made. 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.

FDA has both the authority and the expertise to perform the necessary oversight of IVDs

[11] When "QS" requirements are discussed throughout this preamble, FDA is referring to the current good manufacturing practice (CGMP) requirements set forth in part 820 (21 CFR part 820). Generally, the requirements are referred to as QS requirements, but that terminology may change when amendments to part 820 are finalized. See 87 FR 10119 (February 23, 2022) and section VI.B.3 for a further discussion of FDA's proposed amendments to part 820.

offered as LDTs and is the only Agency for which that is the case. One of FDA's most basic and well-understood responsibilities is helping to ensure the safety and effectiveness of medical products. FDA employs staff across a wide range of disciplines, including physicians, statisticians, engineers, biologists, chemists, geneticists, and others, to evaluate the science behind medical products before they reach the market. Understanding the complex technical information in applications, such as clinical trial data, bench testing results, and product manufacturing and design characteristics--and putting that information in context to assess whether a product can be marketed--is within the unique expertise of FDA. This type of expertise is no less important for IVDs, which can have a wide variety of public-health consequences, as described elsewhere in this rule. During review of an application for an IVD, FDA reviewers closely examine data relevant to analytical validity, clinical validity, and safety, and draw on their expertise and experience to understand both the product and the science supporting the product.

Review of the underlying science behind an IVD is based on what the IVD does and is in no way related to where the IVD is made. Thus, FDA's experience and expertise with respect to oversight of other IVDs is directly applicable to oversight of LDTs. In fact, FDA has already applied its expertise to the review of some IVDs offered as LDTs--for example, during public health emergencies. As stated above, FDA has reviewed many EUA requests for tests from laboratories during the public health response to COVID-19.

Entities outside FDA have also recognized that FDA should oversee LDTs, and that greater oversight is needed. For example, the Secretary's Advisory Committee on Genetics, Health, and Society, in its April 2008 report entitled "U.S. System of Oversight of Genetic Testing," stated that "FDA should address all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or laboratory-developed test), in a manner that takes advantage of its current experience" (Ref. 41). The American Cancer Society Cancer Action Network has taken a similar position, noting in a November 2016 statement that "[c]urrent

oversight of LDTs falls short of ensuring these tests produce accurate and meaningful results… [t]he FDA is the most appropriate agency to evaluate the analytical and clinical validity of diagnostic tests, along with their safety, to help ensure that cancer patients and their doctors are able to make appropriate treatment decisions based on accurate information" (Ref. 42). Likewise, the Advanced Medical Technology Association (AdvaMed) stated in November 2021 that the association has "long supported the idea that all diagnostic test developers … should be subject to the same FDA standards and processes" (Ref. 43).

4. FDA Should Increase Oversight in a Manner That Recognizes the Current State of the Testing Market

As discussed throughout this section, increased oversight of IVDs offered as LDTs is needed. However, FDA has also made a preliminary determination that our general enforcement discretion approach should be phased out in a manner that accounts for the level of public health concern and the importance of avoiding undue disruption to the testing market, including undue disruption to the provision of care. Therefore, we are proposing a gradual phaseout to occur in stages over a total period of 4 years, as described in section VI.B. FDA anticipates that this phaseout policy should ultimately enable IVDs offered as LDTs that are supported by sound science to remain on the market. FDA also recognizes that some IVDs may need to 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 chooses not to invest resources to meet those requirements. To the extent that withdrawal from the market of these IVDs implicates any reliance interests, FDA has made a preliminary determination that the public-health benefits associated with the reasonable assurance of safety and effectiveness of IVDs offered as LDTs outweigh any such interests. In addition, in the long run, it is possible that any reduction in the number of current IVDs offered as LDTs may be offset by the market entry of IVDs from other manufacturers who will have benefitted from a more consistent oversight approach and increased stability spurring innovation.

C. FDA's Current Regulatory Framework

The FD&C Act, as amended by the MDA and subsequent statutes, establishes a comprehensive system for the regulation of devices, defined in section 201(h)(1) of the FD&C Act, that are intended for human use. 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).

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; and current good manufacturing practice (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 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).

In addition, 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 investigational device exemption (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).

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).

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, including premarket notification, reporting requirements regarding adverse events and corrections and removals, IDE requirements (though most 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 of the regulations (21 CFR part 809).

D. History of the Rulemaking

1. FDA's Longstanding Recognition That IVDs Manufactured by Laboratories Are Devices

FDA has made clear, on many occasions and over many years, that LDTs are devices under the FD&C Act (for the legal reasoning for this conclusion, see section V.B). Over 25

years ago, FDA explained that clinical laboratories that develop tests are acting as manufacturers of medical devices (62 FR 62243 at 62249 (November 21, 1997)). FDA reiterated that position in a citizen petition response a year later (Ref. 44), and in the preamble to a final rule 3 years after that (65 FR 18230 at 18231 (April 7, 2000)). In 2006, FDA again cited its prior statement that clinical laboratories that develop tests are acting as manufacturers of medical devices (Ref. 45 (quoting 62 FR 62243 at 62249)). In 2014, FDA expressly considered and rejected arguments that LDTs are not devices under the FD&C Act, stating in a citizen petition response that "LDTs are devices within the plain language of the [statutory] definition" (Ref. 46). Five years later, FDA issued a warning letter stating that "FDA has not created a legal 'carve-out' for LDTs such that they are not required to comply with the requirements under the Act that otherwise would apply. . . . Although FDA has generally exercised enforcement discretion for LDTs, the Agency always retains discretion to take action when appropriate, such as when it is appropriate to address significant public health concerns" (Ref. 47). A wide range of other FDA documents, including guidance documents, safety communications, compliance letters, and other public statements, have indicated or otherwise taken as their premise that IVDs are devices even when the manufacturer is a laboratory (see, e.g., Refs. 11, 18, 27, 28, and 48 to 56).

FDA has also taken regulatory actions consistent with these statements and documents. Since 2017, the Agency has reviewed over 40 PMAs, 510(k)s, and De Novo classification requests for tests identified by the manufacturer as LDTs, and has approved, cleared, or granted De Novo classification for roughly half of those tests under authorities in the FD&C Act specifically reserved for "devices." FDA has also received many EUA requests from laboratories and has authorized over 150 such tests for emergency use, an authority that is also limited to "devices" or other FDA-regulated medical products.

2. Past FDA Initiatives To Address LDTs

In light of FDA's recognition that LDTs are devices and our increasing concerns about IVDs offered as LDTs (as detailed in the "Need for the Rule" section, section III.B of this

document), over the years the Agency has considered various ways to address IVDs manufactured by laboratories that raise safety or effectiveness concerns. In 1997, FDA sought to address these concerns by establishing restrictions on the sale, distribution, and use of analyte specific reagents (ASRs), which the Agency described as the "primary ingredients" of most LDTs (62 FR 62243 at 62249). In 2006, FDA issued a draft guidance outlining a different enforcement approach for a type of LDT known as an in vitro diagnostic multivariate index assay (IVDMIA),[12] which raised particular safety and effectiveness concerns (Ref. 45). FDA later determined that it should engage in a more comprehensive effort to oversee LDTs, in part due to stakeholder feedback.

Consistent with this determination, in 2010, FDA announced plans to develop a broader approach to the oversight of LDTs. The Agency held a 2-day public meeting and opened a docket for public comment (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) (Refs. 48 and 49). In those draft guidance documents, FDA proposed to implement a risk-based oversight framework for IVDs offered as LDTs, with a phased enforcement strategy. 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

[12] As defined in the draft guidance document, IVDMIAs are "test systems that employ data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease." The draft guidance document further characterized IVDMIAs as having the following three features: they use clinical data to empirically identify variables and derive weights/coefficients used in an algorithm; they employ that algorithm to calculate a patient-specific result, which cannot be independently derived and confirmed by another laboratory (absent access to proprietary information used in the development and derivation of the test); and they report that result, which cannot be interpreted by a well-trained healthcare practitioner using prior knowledge of medicine in the absence of information from the test developer regarding clinical performance and effectiveness.

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 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.

On January 13, 2017, FDA issued a discussion paper (2017 Discussion Paper) synthesizing the feedback that had been provided to the Agency, following a choice by FDA not to finalize the draft guidance documents to allow for further public discussion and to provide an opportunity for Congress to develop legislation for a new regulatory framework encompassing all IVDs that appropriately balances patient protection with continued access and innovation (Ref. 50).

In August 2020, HHS posted a statement on its website entitled "Rescission of Guidances and Other Informal Issuances," which stated, among other things, that "the department has determined that the Food and Drug Administration ('FDA') will not require premarket review of laboratory developed tests ('LDT') absent notice-and-comment rulemaking" (Ref. 57).[13] This statement was informed by advice in a legal memorandum from the HHS Office of General Counsel (see Ref. 59). In November 2021, based on new advice from the HHS Office of General Counsel, HHS leadership determined that the August 2020 statement no longer represented the Department's policy or legal views (Ref. 59). HHS Secretary Xavier Becerra publicly announced the withdrawal of the statement on November 15, 2021 (Ref. 60). Various news outlets have reported on these events (Refs. 61 to 64).

[13] HHS also posted an accompanying document entitled "FAQs on Laboratory Developed Tests (LDTs)" on its website (Ref. 58).

IV. Legal Authority

FDA is proposing to issue 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 (21 U.S.C. 321(h)(1), 331, 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 371, 372, 374, and 381). 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 "FDA's Current Regulatory Framework" section (section III.C.). For additional discussion of how these legal authorities apply to LDTs, see "Legal Basis for the Proposed Amendment" section (section V.B.).

V. Description of the Proposed Amendment to the Definition of In Vitro Diagnostic Products

A. Proposed Amendment

We are proposing to amend part 809, subpart A, specifically § 809.3, by updating the definition of "in vitro diagnostic products" to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory. IVDs are defined 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" (§ 809.3). This amendment would reflect FDA's longstanding view that LDTs are devices under the FD&C Act, and would reflect the fact that the device definition in the FD&C Act does not differentiate between entities manufacturing the device. In other words, whether an IVD is a device does not depend on where or by whom the IVD is manufactured.

FDA is also proposing to amend 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, 134 Stat. 4915). 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).

B. Legal Basis for the Proposed Amendment

If amended as proposed, § 809.3 would express in plain terms that IVDs, including test systems, fall within the definition of a device in section 201(h)(1) of the FD&C Act when they have been manufactured by laboratories. In this subsection, FDA sets forth the legal reasoning for this position.

1. In Vitro Diagnostic Test Systems Are Devices

The FD&C Act defines a device as, in relevant part, "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" (see 21 U.S.C. 321(h)(1); see also 21 U.S.C. 360j(o) (identifying circumstances under which software is and is not within the device definition)). This definition includes IVD test systems. Test systems

are sets of IVDs--for example, reagents, instruments, specimen collection devices, software, and other related materials--that function together to produce a test result. See, e.g., § 809.10(a)(9)(iii) (21 CFR 809.10(a)(9)(iii)) (discussing "multiple unit products which require the use of included units together as a system"); id. § 809.10(b) (referring to reagents and instruments within a system). According to a straightforward reading of the statutory text, these systems are "apparatus[es]," "contrivance[s]," and articles that are "similar or related" to "instrument[s]" and "in vitro reagent[s]," that are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease. They consist of individual parts that have their own regulatory identity, but, when combined, constitute a new device.

The device definition expressly contemplates this scenario because it provides that both an overall article and each of its "components" and "parts" are devices subject to regulation. (21 U.S.C. 321(h)(1); *cf. Shuker* v. *Smith & Nephew, PLC*, 885 F.3d 760, 768 (3d Cir. 2018) (describing the distinct status of a "system that is itself a 'device' but that is comprised of Class II [device] components in addition to one or more Class III [device] components").) The word "apparatus," which is defined as "a set of materials or equipment designed for a particular use," encompasses test systems by its plain terms. (See Apparatus, Merriam-Webster.com (last accessed June 28, 2023); 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").) Consistent with this analysis, FDA's definition of an "in vitro diagnostic product," which was first promulgated in 1973 and is still in effect today, identifies a "system" as a type of IVD and a device under the FD&C Act. (Section 809.3 (IVDs include "reagents, instruments, and systems"); see 38 FR 7096 at 7098 (March 15, 1973).)

The regulation of test systems is important because test systems are generally the IVDs that produce a result--a "positive" or "negative" (such as what patients receive in the context of COVID-19 diagnostic tests), a quantitative value (such as a concentration of glucose), or perhaps

a more detailed report of results. The quality of test results is generally what defines both the risks and benefits of IVDs: the risks stem from inaccurate, unreliable, incomplete, or misleading test results, and the benefits stem from accurate, reliable, and complete test results. For that reason, test systems and their results are a key focus of FDA's regulation of IVDs. FDA has issued over 350 regulations classifying different types of test systems (see generally 21 CFR parts 862, 864, 866) and has evaluated the performance and results of innumerable test systems over the course of decades. Patients and healthcare professionals rely on FDA to help ensure the validity of test systems, and conventional IVD manufacturers have built their business around this premise.

The focus on test systems and their results is not new; it has been a consistent theme throughout the history of FDA's regulation of IVDs. Congress expressly granted FDA authority over diagnostic products in 1938. (Federal Food, Drug and Cosmetic Act (June 25, 1938), Pub. L. 75-717, 52 Stat. 1040 (defining "drug" and "device" with reference to an intended use in "diagnosis," among other things).) Following the 1938 Act, FDA took action against diagnostic products, including against a system intended to diagnose illness based on human blood samples. (See *Drown* v. *United States*, 198 F.2d 999, 1001 (9th Cir. 1952).) And, in the early 1970s, FDA established a specific IVD regulatory program in response to "rapid growth in development of in vitro diagnostic products combined with the increasing use and reliance on the results by physicians, hospital personnel, and clinical laboratories." (37 FR 819, January 19, 1972). This program addressed the "need [for] closer scrutiny because of the possibility that inaccurate and unreliable results may be obtained." Id. FDA issued final regulations establishing controls over IVDs, including "systems," in 1973 (38 FR 7096 at 7098) (creating, among other things, "product class standards" to set "performance requirements necessary to assure accuracy and reliability of results"). FDA's increasing concerns about these products was evident from the fact that--even before Congress expanded the Agency's device authorities in 1976--it applied the *drug* authorities to certain IVDs. The Supreme Court upheld that application in *Bacto-Unidisk*,

394 U.S. at 800-01.

In 1976, Congress enacted the MDA, sweeping legislation meant to broaden and strengthen FDA's authority over devices. (See, e.g., H.R. Rep. 94-853 at 11 (February 29, 1976).) The MDA included revisions to the definition of "device" to clarify that IVDs should be regulated under the new, more robust device authorities. (Medical Device Amendments of 1976, Pub. L. 94-295, 90 Stat. 539 (adding the term "in vitro reagent" to the definition of a device); S. Rep. No. 93-670 at 16 (January 29, 1974) ("The 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 legislative history shows that Congress had serious concerns about test systems and sought to empower FDA to address them. (See, e.g., S. Rep. No. 93-670 at 3-4 (January 29, 1974) (describing with concern "quack devices" such as a "diagnostic service" in which "[p]ractitioners . . . mailed in the blood spots taken from their patients," "[t]he blood-spotted paper was put into a slot of the electrical device called the 'Radioscope' while the operator stroked with a wand the abdomen of a person holding metal plates connected to the device," and "the operator determined from this the identity, kind, location, and significance of any disease present").) Congress also contemplated performance standards relevant to test systems, such as required labeling with "ranges of accuracy of diagnosis." (H.R. Rep. 94-853 at 27.) Thus, in the MDA, Congress endorsed FDA's focus on test systems and their results.

2. Test Systems Manufactured by Laboratories Are Devices

The definition of "device" in the FD&C Act encompasses test systems regardless of where or by whom they are manufactured. (See 21 U.S.C. 321(h)(1).) In particular, the definition contains no exception or limitation for devices manufactured by laboratories. "Congress expresses its intentions through statutory text passed by both Houses and signed by the President (or passed over a Presidential veto)." (*Oklahoma* v. *Castro-Huerta*, 142 S. Ct.

2486, 2496 (2022).) If Congress had intended such a limitation, it could have said so. Instead, Congress made clear that the definition does not turn on the type of entity manufacturing the device: for example, the statute expressly recognizes that even "practitioners licensed by law to prescribe or administer … devices" (the professionals most closely associated with traditional medical practice) can "manufacture … devices," though they may be exempt from certain requirements when they do so "solely for use in the course of their professional practice."[14] (See 21 U.S.C. 360(g)(2); see also 21 U.S.C. 360i(c)(1), 374(a)(2)(B).)

Courts have repeatedly recognized that articles manufactured by medical professionals fall within FDA's jurisdiction (e.g., *United States* v. *Regenerative Sciences*, 741 F.3d 1314 (D.C. Cir. 2014) (holding that doctors "producing, as part of their medical practice," a "drug" under the FD&C Act violated the FD&C Act); *Drown* v. *United States*, 198 F.2d 999, 1001 (9th Cir. 1952) (upholding FDA action against chiropractor who "manufacture[d] certain photographic, therapeutic and diagnostic instruments of her own design which she use[d] in her practice")). As the D.C. Circuit in *Regenerative Sciences* observed, an approach that rejects "the [FD&C Act]'s regulation of doctors" would "create an enormous gap in the [FD&C Act]'s coverage." (741 F.3d at 1320.)

The inclusion of articles in the FD&C Act's definition of a device without regard to the identity of their manufacturer makes particular sense in the context of test systems. Today, in FDA's experience, there is little distinction between the test systems manufactured by laboratories and other manufacturers. These systems generally consist of highly specialized

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[14] These exemptions apply when a practitioner (1) is licensed by law to prescribe or administer a device such as an IVD, (2) manufactures that device, and (3) does so "solely for use in the course of [his or her] professional practice." Thus, these exemptions apply to practitioners, not entities such as corporate or hospital laboratories that employ licensed practitioners. For example, FDA has long held that hospitals that reprocess single-use devices are subject to registration and other requirements under the FD&C Act because they are the owners/operators, manufacturers, etc. even though those hospitals employ licensed practitioners. *See Frequently-Asked-Questions about the Reprocessing and Reuse of Single-Use Devices by Third-Party and Hospital Reprocessors; Final Guidance for Industry and FDA Staff* (July 2001), available at https://www.fda.gov/media/71057/download (stating "Third-party and hospital reprocessors of single-use devices (SUDs) are subject to all the regulatory requirements currently applicable to original equipment manufacturers, including premarket submission requirements" and including a Q&A that provides instructions on how to register and list for such entities).

components with complex functionality working in combination; they rarely resemble the "1976-type" tests discussed in this rule. For example, a modern-day next generation sequencing (NGS) test system for genetic testing typically consists of (among other things) a DNA extraction kit to extract nucleic acids from a human sample; an NGS instrument that analyzes the nucleic-acid output and (after days) generates gigabytes of sequencing raw data; and multiple pieces of computer software that translate that raw data into a test report. The systems look the same, and function the same way, regardless of who manufactures them. And although not all systems look exactly like an NGS system, they do typically involve sophisticated instruments with advanced software that, when used in conjunction with other test components, produce the system's results. Their manufacture generally requires knowledge of bioinformatics, software development, and an underlying specialty, such as medical genetics--knowledge that is neither traditionally associated with nor unique to laboratories. FDA understands that many test systems offered as LDTs are designed at Fortune 500 companies (see Ref. 65) by a "development team," similar to how systems from conventional manufacturers are designed. And in FDA's experience, the individuals on these development teams generally have the same training and expertise regardless of whether they are employed by a "laboratory" organization or a conventional manufacturer. Even smaller laboratories use the same complex equipment for their systems, although they may purchase and use components that are labeled by other companies for "research use only." In short, there is nothing inherent in the nature or design of laboratory developed test systems that would justify exclusion from FDA's jurisdiction.

That is not to say that laboratories and conventional IVD manufacturers are identical. Laboratories do occupy a distinct role in diagnostic testing because they are the entities that generally *perform* the tests. Like many devices, such as a magnetic resonance imaging unit used by a trained technician, test systems are usually used by trained professionals. Laboratories that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing employ trained laboratorians to "run" test systems, and CLIA is the statutory

scheme that governs that work, as discussed in more detail in section III.B. However, a laboratory's role in performing test systems does not change its obligations under the FD&C Act when it is *manufacturing* test systems. As previously noted, the FD&C Act does not exclude medical professionals who manufacture devices from its scope, and the mere fact that a device is manufactured in connection with a medical service or procedure does not eliminate FDA's jurisdiction. (See *United States* v. *Regenerative Sciences*, 741 F.3d at 1319 ("Notwithstanding appellants' attempt to characterize this case as an effort by the FDA to 'restrict[] the use of an autologous stem cell *procedure*,' the focus of the FDA's regulation is on the *Mixture* [that is, the product that is created in connection with the procedure].").)

Although some commentators have argued that laboratory manufacturing is immune from regulation because it is within the "practice of medicine," that argument misconstrues the scope of the FD&C Act's "practice of medicine" provision. Section 1006 of the FD&C Act (21 U.S.C. 396) provides: "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." Section 1006 carves out a specific zone of protected conduct that does not reach laboratory manufacturing of test systems. 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. (*Judge Rotenberg Educ. Ctr., Inc.* v. *United States*, 3 F.4th at 395 (emphases added); *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").) The statutory provision 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." It does not apply to the manufacture of

new test systems. The manufacture of a new device falls squarely within FDA's realm. *Cf. United States* v. *Regenerative Sciences*, 741 F.3d at 1320 ("[W]hile the [FD&C Act] was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for prescribing by physicians.") (quoting *United States* v. *Evers*, 643 F.2d 1043, 1048 (1981)). The fact that healthcare practitioners may prescribe a device, such as a test system, in the context of a healthcare practitioner-patient relationship does not mean that entities manufacturing that device can escape regulation. If that were the case, few devices would be regulated, because most are intended for use by healthcare practitioners in the context of a healthcare practitioner-patient relationship.

Furthermore, contrary to what some commentators have suggested, CLIA did not repeal FDA's authority over IVDs manufactured by laboratories, which dates back to at least 1938. CLIA does not expressly repeal FDA's authority, nor was FDA's authority repealed by implication. "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. 40). As explained in section III.B, CLIA puts a focus on the proficiency with which laboratories perform clinical testing, and the FD&C Act puts a focus on the manufacturing of test systems. 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.* v. *Sullivan*, 791 F. Supp. 1499, 1509 (D. Kan. 1992) (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).)

In fact, Congress has affirmed that test systems manufactured by laboratories are devices under the FD&C Act. In the Protecting Access to Medicare Act of 2014 (PAMA) (Pub. L. 113-93), Congress listed 510(k) clearance or premarket approval under the FD&C Act as one of several bases for Medicare payment for an "advanced diagnostic laboratory test," which is defined in part as a clinical diagnostic laboratory test "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)" (section 216(a) of PAMA). If such laboratory tests were not devices, the 510(k) clearance and premarket approval provisions would not apply to them and the inclusion of such provisions would be pointless and ineffectual. In addition, Congress indicated that clinical laboratory tests are devices in 2016 amendments to the FD&C Act. (21 U.S.C. 360j(o)(1)(D) (repeatedly referring to "clinical laboratory test or *other* device data") (emphasis added).)

The FD&C Act confers jurisdiction on FDA to regulate test systems, a point that has been codified in FDA's regulations for more than half a century. And nothing in the text, history, or purpose of the statute suggests that test systems manufactured by laboratories are excluded from that jurisdiction. This interpretation is not only the most straightforward reading of the statute, it is also the most reasonable: any other interpretation would create a bifurcated scheme in which systems that are functionally identical are treated differently under the law.

3. FDA's Jurisdiction Over IVDs Manufactured by Laboratories Is Not Altered by the FD&C Act's Provisions Related to Interstate Commerce and Commercial Distribution

Modern Commerce Clause jurisprudence holds that Congress has "authority to regulate even purely local activities that are part of an economic 'class of activities' that have a substantial effect on interstate commerce." (*United States* v. *Regenerative Sciences*, 741 F.3d at 1320 (quoting *Gonzales v. Raich*, 545 U.S. 1, 17 (2005)).) Thus, few have disputed that Congress possesses the power to grant FDA authority to regulate even purely intrastate activities.

However, some commentators have asserted that language in the FD&C Act referencing "interstate commerce" and "commercial distribution" precludes FDA from regulating IVDs that are designed, manufactured, and used in a single laboratory. As discussed below, these assertions lack merit.

a. Interstate commerce. There is no overarching requirement in the FD&C Act that FDA-regulated articles have a particular nexus with interstate commerce. Interstate commerce is not a prerequisite to FDA jurisdiction (beyond the constitutional minimum). Rather, under the FD&C Act, a limited number of provisions include specific interstate commerce "elements," and thus require a particular connection with interstate commerce in order for those provisions to apply. For example, certain of the FD&C Act's "prohibited acts" contain an interstate commerce element that must be satisfied before the government can bring an enforcement action under those provisions (e.g., 21 U.S.C. 331(a), (c), (d), and (k)). But relatively few of the FD&C Act's device provisions 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); id. 331(p) (prohibiting the failure to register a device establishment without reference to interstate commerce); id. 331(q)(1) (prohibiting the failure to comply with device investigational-use requirements without reference to interstate commerce); id. 331(fff)(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 to interstate commerce); see generally *United States* v. *Walsh*, 331 U.S. 432, 434-36 (1947) (finding no interstate commerce element to 21 U.S.C. 331(h), which prohibits false guaranties) ("[21 U.S.C. 331(a)] is directed to illegal interstate shipments, while [21 U.S.C. 331(h)] is directed to the giving of false guaranties").) 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. For devices, the FD&C Act

imposes obligations even where there is no interstate commerce element and likewise gives FDA authority to take action when there is a violation of those obligations. Thus, FDA does not, for example, somehow lose jurisdiction if a particular device has not been "introduced" into interstate commerce.

In fact, Congress intentionally revised a provision of the FD&C Act to ensure that FDA could take action against devices without satisfying any particular interstate commerce element. In the MDA, Congress revised the seizure provisions in section 304 of the FD&C Act to "permit seizure of devices without reference to interstate commerce" because the previous interstate commerce requirement "ha[d] been a burden to the effective enforcement of existing authorities" and "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." (H.R. Rep. 94-853 at 15; see 21 U.S.C. 334(a)(2).) In other words, Congress recognized that the interstate commerce element in this provision did not advance the goals of the MDA. Consistent with that view, the FD&C Act grants FDA wide-ranging authority over devices, including IVDs, and that general authority does not turn on a connection with interstate commerce above the constitutional minimum.

In addition, 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 applies even when a problematic device has not been introduced in 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 is satisfied if the components used in manufacturing the product have traveled in interstate commerce. (See *United States* v. *Regenerative Sciences*, 741 F.3d at 1320-21 (upholding FDA enforcement action under 331(k) because a drug component had traveled in interstate commerce); *Baker* v. *United States*, 932 F.2d

813, 815 (9th Cir. 1991); *United States* v. *Dianovin Pharm., Inc*., 475 F.2d 100, 102 (1st Cir. 1973).) At least some components of test systems, such as general purpose reagents, ASRs, instruments, and collection devices, are usually shipped in interstate commerce even if the system itself is designed, manufactured, and used solely in the laboratory (i.e., intrastate). And section 709 of the FD&C Act (21 U.S.C. 379a) establishes a presumption of interstate commerce in 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.").

Some commentators have cited the interstate commerce element in section 510(k) of the FD&C Act to raise questions about FDA's authority over LDTs. Section 510(k) provides 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. Under this line of argument, laboratories that design, manufacture, and use an IVD in a single laboratory are not proposing to introduce their IVD into interstate commerce, and therefore section 510(k) does not apply to them. That argument, however, does not lead to the conclusion that FDA lacks jurisdiction over LDTs or that none of the FD&C Act requirements apply to LDTs. It would mean only that section 510(k) does not apply. And if accepted, the only practical consequence of that assertion would be that affected laboratories are subject to *more burdensome* requirements under the FD&C Act.

In particular, if section 510(k) is construed to mean that such IVDs are not eligible for the premarket notification pathway, that would only mean that those IVDs (unless they are 510(k)-exempt, in which case section 510(k) would not apply anyway, or are for investigational use) would be forced into the more rigorous review pathways of premarket approval or authorization through the De Novo pathway. That is because under section 513(f)(l) of the FD&C Act, a postamendments device, i.e., a device that was "not introduced or delivered for introduction into

interstate commerce for commercial distribution before [May 28, 1976]," is a class III device by operation of law (21 U.S.C. 360c(f)(1)). If such a device cannot be found to be substantially equivalent through the premarket notification pathway, it must either have an approved PMA (21 U.S.C. 360e(a)), or be reclassified and gain authorization through a pathway such as the De Novo process (21 U.S.C. 360c(f)(2)(A)(ii)). Thus, under this theory, laboratories would not escape FDA regulation--they would face heavier regulation. However, because section 510(k) does not, in fact, preclude regulated entities from submitting premarket notifications even assuming their devices are not introduced into interstate commerce, and because laboratories have every incentive to take the less burdensome path to market of 510(k) notification, the 510(k) pathway should play the same role in device reclassification (21 U.S.C. 360c(f)) for IVDs offered as LDTs as for any other device. 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.

b. Commercial distribution. The phrase "for commercial distribution" also appears in various device provisions of the FD&C Act, and some commentators have asserted that this phrase, too, signals that FDA lacks authority over LDTs. For example, they point to the 510(k) premarket notification requirement, which is triggered when a person who is required to register "proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use" (21 U.S.C. 360(k)). As with "interstate commerce," the presence of this phrase in that provision and certain other specific device provisions does not bear on the Agency's overall jurisdiction. Furthermore, LDTs are for commercial distribution, so the presence of the phrase does not change the operation of those provisions with respect to these IVDs.

Under our longstanding, judicially endorsed interpretation, "commercial distribution" does *not* require the physical transfer of an object, as some commentators have argued. Instead, the legislative history, FDA's near-contemporaneous regulation, and at least one judicial decision

reflect that the phrase "commercial distribution" means "on the market." A House Report issued 3 months before enactment of the MDA contains an unusually clear statement of the intended meaning of the phrase: "'Commercial distribution' is the functional equivalent of the popular phrase 'on the market.'" (H.R. Rep. No. 94-853 at 36) FDA's regulations implementing the registration, listing, and 510(k) provisions, which were finalized in 1977 (soon after enactment of the MDA), similarly define commercial distribution as "any distribution of a device intended for human use which is held or offered for sale." (21 CFR 807.3(b)) In the preambles to the proposed and final rule, FDA equated the term with the phrase "on the market" (41 FR 37458 at 37459 (September 3, 1976); 42 FR 42520 at 42524 (August 23, 1977)). A court has also endorsed this interpretation of the term (*United States* v. *An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 994-95 (W.D. Mich. 1985) (giving deference to FDA's reasonable interpretation of "commercial distribution" to mean, "in its popular sense, 'on the market'")). These sources show that the term does not relate to physical movement, and because IVDs manufactured by laboratories (including LDTs) generally are "on the market," they are for commercial distribution.

VI. Description of the Proposed Enforcement Policy

Based on the considerations set forth in this preamble, FDA is proposing to end the general enforcement discretion approach for LDTs. However, FDA also recognizes that many IVDs manufactured by laboratories are currently being marketed as LDTs, and that a sudden change could negatively affect the public, including patients and industry. In particular, FDA understands that the healthcare community and patients have been using these IVDs, and that coming into compliance will take time for manufacturers. FDA also recognizes that we should consider Agency resources. For additional information regarding the estimated costs associated with this rulemaking, see the Preliminary Economic Analysis of Impacts (Ref. 34).

To achieve greater oversight in a manner that accounts for the various considerations, FDA is proposing to gradually end its general enforcement discretion approach in stages, as

described below (hereinafter "the phaseout policy"). FDA's intent is that, following a 4-year phaseout period, IVDs offered as LDTs generally would be expected to meet applicable requirements.

Although FDA is proposing to gradually end 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 continued enforcement discretion approach for certain IVDs discussed below, FDA retains discretion to pursue enforcement action at any time against violative IVDs when appropriate.

Moreover, FDA has adopted and intends to continue adopting enforcement discretion policies for certain types of IVDs in certain circumstances, as appropriate. For example, FDA issued guidance documents with enforcement discretion policies for certain COVID-19 and Mpox tests at the beginning of each declared emergency (as described further below), and intends to issue a draft guidance with an enforcement policy for IVDs for emerging outbreaks offered prior to FDA review to address the immediate public health need. FDA will seek public comment on such draft guidance in accordance with good guidance practices (see 21 CFR 10.115).

With this notice of proposed rulemaking, FDA seeks public comment on whether specific enforcement discretion policies would be appropriate for IVDs offered as LDTs for other public health scenarios. If so, please provide a description of those scenarios, an explanation of why enforcement discretion policies with respect to those scenarios would be appropriate, and any relevant evidence to support such policies. FDA would also appreciate public comment on what, if any, unintended consequences may result from the proposed phaseout policy to certain patient populations (for example, Medicare beneficiaries, rural populations, etc.) and what steps could be taken to mitigate those consequences.

FDA's proposed phaseout policy, including the scope and phaseout timeline, is set forth

below.

A. Scope

While FDA's general enforcement discretion approach has been focused on LDTs, FDA is proposing a broader scope for the phaseout policy. Specifically, FDA is proposing to apply 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,[15] 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.[16] Throughout this preamble, these IVDs are referred to as "IVDs offered as LDTs." FDA is proposing 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 they do not fit what FDA generally considers to be an LDT. As previously discussed, FDA has made a preliminary determination to structure the phaseout in a way that avoids undue disruption to the testing market. This is important even for certain IVDs currently on the market that do not fall within the scope of FDA's general enforcement discretion approach.

Although FDA is proposing this broader scope for the phaseout policy, it does not intend to sweep in certain tests that were excluded from the general enforcement discretion approach, as reflected in compliance patterns, multiple public FDA actions and communications, or both. These tests are:

1. Tests that are intended as blood donor screening or human cells, tissues, and cellular and tissue-based products (HCT/Ps) donor screening tests required for infectious

[15] 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. 32, 40, and 54).

[16] 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.

disease testing under 21 CFR 610.40 and 1271.80(c), respectively, or for determination of blood group and Rh factors required under 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 licensed, approved, or cleared by FDA for such use. Blood and HCT/P establishments must register with FDA and are subject to FDA inspection (see 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. Based on FDA experience, establishments have been generally complying with these requirements (see, e.g., Refs. 66 and 67).

2. 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. 51 and 52). In addition, consistent with the Government Accountability Office's 2022 recommendation that "FDA should develop a policy for the use of enforcement discretion regarding unauthorized tests in future public health emergencies," FDA intends to issue guidance on factors to consider in adopting such enforcement discretion policies (Ref. 68). FDA has communicated its expectations regarding tests for emergency use in guidance and elsewhere, including "It has come to

our attention" letters posted on FDA's website and other public communications (see, e.g., Refs. 51 to 54, 69, and 70).

3. 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. 48, 55, and 71 to 75). 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, and make decisions (such as a decision to stop medication) without this expert intermediary, there is a heightened need for FDA oversight.

For these categories of tests, FDA has generally expected applicable requirements to be met, and we are not proposing to change that approach.

FDA notes that the manufacturing of test components *outside* of a laboratory--for example, when the same entity owns both the laboratory and a manufacturing facility separate from the laboratory--does not fall within FDA's general enforcement discretion approach. FDA's approach has long been specific to *laboratory* development (e.g., 61 FR 10484 ("*in-house* developed tests have not been actively regulated by the Agency") (emphasis added); Ref. 48 (describing an LDT as an IVD that is "designed, manufactured, and used within a single laboratory"). The proposed phaseout policy would not change FDA's longstanding expectation that IVD manufacturing activities occurring outside of a CLIA-certified laboratory comply with applicable device requirements.

In addition, for certain categories of tests manufactured by laboratories, FDA is proposing to continue to apply the current general enforcement discretion approach going forward. 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: use of manual techniques (without automation) performed by laboratory personnel with specialized expertise; use of components legally marketed for clinical use; and 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.A). 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 made a preliminary determination that the risks are sufficiently mitigated such that FDA's general enforcement discretion approach for LDTs should continue to apply. 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.

FDA is also proposing to continue to apply the general enforcement discretion approach to Human Leukocyte Antigen (HLA) tests that are designed, manufactured, and used in 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. FDA has made a preliminary determination that HLA LDTs for transplantation used in histocompatibility laboratories that meet the regulatory requirements under CLIA to perform high complexity testing, when used in connection with organ, stem cell, and tissue transplantation for certain purposes as described in this paragraph, are unique in that they are generally developed, and the testing is generally performed, in urgent, life-saving situations for the patient. 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. Further, these tests are often individualized within each medical facility, for example, they include reagents that reflect local HLA polymorphisms and patient demographics. Note that the general enforcement discretion approach does not apply to HLA tests used for blood transfusion as such tests are highly standardized across institutions; FDA intends to continue to enforce applicable requirements for HLA tests used for blood transfusion.

FDA also intends to maintain its longstanding enforcement discretion approach for tests intended solely for forensic (law enforcement) purposes. This approach has been in place for over 20 years and 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. We seek comment on any implications of continued enforcement discretion with regard to LDTs used for law enforcement purposes and any factors that FDA should consider--particularly as it relates to civil rights and equity--related to the scientific validity and accuracy of these tests.

In addition, tests exclusively used 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. These tests would not be affected by the phaseout policy. The results of these tests are generally used for trending on a population basis. Public health authorities also have access to test results from non-surveillance tests that are FDA approved, cleared, or authorized and that are reported under State reporting

laws for infectious and other diseases. In addition, during a public health emergency, if there was a 564 declaration (as there was for past public health emergencies), FDA could require test result reporting to public health authorities under emergency use authorizations, as appropriate.

In 2017, FDA indicated support for less oversight of other categories of tests, such as low-risk tests (class I devices), tests currently on the market, and tests for rare diseases. However, FDA has accumulated information in the intervening years that suggests we should treat these categories of tests similarly to other FDA-regulated tests. For example, as discussed above in section III.B, FDA has gained additional information showing that there is a high variability in the performance of IVDs offered as LDTs that are currently on the market, including in circumstances where the test technology is relatively simple and well-understood, where the tests are for rare diseases, and where the tests are low risk. Among other things, FDA's recent experience with tests for COVID-19 suggests that many tests manufactured by laboratories are not appropriately validated. Compliance with premarket review requirements (when applicable), QS requirements, and registration and listing requirements would help assure that these IVDs work as intended, enable FDA to keep track of IVDs offered as LDTs (and, for example, help FDA locate IVDs that are raising concerns or independently evaluate the risk status of marketed IVDs), assist with FDA's inspection and planning efforts, and make information available to patients and healthcare providers that may inform the selection of particular IVDs for use. Therefore, FDA is now proposing to end the general enforcement discretion approach, via a phaseout approach, with respect to premarket review requirements (as applicable), QS requirements, and registration and listing requirements for these tests, in addition to medical device reporting (MDR) requirements (i.e., reporting of adverse events), correction and removal reporting requirements, and other requirements applicable to such tests. Based on the information available at this time, FDA has made a preliminary determination that this proposal appropriately balances the relevant considerations with respect to these tests, including currently marketed IVDs offered as LDTs.

However, FDA expects that some stakeholders will suggest that FDA continue to maintain the current general enforcement discretion approach with respect to premarket review and some or all QS requirements for currently marketed LDTs or a subset of currently marketed LDTs (i.e., what some previously referred to as "grandfathering"). To the extent commenters suggest such an approach for FDA's consideration, FDA requests information to support such an approach, including the following:

- Given the information in the "Need for the Rule" section of this preamble in particular, what would be the public health rationale for generally exercising enforcement discretion with respect to premarket review and some or all QS requirements, for LDTs that are being offered as of the date of issuance of this proposed rule and are not changed with respect to indications for use or performance after that date? Please provide data to support such an approach. Also, if you think there are steps that might help support such an approach, including ideas that might help to address the public health concerns discussed in the "Need for the Rule" section, please describe them, and include a rationale and any supporting evidence.
- If commenters suggest maintaining the general enforcement discretion approach with respect to premarket review and QS requirements for a subset of LDTs (e.g., low and moderate risk LDTs) currently on the market that are being offered as of the date of issuance of this proposed rule and are not changed with respect to indications for use or performance after that date, what would be the public health rationale to support such an approach? Please provide any data supporting such an approach. Also, if you think there are steps that might help support such an approach, including ideas that might help to address the public health concerns discussed in the "Need for the Rule" section, please describe them and include a rationale and any supporting evidence.

FDA recognizes that the phaseout of the general enforcement discretion approach described in this section may have a relatively greater impact on small laboratories. Therefore,

FDA seeks comment on the following:

- Is there a public health rationale to have a longer phaseout period for IVDs offered as LDTs by laboratories with annual receipts below a certain threshold (e.g., $150,000) (see Table 43 in the Preliminary Economic Analysis of Impacts (Ref. 34))? If so, please provide relevant data and comment specifically on an alternative recommended timeline.

In addition, FDA is aware that some AMCs have claimed that their laboratories operate under unique circumstances (such as being integrated into direct patient care) and therefore their tests should be treated differently than tests manufactured by other laboratories. Although FDA is not aware of an established definition of an AMC laboratory, one possible description is: a laboratory for which a certificate is in effect under CLIA and that meets the requirements under CLIA to perform tests of high-complexity; that is part of an accredited public or nonprofit private AMC that has a medical residency training program or fellowship program related to test development, application, and interpretation; and that is integrated into the direct medical care for a patient, including specimen collection, testing, interaction with the treating provider, and, as appropriate, patient treatment based on the test, all at the same physical location. FDA seeks comments on the following:

- What are the characteristics of AMC laboratories? Do the characteristics included above accurately describe AMC laboratories and in fact distinguish them from other laboratories?
- Should FDA continue the general enforcement discretion approach with respect to any requirements, such as premarket review requirements, for tests manufactured by AMC laboratories?
- If FDA should continue the general enforcement discretion approach with respect to any requirements, such as premarket review requirements, for tests manufactured by AMC laboratories, are there any additional considerations that should be taken into

account with respect to this approach, for example, whether an FDA cleared or approved test is available for the same intended use as the test manufactured by an AMC laboratory? Please provide a rationale and other information (e.g., data) to support any additional considerations.

- If FDA should have a different policy for AMC laboratories, what would be the public health rationale to support such a policy? For example, if integration of an AMC laboratory into direct patient care is included as a basis for a different policy, please include a public health rationale when explaining why and how such integration supports the different policy, and how integration could ensure that there is a reasonable assurance of IVD safety and effectiveness.
- If FDA should have a different policy for AMC laboratories, is there evidence to support such a policy?

FDA also is interested in and seeks comment on leveraging programs such as the New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP) or those within the Veterans Health Administration (VHA), as appropriate. In particular, FDA requests comment on whether it may 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. If FDA should continue to exercise enforcement discretion under these circumstances:

- What specific characteristics of and activities within these programs justify such an approach?
- Should the scope of such a policy be more limited for each program in question? For example, should FDA continue enforcement discretion for premarket review requirements and intend to enforce other requirements, such as reporting adverse events?
- Are there any additional considerations that should be taken into account?

Please provide a rationale and other information (e.g., data) to support any suggestions.

B. Stages

As previously discussed, FDA is proposing to gradually phase out its current general enforcement discretion approach so that most IVDs offered as LDTs would generally fall under the same enforcement approach as other IVDs. In developing the proposed phaseout policy, FDA has considered a number of factors, including the public health importance of better assuring the safety and effectiveness of IVDs offered as LDTs, the desire to avoid undue disruption to the testing market, the time it may take for laboratories to come into compliance with FDA requirements, the need for adequate resources to implement the phaseout policy in a manner that does not undermine reasonable expectations with regards to premarket review timing (per the Medical Device User Fee Amendments (MDUFA) V agreement), and the benefits of a relatively simple policy that can be easily understood and implemented. Keeping these factors in mind, FDA has structured the phaseout policy to contain five key stages:

- Stage 1: End the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements 1 year after FDA publishes a final phaseout policy, which FDA intends to issue in the preamble of the final rule.
- Stage 2: End the general enforcement discretion approach with respect to requirements other than MDR, correction and removal reporting, QS, and premarket review requirements 2 years after FDA publishes a final phaseout policy.
- Stage 3: End the general enforcement discretion approach with respect to QS requirements 3 years after FDA publishes a final phaseout policy.
- Stage 4: End the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs 3½ years after FDA publishes a final phaseout policy, but not before October 1, 2027.
- Stage 5: End the general enforcement discretion approach with respect to premarket review requirements for moderate risk and low risk IVDs (that require premarket

submissions) 4 years after FDA publishes a final phaseout policy, but not before April 1, 2028.

Each of these stages is discussed in further detail below. For each stage, FDA is proposing a period of time for laboratories to come into compliance before FDA intends to end the general enforcement discretion approach. FDA encourages laboratory manufacturers to begin early and work toward compliance with requirements sooner than the end of the specified timeframes. 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.

1. Stage 1: End the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements 1 year after FDA publishes a final phaseout policy.

FDA has structured the phaseout policy to obtain information about potentially harmful IVDs offered as LDTs as soon as feasible. As detailed elsewhere in this preamble, FDA is concerned that some of the IVDs offered as LDTs may be posing risks to patients. Therefore, FDA is prioritizing the phaseout of the general enforcement discretion approach for requirements that would help FDA identify and monitor significant issues with IVDs offered as LDTs, consistent with other considerations described in this proposed policy.

Enforcement of the MDR requirements under 21 U.S.C. 360i(a) through (c) and 21 CFR part 803, in particular, would 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 preliminary determination that gathering this information 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 analytical and clinical validity 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. Because FDA intends for the phaseout of the general enforcement discretion approach with respect to correction and removal reporting requirements to occur before phaseout of the general enforcement discretion approach with respect to registration and listing requirements, FDA intends to exercise enforcement discretion, such that it generally does not intend to enforce, the requirement to use the establishment registration number on such reports (21 CFR 806.10) when laboratories use their CLIA certificate number instead prior to registering.

FDA's proposal to phase out enforcement discretion for MDR requirements within 1 year after finalization of the policy is informed by comments FDA received in response to the draft guidance documents that FDA issued in 2014 proposing to implement an oversight framework for IVDs offered as LDTs. In 2014, FDA proposed a 6-month timeline for laboratory compliance with MDR requirements (Ref. 48), and we received comments suggesting that a longer period may be appropriate for the establishment of a system to identify, review, and report adverse events. Based in part on those comments, FDA is now proposing a 1-year time period for laboratories to come into compliance with the MDR requirements. In conjunction with the phaseout of the general enforcement discretion approach with respect to the MDR requirements, FDA is also proposing to end the general enforcement discretion approach with respect to the requirements of part 806, concerning reports of corrections and removals. Because MDRs frequently are a basis for corrections and removals, FDA views these requirements as working together to provide information to FDA about issues with device performance or quality. We anticipate that this 1-year time period is adequate, particularly given that laboratories should already have some processes in place for detecting

problems with their IVDs to comply with CLIA regulations.

2. Stage 2: End the general enforcement discretion approach with respect to requirements not covered during other stages of the phaseout policy 2 years after FDA publishes a final phaseout policy.

FDA is proposing to end the general enforcement discretion approach for requirements besides MDR, correction and removal reporting, QS, and premarket review requirements 2 years after the final policy is published. These other requirements include registration and listing requirements under 21 U.S.C. 360 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. 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.[17] We are therefore including these requirements in the phaseout policy.

FDA recognizes that this proposal is different from FDA's prior statements in the 2017 Discussion Paper regarding oversight of IVDs manufactured by laboratories with respect to certain requirements, for which the timing of FDA's expectations for compliance generally depended on the type of premarket review applicable to the device. However, upon review, FDA anticipates that it would better serve the public health and be simpler to phase out the general enforcement discretion approach for these requirements at the 2-year mark. For example, under this timeline, laboratories could work toward compliance with the stage 2 requirements without necessarily determining the risk category of their IVDs until later stages

[17] 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. 48).

of the proposed phaseout policy. Another advantage of this timeline is that FDA would obtain registration and listing information before the enforcement discretion phaseout date for premarket review requirements, which could give the Agency an initial understanding of the universe of IVDs offered as LDTs to facilitate premarket review of those IVDs. Based on its experience, FDA anticipates that 2 years is adequate time to come into compliance with the various requirements.

3. Stage 3: End the general enforcement discretion approach with respect to QS requirements 3 years after FDA publishes a final phaseout policy.

At the 3-year mark, FDA would expect compliance with the device CGMP requirements of the QS requirements under 21 U.S.C. 360j(f) and part 820 (21 CFR part 820). However, for IVDs for which all 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, FDA would expect compliance at the 3-year mark with some, but not all, of the QS requirements. 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 manufacturing activities regulated by FDA. For FDA to effectively leverage the CLIA assurances, this proposed approach would apply only when all manufacturing activities occur within a single laboratory and the IVD is not distributed outside that laboratory. However, even in the context of this approach, there are certain QS requirements for which CLIA regulations do not provide the assurances that FDA requirements would provide. These requirements include design controls under 21 CFR 820.30; purchasing controls (including supplier controls) under 21 CFR 820.50; acceptance activities (receiving, in-process, and finished device acceptance) under 21 CFR 820.80 and 21 CFR 820.86; corrective and preventative actions (CAPA) under 21 CFR 820.100; and records requirements

under part 820, subpart M. Because CLIA does not provide assurances relevant to these requirements, FDA is proposing to end the general enforcement discretion approach for these specific requirements for IVDs for which all manufacturing activities occur within a single CLIA-certified laboratory that meets the regulatory requirements to perform high complexity testing, and which are not distributed outside that laboratory, 3 years after finalizing this policy. For all other IVDs offered as LDTs and subject to this phaseout policy, FDA is proposing to end the general enforcement discretion approach for all QS requirements 3 years after finalizing this policy.

Based on its experience, FDA anticipates that 3 years is adequate time for laboratories to come into compliance with QS requirements. In addition, based on the discussion above regarding concerns with the quality and validation of IVDs offered as LDTs, FDA has made a preliminary determination that phasing out the general enforcement discretion approach for QS requirements later than 3 years would not be in the best interest of the public health. Compliance with QS requirements is critical to the quality and validity of IVDs offered as LDTs. For example, under the design controls of the QS requirements, laboratories would, among other things, generally have better procedures for validating the design of their tests, which would help to ensure that they are analytically and clinically valid (see Ref. 76).

FDA also notes that on February 23, 2022, FDA proposed to amend the device QS regulation, part 820, to align more closely with international consensus standards for devices (87 FR 10119). As stated in that proposed rule, the requirements, if finalized, would be substantially similar to the requirements of the current part 820, providing a similar level of assurance in a firm's quality management system, and FDA intends for this phaseout policy to apply with respect to any regulations promulgated through that rulemaking.

FDA intends to finalize amendments to the QS regulation expeditiously, such that the amended QS requirements would be in effect before the proposed beginning of stage 3. Upon the start of stage 3, or if the laboratory complies with QS requirements prior to the start of

stage 3, FDA would expect compliance with the QS requirements that are in effect at that time. For further information on the QS requirements that would be established pursuant to the amendments to the QS regulation, if finalized as proposed, please refer to the proposed codified at 87 FR 10119 at 10133 and 10134. Notably, the requirements relating to design controls, purchasing controls, acceptance activities, CAPA, and records requirements are set forth in the following ISO 13485 clauses as modified by the proposed 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 8.2.5, Subclause 8.2.6, and Subclause 8.3.

In addition, 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 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 21 CFR 820.1).

4. Stage 4: End the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs 3½ years after FDA publishes a final phaseout policy, but not before October 1, 2027.

FDA proposes that the phaseout date for the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs offered as LDTs (IVDs that may be eligible for classification into class III) should occur 3½ years from the time that FDA issues a final phaseout policy. The premarket review requirements are set forth in 21 U.S.C. 360e and 21 CFR part 814. FDA is proposing this time period because it is mindful that phasing out the general enforcement discretion approach on a timeline that is too short could cause undue disruption in the testing market. Among other things, we anticipate that 3½ years would provide sufficient notice and opportunity for laboratories manufacturing IVDs to plan for and prepare

PMAs and would appropriately account for any reliance interests. We note that 3½ years is a longer time period than was discussed in either the 2014 draft guidance documents or the 2017 Discussion Paper for the phaseout of the general enforcement discretion approach for premarket review requirements.

This timeline is also intended to align the phaseout date for the general enforcement discretion approach for premarket review requirements for high-risk IVDs offered as LDTs with the start of fiscal year 2028, which coincides with the beginning of a new user fee cycle. This alignment would provide an opportunity for industry participation in negotiations regarding the next user fee cycle with the knowledge that laboratory manufacturers would be expected to comply with premarket review requirements. (Although a trade association representing laboratories previously has participated in MDUFA negotiations, the prior negotiations have not incorporated similar expectations regarding laboratory compliance with premarket requirements.) Thus, we propose that this amount of time is appropriate to foster stability and consistency in the marketplace for the current MDUFA cycle, and would 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 would work with FDA to determine whether PMAs should be submitted for their IVDs.

Under FDA's proposed policy, FDA generally would not intend to enforce against IVDs offered as LDTs after a PMA has been submitted (within the 3½-year timeframe) until FDA completes its review of the application. 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.

Finally, FDA recognizes that the 2017 Discussion Paper described a possible premarket-review approach specific to LDTs for unmet needs. FDA has not included such an approach in this proposed policy because we anticipate that the 3½-year timeframe should be

sufficient for laboratories to meet premarket review requirements for each of their marketed IVDs, as applicable, including IVDs for unmet needs. FDA also anticipates that programs currently in place may facilitate the development and premarket authorization of IVDs for unmet needs. These programs include the Humanitarian Use Devices (HUD)/Humanitarian Device Exemption (HDE) program,[18] which, among other things, provides an exemption from the requirement to establish a reasonable assurance of effectiveness for devices intended for use in the treatment or diagnosis of rare diseases or conditions (21 U.S.C. 360j(m); 21 CFR part 814, subpart H), and the Breakthrough Devices program, which 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).

5. Stage 5: End the general enforcement discretion approach with respect to premarket review requirements for moderate risk and low risk IVDs (that require premarket submissions) 4 years after FDA publishes a final phaseout policy, but not before April 1, 2028.

FDA is proposing to end 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 after FDA publishes the final phaseout policy. 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

[18] Under the proposed phaseout policy, laboratories that intend to submit an HDE application should do so within the same 3½-year timeframe provided for submission of PMAs. As in the case of PMAs, under FDA's proposed policy, FDA generally would not intend to enforce against IVDs after an HDE application has been submitted (within the 3½-year timeframe) until FDA completes its review of the application.

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 intends this stage to begin no earlier than April 1, 2028. FDA's reasons for proposing this time period to phase out the general enforcement discretion approach with respect to premarket review requirements for moderate risk and low risk IVDs offered as LDTs are similar to those for the "stage 4" time period, except that FDA has lengthened the time period by 6 months in order to prioritize the review of applications for high-risk IVDs offered as LDTs (subject to premarket approval requirements), so that FDA can focus first on IVDs for which the consequences of a false result are most significant. FDA also recognizes that a greater number of IVDs are subject to the 510(k) requirements, as compared with premarket approval requirements, so a longer period of time for laboratories to come into compliance with these requirements may be appropriate, particularly for laboratories with large test menus.

FDA generally would not intend to enforce against IVDs offered as LDTs after a 510(k) or De Novo request has been submitted (within the 4-year timeframe) until FDA completes its review of the submission.

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. 77). We anticipate interest in the Third Party review program among test manufacturers, as well as potential new Third Party review organizations. In particular, FDA is aware of certain CLIA accreditation organizations that may be interested in potentially becoming Third Party reviewers under FDA's program, and to the extent laboratories are already familiar with these organizations, laboratories may be 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.

VII. Proposed Effective Date

The Agency proposes that any final rule based on this proposed rule will become effective 60 days after the date of publication of the final rule in the *Federal Register*.

VIII. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Executive Orders 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 Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they "have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of [the Office of Information and Regulatory Affairs (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 proposed rule is a significant regulatory action under Executive Order 12866 Section 3(f)(1).

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 proposed rule is likely to impose a substantial burden on the affected small entities, we find that the proposed 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 us to prepare a written statement that includes estimates of

anticipated impacts, before proposing "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 proposed rule would result in an expenditure in at least one year that meets or exceeds this amount.

This proposed rule, if finalized, would amend 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 VI, FDA intends to phase out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory would 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 would include a reduction in healthcare costs associated with unsafe or ineffective tests, including tests promoted with false or misleading claims, and from therapeutic decisions based on the results of those tests. Quantified benefits are the annualized sum of both health and non-health benefits. Unquantified benefits would include the reduction in costs from lawsuits and reduction in costs to healthcare systems.

Table 1 summarizes the annualized benefits, costs, and transfers of the proposed rule. At a 7 percent discount rate, 20-year annualized benefits range from $2.67 billion to $86.01 billion, with a primary estimate of $31.41 billion per year. At a 3 percent discount rate, 20-year annualized benefits range from $1.81 billion to $61.41 billion, with a primary estimate of $22.33 billion per year. At a 7 percent discount rate, 20-year annualized costs range from about $2.52 billion to $19.45 billion, with a primary estimate of $5.87 billion per year. At a 3 percent discount rate, annualized costs range from about $2.39 billion to $18.55 billion, with a primary estimate of $5.60 billion per year. At a 7 percent discount rate, 20-year annualized transfers range from $100 million to $452 million, with a primary estimate of $226 million per year. At a

3 percent discount rate, 20-year annualized transfers range from $121 million to $538 million, with a primary estimate of $269 million per year.

Table 1. Summary of Benefits, Costs and Transfers of the Proposed 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)	$31,408	$2,670	$86,013	2022	7%	20 years	
		$22,332	$1,810	$61,413	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized ($m/year)	$5,874	$2,522	$19,452	2022	7%	20 years	A portion of foreign costs could be passed on to domestic consumers. We estimate that up to $30.73 million in annualized costs (7%, 20 years) to foreign facilities could be passed on to domestic consumers.
		$5,598	$2,392	$18,549	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized ($m/year)	$226	$100	$452	2022	7%	20 years	
		$269	$121	$538	2022	3%	20 years	
		From: Device Industry			To: FDA			
	Other Annualized Monetized ($m/year)					7%		
						3%		
		From:			To:			
Effects	State, Local, or Tribal Government: Small Business: The proposed rule is likely to have a significant economic impact on a substantial number of small laboratories that manufacture IVDs offered as LDTs. Wages: Growth:							

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 34) 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 tentatively concludes that this proposed rule contains no new collections of information. However, FDA does assume that there will need to be corresponding adjustments to the burden estimates for relevant approved collections of information before the relevant phaseout stage begins and any such collection of information would not be as a result of the implementation of the proposed rule. FDA tentatively concludes that the following information collections will need adjustment before the relevant phaseout stage begins: Office of Management and Budget (OMB) control number 0910-0437, Medical Device Reporting; OMB control number 0910-0359, Corrections and Removals; OMB control number 0910-0625, Device Registration and Listing; OMB control number 0910-0485, Labeling; OMB control number 0910-0078, Investigational Device Exemption; OMB control number 0910-0073, Quality Systems; OMB control number 0910-0231, Premarket Approval; OMB control number 0910-0332, Humanitarian Device Exemption; OMB control number 0910-0756, Q-Submissions; OMB control number 0910-0120, Premarket Notification; and OMB control number 0910-0844 De Novo. 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).

XI. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined 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. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required. Through publication of this proposed rule, we are providing notice and an opportunity for State and local officials to comment on this

rulemaking.

XII. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined 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. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XIII. Other Issues for Consideration

FDA anticipates that this proposed rule, if finalized, may require conforming amendments to other FDA regulations, including provisions regarding IVD labeling and ASRs in part 809. FDA intends to consider and propose conforming amendments, where appropriate, at a future date.

In addition, we note that various bills have been introduced in Congress that would change the legal status of IVDs as devices (under these bills, IVDs would generally be regulated as "in vitro clinical tests" and would be subject to new statutory authorities).[19] We recognize that the enactment of such legislation would directly impact this rule, given that it is being proposed under the statutory device authorities and other authorities under the FD&C Act.

XIV. 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

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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. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but 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, FDA proposes to amend 21 CFR part 809 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.

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.

* * * * *

Dated: September 27, 2023.

Robert M. Califf,

Commissioner of Food and Drugs.

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