DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Laboratory Developed Tests Proposed Rule

Docket No. FDA-_____-2023-N-2177

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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Executive Summary

This proposed rule would, if finalized, amend FDA's regulations in part 809 (21 CFR part 809) to make explicit that "in vitro diagnostic products" (IVDs) are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(h)(1)) including when the manufacturer of the IVD is a laboratory. This amendment would reflect FDA's longstanding position that laboratory developed tests (LDTs) are subject to the device provisions of the FD&C Act.[1] This amendment would be accompanied by a change in FDA's general enforcement discretion approach for LDTs that would phase out the approach for most LDTs, as discussed further in section VI of the proposed rule.

We quantify benefits to patients from averted health losses due to problematic IVDs offered as LDTs.[2,3,4,5] 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 associated with averted health losses for other diseases and conditions. 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. We estimate that the annualized benefits over 20 years would range from $2.4867 billion to $160.5086.01 billion at a 7 percent discount rate, with a primary estimate of $51.7831.41 billion and from $2.551.81 billion to $170.1661.41 billion at a 3 percent discount rate, with a primary estimate of $54.8522.33 billion. 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.

[1] FDA has made clear, on many occasions and over many years, that LDTs are devices under the FD&C Act. See, e.g., 62 FR 62243 at 62249 (November 21, 1997), explaining that clinical laboratories that develop tests are acting as manufacturers of medical devices. A more detailed discussion of this history is provided in section III.D of the proposed rule.

[2] See discussion of "problematic IVDs" in section I.B below.

[3] See discussion of "IVDs offered as LDTs" in section VI.A of the rulemaking and section II.D below.

[4] See discussion of "problematic IVDs" in section I.B below.

[5] See discussion of "IVDs offered as LDTs" in section VI.A of the rulemaking and section II.D below.

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I. Introduction and Summary

A. Introduction

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 ~~any~~at least one year that meets or exceeds this amount.

B. Summary of Benefits, Costs, and Transfers

This proposed rule, if finalized, would amend FDA's regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) including when the manufacturer of the IVD is a laboratory. As discussed in section VI of the proposed rule, 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 IVDs, including IVDs promoted with false or misleading claims (generally referred to in this document as "problematic IVDs"), 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. We discuss the benefits of the rule in section II.E.

~~We discuss the benefits of the rule in section II.E.~~ 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. We discuss the costs of the rule in section II.F. ~~There will be transfers~~These costs overlap somewhat with effects associated with this rule

in the form of user fees, including annual registration fees, fees for premarket applications/submissions, and annual fees for periodic reporting concerning class III devices, which are paid from laboratories to FDA. These fees are ~~costs for~~paid by laboratories but revenue for FDA ~~and are thus transfers of welfare rather than~~ ; the approach to estimating fee effects is distinct from the approaches for either benefits or costs, so they will be presented as transfers. We discuss transfers in section II.G.

Table 1 summarizes the annualized benefits, costs, and transfers of the proposed rule. At a seven percent discount rate, 20-year annualized benefits range from $2.~~48~~7 billion to $~~160.50~~86 billion, with a primary estimate of $~~51.78~~31.4 billion per year. At a three percent discount rate, 20-year annualized benefits range from $~~2.55~~1.8 billion to $~~170.16~~61.4 billion, with a primary estimate of $~~54.85~~22.3 billion per year.

At a seven 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 three 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 seven 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 three percent discount rate, 20-year annualized transfers range from $121 million to $538 million, with a primary estimate of $269 million per year~~At a three percent discount rate, 20-year annualized transfers[6] range from $121 million to $538 million, with a primary estimate of $269 million per year. These estimates do not include anticipated offsets from user fees. Factoring in offsets

[6] 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.

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. 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.

~~The present value of benefits with seven percent discounting over 20 years (not shown in Table 1) ranges from about $26 billion to $1,700 billion, with a primary estimate of about $549 billion. The present value of benefits with three percent discounting over 20 years (not shown in Table 1) ranges from about $38 billion to $2,532 billion, with a primary estimate of $816 billion. The present value of costs with seven percent discounting over 20 years (not shown in Table 1) ranges from about $27 billion to $206 billion, with a primary estimate of about $62 billion. The present value of costs with three percent discounting over 20 years (not shown in Table 1) ranges from about $36 billion to $276 billion, with a primary estimate of $83 billion. The present value of transfers with seven percent discounting over 20 years (not shown in Table 1) ranges from about $1 billion to $5 billion, with a primary estimate of about $2 billion. The present value of transfers with three percent discounting over 20 years (not shown in Table 1) ranges from about $2 billion to $8 billion, with a primary estimate of $4 billion.~~

We request comment on our estimates of benefits, costs and transfers of this proposed rule.

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)	$~~51,782~~ 31,408	$2,~~477~~67 0	$~~160,503~~ 86,013	2022	7%	20 years	
		$~~54,847~~ 22,332	$~~2,553~~1, 810	$~~170,163~~ 61,413	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized ($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:							

II. Preliminary Economic Analysis of Impacts

A. Background

In 1976, the Medical Device Amendments (MDA) amending the FD&C Act created a comprehensive system for the regulation of devices intended for human use, including IVDs. Since 1976, FDA has considered IVDs to be devices within the meaning of the device definition in the FD&C Act (see section 201(h)(1) of the FD&C Act (21 U.S.C. 321(h~~);~~)(1)); 21 CFR 809.3(a)). However, in implementing the MDA, FDA adopted a general enforcement discretion approach for LDTs because they were mostly manufactured in small volumes by local laboratories; generally were intended for use in diagnosing rare diseases or to meet the needs of a local patient population, or were generally similar to well-characterized, standard tests; tended to employ manual techniques (and did not use automation) performed by laboratory personnel with special expertise; generally were 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 tended to be manufactured using components legally marketed for clinical use. This enforcement discretion approach for LDTs developed as a matter of general practice.

However, since 1976, the LDT landscape has evolved considerably, as we are seeing LDTs that are more complex, sometimes including black box algorithms. They are often run in large volumes in reference laboratories for patients from different institutions around the world and are sometimes assembled using components intended for research use only. Today's LDTs are also 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 FDA's general enforcement discretion approach.

While laboratories are regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), the focus of CLIA is on laboratory operations and personnel qualifications and not on assessing the development of individual tests in a laboratory.[7] (Ref. [1]). By contrast, the device provisions of the FD&C Act and FDA's regulations focus on providing a reasonable assurance of the safety and effectiveness of the tests themselves. Given this distinction, CMS has described the FDA and CMS "regulatory schemes" as "different in focus, scope and purpose, but they are intended to be complementary."[8]

This proposed rule 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 and would be accompanied by a phaseout of FDA's general enforcement discretion approach for LDTs. (Ref. [1])."

B. Need for Federal Regulatory Action

Clinical laboratory testing is foundational to healthcare. The Centers for Disease Control and Prevention (CDC) estimates that 70% of medical decisions are based on laboratory test results.[9] (Ref. [2]). IVDs offered as LDTs are a growing sector of that market.[10] (Ref. [3]). However, currently, patients may be at risk when their providers rely on certain IVDs offered as LDTs to guide their care. Although many of the IVDs offered as LDTs today are similar to other IVDs, and may often serve the same role in clinical practice, FDA has generally not enforced

[7] https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf
[8] https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf.
[9] CDC, "Division of Laboratory Systems (DLS): Strengthening Clinical Laboratories," November 15, 2018, available at https://www.cdc.gov/csels/dls/strengthening-clinical-labs.html (last accessed on March 31, 2023).
[10] Grand View Research, 2023.

applicable device requirements for LDTs. As a result, there is generally less assurance of the safety and effectiveness of IVDs offered as LDTs compared to other IVDs. Results from problematic IVDs can lead to delayed diagnosis or treatment of the true disease~~/~~ or condition, unwarranted interventions (some of which may carry risk of serious side effects), needless distress, progression of disease (in some cases without the opportunity for life-saving treatment), and the spread of infectious diseases. The growing number of IVDs offered as LDTs entering the market (some of which may be problematic IVDs) typically are not reviewed by FDA.

Increasingly complex IVDs are being offered as LDTs, often to broad populations and often to provide information that is critical to patient care. For example, IVDs offered as LDTs are used in determining cancer treatments and for non-invasive prenatal screening. Given the role these tests play in modern healthcare, their safety and effectiveness significantly impact public health. Further, some IVDs offered as LDTs are manufactured by corporations that market the tests nationwide as they accept specimens from patients across the country and run their tests in very large volumes in a single laboratory.[11]

FDA's general enforcement discretion approach ~~has never applied~~does not apply to certain types of LDTs, such as LDTs intended for emergencies/potential emergencies/material threats declared under section 564 of the FD&C Act. FDA's experience with emergency use authorization (EUA) requests from laboratories for COVID-19 tests during the COVID-19 pandemic increased FDA's concerns about the safety and effectiveness of IVDs offered as LDTs. While FDA has received requests for EUAs for LDTs in prior emergencies, the scope of the COVID-19 pandemic resulted in an unusually high number of EUA requests from ~~hundreds of~~

[11] See, e.g., Pew Research Center (Ref. [13]), Grand View Research (Ref. [3]), and Congressional Research Service (Ref. [68]). 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.

laboratories. These submissions provided a window into the approach that many laboratories may take to test validation. In an analysis of the first 125 EUA requests received from laboratories during the COVID-19 pandemic for molecular diagnostic tests, FDA found that 82 tests had design and/or validation problems. These results were particularly surprising given that the tests involved relatively well-understood techniques. And the laboratories represented these tests as appropriately validated.[12] To the extent that this sample represents larger trends in the performance of IVDs offered as LDTs, it underscores the need for greater oversight.

Problems with IVDs offered as LDTs have also come to light in the scientific literature, news articles, and anecdotal reports submitted to the Agency, among other sources. Multiple publications in the scientific literature have described a high degree of variability among IVDs offered as LDTs ~~and~~. For example, in one study, analytical accuracy was significantly lower than that of the parallel test approved by FDA for almost half of the tests studied (Ref. [4]). In another study of 60,502 newly diagnosed metastatic non-small cell lung cancer (NSCLC) patients, Cheng, et al. 2017 estimated that 2% (1,422) of patients would be misclassified with IVDs offered as LDTs versus 1% (577) with an FDA-approved test (Ref. [2]). Hence, IVDs offered as LDTs in this study were twice as likely as FDA-approved tests to result in misclassification. The authors also found that "aggregate treatment costs for patients tested with LDTs were approximately $7.3 million more than with the FDA-approved test, due to higher drug and adverse event costs among patients incorrectly treated with targeted therapy or chemotherapy, respectively" (Ref. [2]). The impact of inaccurate testing estimated in individual analyses is not generalizable across all IVDs offered as LDTs, because the consequences of

[12] Memorandum to File from Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, RE: Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2 (September 22, 2023), available in Docket No. FDA-2023-N-2177

patient misclassification or misdiagnosis depend in most part on the differential safety and efficacy of the indicated treatment regimens, and on the size of the population afflicted (Ref.).[2]). General news sources and other outlets have reported on problems with IVDs offered as LDTs, including in the New York Times[13], (Ref. [5]), and lawsuits have been filed relating to IVDs offered as LDTs for pharmacogenomic testing and non-invasive prenatal screening.[14] FDA has received complaints, allegations, and reports regarding IVDs offered as LDTs in the oncology space, for non-invasive prenatal screening, and for infectious disease testing, among others. Some laboratories have submitted data to FDA in premarket submissions/applications for their IVDs offered as LDTs, and we have observed that many failed to perform the appropriate studies to show that their tests work. Some have submitted data from appropriate studies, but the data show that their tests do not work. In both cases, laboratories have continued to offer such tests for clinical use.

FDA is aware that some industry players have created business models that claim a connection to laboratories to circumvent FDA oversight.FDA is aware that some entities have adopted business practices that claim a connection to laboratories and offer IVDs as LDTs; for example, conventional manufacturers offering home-use test kits as LDTs, software developers offering software without validation for high risk clinical use with LDTs through laboratory partnerships, research use only test kit manufacturers marketing their kits to clinical labs through

[13] Kliff, S., and A. Bhatia, "When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong," *New York Times*, January 1, 2022. Available at https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html.

[14] See Complaint, *In re Myriad Genetics, Inc. Sec. Litig*., No. 2:19-cv-00707-DBB (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, *Law* v. *Natera, Inc*., No. 3:22-cv-01162 (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); and Notice of Removal, *Martinez* v. *Lab. Corp. of Am*., No. 3:22-cv-00631 (S.D. Cal. May 4, 2022).

laboratory partnerships, custom home collection test kit manufacturers that connect entities interested in developing home-use tests with often unspecified laboratories and a platform to scale testing, and contract manufacturers claiming to be consulting firms that design and validate tests for customer laboratories to perform. 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 for example Refs. [6] and [7]). This puts non-laboratory, conventional test manufacturers who develop IVDs, whose IVDs have not been under FDA's general enforcement discretion approach for LDTs, at a competitive disadvantage compared to laboratory manufacturers of IVDs offered as LDTs.

For patients and healthcare providers to make informed healthcare decisions, they need tests with a reasonable assurance of safety and effectiveness. With such tests, both patients and their healthcare providers (as a team) could weigh the costs and benefits of treatment alternatives expecting to yield benefits that would at least be equal to the costs (which would also take risks into account). This level of care that would be chosen by a fully informed team (patient and healthcare provider) would be considered the efficient or optimal level of care. However, in today's market, the ability for the team to make informed choices is limited by the prevalence of IVDs offered as LDTs ~~that are not in compliance with requirements designed to provide~~for which there currently is not a reasonable assurance of safety and effectiveness. As IVDs offered as LDTs have increased in both availability and complexity, they increasingly compete with IVDs that are in ~~compliance~~alignment with FDA requirements.

It is possible that, over time, patients and providers might learn the differences between competing tests and eventually stop purchasing ineffective tests regardless of regulation. However, in practice, without widespread awareness of the difference between IVDs offered as

LDTs and IVDs aligned with FDA requirements, we expect that learning of this kind may be rare. . As for patients, ability to internalize the relevant risks may be precluded by not knowing the difference between LDTs and FDA-approved IVDs or having meaningful informed choice in the purchase decision.

Even for laboratories attempting to serve the best interest of the patient, it is possible that other financial incentives may be in conflict. For example, as discussed in section E.3, when laboratories make decisions about whether to use IVDs offered as LDTs, some of their choices may rest on the potentially lower costs of product adoption, which generally favor IVDs offered as LDTs. At the same time, a narrow focus on the costs of product adoption does not consider potential costs to patients and the broader healthcare system when the performance of IVDs offered as LDTs is less reliable relative to other IVDs (Ref. [8]).

Although laboratories that offer ~~LDTs~~IVDs are also subject to CLIA, which is primarily administered by ~~CMS~~CMS[15], 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 laboratory test development; does not evaluate the performance of an ~~LDT~~IVD before the test is offered to patients and healthcare providers; does not assess clinical validity (i.e., the accuracy

[15] Three federal agencies are responsible for administering the CLIA program: the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). Each agency has a unique role. FDA's role is limited to categorizing the complexity of tests, generally following FDA clearance or approval, whereas CMS generally is responsible for oversight of clinical laboratories. Additional information is available on FDA's website at: https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia.

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 ~~LDT~~IVD 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."~~[16]~~ (Ref. [1]) Where CLIA does play a role, FDA has tailored its proposed phaseout policy accordingly.

~~Currently,~~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 who 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~~. By~~ (Refs. [9] and [10]). We anticipate that applying the same oversight approach to laboratories and non-laboratories that manufacture IVDs~~, FDA~~ would better assure the safety and effectiveness of LDTs, and would remove a disincentive for non-laboratory manufacturers to develop novel tests ~~and enter the IVD marketplace~~, thereby spurring innovation and access to IVDs for which there is a reasonable assurance of safety and effectiveness. In the meantime, without better assurance of the safety and effectiveness of IVDs offered as LDTs, limited investment and healthcare funding may be expended on problematic IVDs ~~rather than on tests that lead to improved care.~~[17].

~~[16] https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf.~~
~~[17] U.S. Food and Drug Administration Discussion Paper on Laboratory Developed Tests (LDTs) January 13, 2017 https://www.fda.gov/media/102367/download~~

The current regulatory environment related to LDTs creates distortions in the diagnostics market.[18] These distortions may not only prevent regulators from having a comprehensive understanding of the IVDs used in clinical practice, which impedes FDA's ability to help ensure the safety and effectiveness of IVDs, but may also create disincentives for some laboratories to maintain high standards of quality control and accuracy which may ultimately bring about social costs.[19]

As a result, FDA has determined that amending the Agency's regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory, paired with a phaseout of 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, is the best means of addressing the problem.

C. Purpose of the Proposed Rule

FDA is proposing to amend 21 CFR part 809 to make explicit that IVDs are devices under section 201(h)(1) of the FD&C Act (21 U.S.C. 321(h)(1)) including when the manufacturer of the IVD is a laboratory. This amendment would reflect the fact that the device definition in the FD&C Act does not differentiate between entities manufacturing the device, and

[18] Market distortions ~~are~~may be associated with events, decisions, or interventions taken by governments, companies, or other agents that influence the market~~.~~ in ways that cause the First Fundamental Theorem of Welfare Economics not to be upheld. Related concepts include market failure, government failure or behavioral bias (Ref. [66]).

[19] Social costs are costs incurred from the viewpoint of society (including external costs), ~~not~~beyond just stakeholders (private costs). When laboratories avoid paying for external costs arising from their actions (such as costs to ~~ensure they~~ manufacture ~~accurate~~ tests with a reasonable assurance of safety and effectiveness, and if borne by individuals not involved in the decision to order such tests—for example, taxpayers funding government health insurance), the costs to society as a whole (such as non-internalized worsened health outcomes from inaccurate test results) remain. External costs ~~must be considered~~, along with private costs ~~to ensure~~, affect whether society ~~operates~~is operating at a socially efficient rate of output~~.~~ (Ref. [67]).

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

As discussed in section VI of the proposed rule, FDA is also proposing 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.

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 current Medical Device User Fee Amendments (MDUFA) V agreement), and the benefits of a relatively simple policy that can be easily understood and implemented.

Overall, the purpose of this rule is to better protect the public health by helping to ensure the safety and effectiveness of IVDs offered as LDTs~~, and to incentivize~~. It may also foster the ~~manufacture~~manufacturing of innovative IVDs for which FDA has determined there is a reasonable assurance of safety and effectiveness, as discussed in section III.B of the proposed rule. This, in turn, can promote more effective treatment and the efficient use of healthcare resources.

D. Baseline Conditions

We consider the current state of the environment, including the general enforcement discretion approach, as a reasonable approximation of the baseline (the projected future without

the rule) against which to measure the costs and benefits of the rule and the regulatory alternatives discussed in section II.~~I~~J.

FDA has generally described LDTs as IVDs that are designed, manufactured, and used in a single laboratory that is certified under CLIA and that meets the regulatory requirements under CLIA to perform high complexity testing~~.~~ (Ref. [11]). As discussed in the proposed rule and section II.F "Costs of the Proposed Rule," while FDA's current 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,[20] even if those IVDs do not fall within FDA's traditional understanding of an LDT because they are not designed, manufactured, and used within a single laboratory.[21] Throughout this document, these IVDs are referred to as "IVDs offered as LDTs."

- As described in section VI of the proposed rule, FDA is proposing to continue to apply ~~the general enforcement discretion approach for a few limited categories of tests going forward. These categories are tests intended solely for forensic (law enforcement) purposes, 1976-type LDTs, and~~general enforcement discretion going forward for

[20] Other laboratories would be out of compliance with CLIA regulations if they were developing and performing tests that are not FDA authorized. As noted in the proposed rule, such tests have never fallen within FDA's general enforcement discretion approach.

[21] According to its website, CMS regulates all laboratory testing (except research) performed on humans in the U.S. through CLIA. In total, CLIA covers approximately 320,000 ~~laboratory entities~~laboratories, but we do not know how many of these laboratories meet the regulatory requirements under CLIA to perform high complexity testing. It is worth noting that the number of CLIA certified laboratories, including laboratories that meet the requirements under CLIA for high complexity testing, can vary over time as new laboratories acquire certifications and others may close or lose their certification~~.~~ ~~https://www.cms.gov/regulations-and-guidance/legislation/clia#:~:text=The%20Centers%20for%20Medicare%20%26%20Medicaid,covers%20approximately%20320%2C000%20laboratory%20entities.~~ (Ref. [1]).

certain categories of tests manufactured by laboratories. One such category of tests is referred to in this document 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 of the proposed rule). 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.

- 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 CLIA-certified, high-complexity histocompatibility laboratory 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 CLIA-certified, high-complexity histocompatibility laboratories, 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.

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. Tests used in the law enforcement setting are subject to protections associated with the judicial process that mitigate risk related to inaccurate tests 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. See, e.g., 65 FR 18230 (April 7, 2000).

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) tests results are not reported to patients or their healthcare providers. These tests would not be affected by the phaseout policy.

We lack the evidence to quantify the number of tests that fall in ~~these~~the above categories and thus would not be affected by the proposed rule (if finalized~~), though we anticipate this~~

~~number would be a very small percentage of the overall number of IVDs offered as LDTs.~~). We request comment on sources of data we can use to evaluate the number of tests that fall within these categories.

We estimate that a number of laboratories offering IVDs as LDTs, and their IVDs offered as LDTs, do not currently meet applicable requirements --including premarket review, quality system, registration and listing, and adverse event reporting requirements-- given FDA's current general enforcement discretion approach for LDTs.

As discussed in detail in section III.B of the proposed rule, FDA has increasingly seen problems with IVDs offered as LDTs that have caused or may be causing harm. The number of known issues with IVDs offered as LDTs likely represent just the tip of the iceberg, as laboratories do not typically report adverse events associated with or submit applications for their IVDs offered as LDTs to FDA~~.~~ under the existing enforcement discretion policy. As a result, FDA does not have complete information relevant to IVD performance or patient harm.

Without registration and listing information it is difficult to estimate the exact baseline number of manufacturers of IVDs offered as LDTs that would be affected by this rule. It is also difficult to estimate the number of IVDs offered as LDTs currently on the market, when or why many of them are used, or exactly how they each perform compared to other IVDs.

Without adverse event reporting or other information that FDA ~~might~~would obtain upon the phaseout of the current enforcement discretion approach, it is difficult to estimate the exact baseline number of patients benefiting from this rule given current information. In order to account for potential uncertainty and variability, we present all estimates in low, central and high ranges. We address baseline risks (and costs due to risks) in the benefits section of this analysis.

1. Number of Affected Entities

Since laboratories that offer IVDs as LDTs have ~~generally~~ not been ~~complying with the same registration~~registering and listing ~~requirements that apply to~~as generally have other IVD manufacturers, we do not know the exact number of laboratories or IVDs offered as LDTs that would be affected by this proposed rule. ~~In 2014, FDA estimated that 650 U.S. laboratories developed and deployed IVDs offered as LDTs (Ref. [3]). At the time, the American Clinical Laboratory Association estimated that there were 11,633 CLIA certified laboratories that met the regulatory requirements under CLIA to perform high complexity testing and develop such tests, but did not estimate the number of such laboratories that were actually making IVDs offered as LDTs.[22]~~

Our current estimate of the number of affected entities is based on ~~three different~~multiple sources~~, including information from CMS and a~~. A 2021 report from the Pew Charitable Trust (Ref. [13])~~)), both of which~~ estimated there are approximately 12,000 CLIA-certified laboratories performing high complexity testing. This is consistent with FDA's own estimate of approximately 12,000 CLIA-certified laboratories performing high complexity testing based on FDA's 2018 review of the CLIA-certified laboratories listed on the CLIA Laboratory Search website,[23] considering the types of laboratories most likely to meet the requirements to perform high complexity testing. Laboratories that meet these requirements are the only laboratories that can perform LDTs under CLIA regulations, because LDTs are considered high complexity tests (Ref. [13]). Additionally, while CLIA regulations contemplate that such laboratories ~~can manufacture and deploy~~may be deploying IVDs offered as LDTs ~~under CLIA regulations, they~~, laboratories certainly are not required to do so, and we do not expect that every such laboratory

~~[22] American Clinical Laboratory Association, "ACLA Written Statement for 21st Century Cures Hearing on LDT Regulation," Sept. 9, 2014, https://www.acla.com/acla-written-statement-for-21st-century-cures-hearing-on-ldt-regulation/.~~

[23] https://wwwn.cdc.gov/clia/Resources/Lab-Search.aspx

is doing so. We are not aware of information describing the exact number of such laboratories that are currently offering IVDs as LDTs.

We rely on information about laboratories and IVDs in New York State (NYS) to estimate the percent of high complexity labs that make ~~LDTs. NYS requires "explicit test-specific approval"~~IVDs offered as LDTs (Ref. [14]). NYS requires laboratories offering tests to NYS residents, whether or not the laboratory is located in NYS, to obtain a permit through the New York State Department of Health (NYSDOH) Clinical Laboratory Evaluation Program (CLEP~~)~~), as well as "explicit test-specific approval" for certain IVDs that are not "designated as FDA-cleared, approved or exempt."[24] (Ref. [15]) To FDA's knowledge, NYS is the only state that requires test approval for IVDs offered as LDTs that are not FDA-cleared, approved, or exempt. Further, NYS is a relatively large space with a variety of demographics, including urban to rural areas, and a variety of laboratories such as academic medical centers, reference laboratories, public health laboratories, and local hospital laboratories, similar to the variety found throughout the U.S. Therefore, FDA determined that the information about laboratories and tests in NYS could be extrapolated to estimate the number of laboratories throughout the U.S. that might be offering IVDs as LDTs.

NYSDOH provided information ~~on the number of~~indicating that there are approximately 500 laboratories located in NYS with a NYSDOH CLEP permit that are certified under CLIA and that meet or exceed the regulatory requirements under CLIA to perform high complexity testing, ~~as well as the number~~and that approximately 50 of such laboratories ~~with~~offers at least one IVD ~~offered~~ as an LDT approved by NYSDOH~~.~~ (Ref. [14]). From these data, we calculate that approximately 10% of laboratories located in NYS that are certified under CLIA and that

[24] ~~https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval~~

meet the regulatory requirements under CLIA to perform high complexity testing are developing IVDs offered as LDTs.

For our primary estimate, we assume that NYS is representative of the U.S. laboratory community ~~and~~, as discussed above. Based on the information from NYS and the assumption that NYS is representative of the entire U.S., we estimate that approximately 10% of 12,000 (or 1,200) laboratories in the U.S. that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing currently manufacture IVDs offered as LDTs. To account for ~~this~~ potential variability across the country, we estimate the proportion of high complexity laboratories making IVDs offered as LDTs to vary from 5% of 12,000 (or 600) laboratories to a high estimate of ~~15~~20% of 12,000 (or 2,400) affected laboratories by reducing the primary estimate by 50% and doubling the primary estimate, respectively.

Based on these three sources and methods, for purposes of this analysis, we use 600, 1,200 and 2,400 as low, central, and high estimates of the number of laboratories affected by this rule. We also expect that there would be new laboratories entering the market every year. To calculate the number of new laboratories per year, we use an average of firms' entry and exit rates from ~~2005~~2010 to ~~2015~~2018 in the United States (approximately 8 percent~~).~~[25]) (Ref. [16]). Multiplying this by the number of affected entities, we estimate the number of new laboratories per year to range from 48 to 192, with a primary estimate of 96.[26]

[25] ~~https://www.brookings.edu/?simplechart=firm-entry-and-exit-rates-in-the-us-1978-2015~~

[26] We also examined census data. According to 2017 Statistics of U.S. Businesses (SUSB) data from the U.S. Census there are 3,365 Medical Laboratories (represented by NAICS code 621511). While data from the Census does not provide information on the number of laboratories under NAICS code 621511 that specifically manufacture IVDs offered as LDTs, if we assumed half of the entities were IVD manufacturers and the other half were laboratories, we would get 1,683 laboratories. The difference between this estimate and our primary estimate is less than 4% of the 12,000 figure from CMS and the PEW Report (Ref.~~4~~). [13]). We therefore consider varying our estimates by -5% and +5% to be sufficient for estimating the range of variability between our low and high estimate.

Because there is no single source containing information on the number of IVDs offered as LDTs currently on the market, FDA also used information about laboratories and IVDs reviewed in NYS to extrapolate estimates for affected tests across the country. According to NYSDOH's website, there are currently approximately 2,200 ~~high or moderate risk~~ IVDs with approval from NYSDOH offered by laboratories located in NYS~~.~~[27] (Ref. [15]). NYSDOH provided the number of distinct laboratories within NYS that are certified under CLIA, that meet the regulatory requirements under CLIA to perform high complexity testing, and that are manufacturing and offering at least one IVD~~.~~ offered as an LDT (Ref. [14]). NYSDOH also provided the percent of IVD submissions received by risk category, as determined by NYSDOH criteria. From these data, FDA calculated that each laboratory in NYS that manufactures IVDs ~~is currently offering~~offers an average of 67 IVDs as LDTs. Extrapolating to the rest of the country, FDA estimates that 40,200, 80,400, or 160,800 IVDs may be affected, based on the ~~high~~low, central, and ~~low~~high estimates of affected entities discussed above. These estimates assume that NYS is representative of the U.S. laboratory community.

We took a similar approach to estimating the number of new IVDs offered as LDTs that are expected to be introduced per laboratory per year. NYSDOH provided information indicating that laboratories within NYS that manufacture IVDs offered as LDTs introduce an average of 6 new IVDs offered as LDTs per year. ~~We~~[28] For purposes of this analysis, we assume that laboratories in NYS are representative of the U.S. laboratory community, and estimate that

[27] ~~https://www.wadsworth.org/regulatory/clep/approved-ldt~~

[28] NYSDOH provided information indicating that, on an annual basis, NYS approves approximately 200 IVDs offered as LDTs across approximately 50 laboratories within NYS, or approximately 4 IVDs offered as LDTs per NYS lab per year. Although they receive test packages for them, NYS does not approve low-risk tests. Based on NYSDOH's accounting of test packages submitted to NYSDOH's CLEP program, we estimate that approximately 34% of the IVDs being offered as LDTs by NYS labs are tests that NYSDOH considers to be low-risk. To account for all tests, including low-risk tests, and assuming that NYS is an appropriate proxy for the rest of the U.S., FDA used an estimate of 6 new IVDs offered as LDTs per laboratory per year.

3,600, 7,200, or 14,400 new IVDs offered as LDTs may be affected per year. We also expect that there would be new IVDs offered as LDTs from new laboratories entering the market every year.[29] The total number of new IVDs offered as LDTs per year is estimated to range from 3,888 to 15,552, with a primary estimate of 7,776. We understand anecdotally that some large reference laboratories may make as many as 100 new IVDs per year, whereas smaller or more specialized laboratories may focus on one or a few IVDs overall and may not introduce many or any new IVDs every year. We have estimated the average, and we request comments on these estimates.

Table 2. Estimated Number of Laboratories and IVDs Offered as LDTs Affected by This Rule

	Low Estimate	**Central Estimate (Primary)**	**High Estimate**
No. Affected Labs	600	1,200	2,400
No. New Labs Entering the Market Per Year	48	96	192
No. Affected IVDs Currently on the Market	40,200	80,400	160,800
No. New IVDs Per Year	3,888	7,776	15,552

Note: The number of new IVDs per year include new IVDs from both affected labs and new labs entering the market per year.

2. Baseline Characteristics of the Market

At the time of passage of the MDA, LDTs were mostly manufactured in small volumes by local laboratories. 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-

[29] We use an average of firms' entry and exit rates from ~~2005~~2010 to ~~2015~~2018 in the U.S. (8 percent) ~~https://www.brookings.edu/?simplechart=firm-entry-and-exit-rates-in-the-us-1978-2015~~ (Ref. [16]).

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 has generally exercised enforcement discretion such that it generally has not enforced applicable requirements for most LDTs.[30]

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 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. The risks associated with 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.

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

3. Baseline Market Revenue

Data from the 2017 U.S. Census for the entire industry under NAICS code 621511 reported $36 billion in annual revenues.[31] According to publicly available industry research, "LDTs constitute about 50% of total in-vitro diagnostics devices that are used in some laboratories." [32](Ref. [3]) If we assume the same proportion of LDTs corresponds to revenues gained, then our estimated annual market revenue for IVDs offered as LDTs would approach $18 billion for the year 2017. We estimate annual industry revenue in 2023 is $23-$25 billion based on a projection from 2017 Census data using CAGR of 4.2% and 6%.

Given our uncertainty about this estimate, we also examined revenue data from five publicly available industry reports, and compared these data with our Census derived market revenue estimate.[33] [34] [35] [36] [37] (Refs. [3] [17] [18] [19] [20]). From the available data, we estimate annual revenues for the U.S. market for IVDs offered as LDTs for 2023 ranging from $2.4 billion to $97 billion. Taking the average reported revenue of $27 billion with a median of $4.21 billion we note that – while there is wide variability in reported market revenue – the difference between the Census estimate and the industry reported estimate is smaller than the variability within revenue estimates from different market reports. The reports also estimate revenue projections to 2030 ranging from $5 to $126 billion, using estimated CAGRs between 4.2% and

[31] Medical laboratories under NAICS 621511. are a subset of NAICS 621500 which is described as medical and diagnostic laboratories and also includes NAICS 621512 for Diagnostic imaging centers. For purposes of this analysis, we only use revenue data associated with NACISNAICS 621511. Source: https://www.census.gov/data/tables/2017/econ/susb/2017-susb-annual.html

[32] https://www.grandviewresearch.com/industry-analysis/laboratory-developed-tests-market-report. Viewed on July 6, 2023

[33] Grand View Research, 2023

[34] https://kaloramainformation.com/product/the-market-for-clinical-ldt-services-and-ldt-supplies/

[35] https://www.digitaljournal.com/pr/global-laboratory-developed-tests-market-2022-over-two-fifths-market-revenue-generated-from-application-in-oncology-pmr

[36] https://www.globenewswire.com/news-release/2023/03/13/2625730/0/en/United-States-Clinical-Laboratory-Services-Market-to-Generate-Revenue-of-US-125-6-Billion-by-2030-Astute-Analytica.html

[37] https://finance.yahoo.com/news/laboratory-developed-tests-market-size-144200090.html

6%. We use these same CAGRs to estimate the 2030 projection in market growth using the Census derived estimate ~~(Table 3).~~(Table 3).

Table 3. Estimated Market Revenue for IVDs Offered as LDTs ($1,000, 2022 U.S. dollars)[38]

Year	**Low** Projection ($1,000) (4.2% CAGR)	**Primary** (Average between low and high projection)	**High** Projection ($1,000) (6% CAGR)
2023	$27,157,057	$28,626,626	$30,096,195
2030	$36,220,692	$40,737,120	$45,253,549

4. Baseline FDA Premarket Reviews of Submissions/Applications

To better understand the magnitude of anticipated premarket submissions/applications for IVDs offered as LDTs that FDA would receive on an annual basis if this proposed rule were finalized, Table 4 below shows the 5 year average number of submissions/applications for all devices (2017-2021) along with the estimated annual number of submissions/applications expected for IVDs offered as LDTs if this proposed rule is finalized.~~[39]~~ (Ref. [21]).

Table 4. FDA CDRH Review Workload by Submission Type

Submission/Application Type	5-Year Average (FY 2017 to 2021)	Estimated One-time Reviews for IVDs Currently Offered as LDTs*			Estimated Annual Reviews for New IVDs Offered as LDTs*		
		Primary	Low	High	Primary	Low	High
Original PMAs, PDPs, Panel-Track PMA Supplements~~, and Premarket Reports~~*	73	4,210	2,105	8,419	407	204	814
510(k) Premarket Notifications	3,877	32,160	16,080	64,320	3,110	1,555	6,221
De Novo Classification Requests	66	4,020	2,010	8,040	389	194	778

Note: *The estimated reviews include original PMAs and panel-track PMA supplements.

[38] Values are also updated to reflect 2022 dollars using CPI of 1.19 for 2017-2022.

~~[39] U.S. Food and Drug Administration. Performance Report to Congress- Medical Device User Fee Amendments, FY 2022. https://www.fda.gov/media/167825/download. Page 21.~~

5. Baseline Population Exposure

From the 2021 report from the Pew Charitable Trust (Ref. [13]), there are roughly 3.3 billion IVDs (including what Pew calls "FDA reviewed" IVDs and "LDT" IVDs) performed in the country each year. Of these IVDs, there is a large yet unknown number of IVDs being offered as LDTs. For estimating population exposure to IVDs offered as LDTs, we assume 50% of the 3.3 billion IVDs performed each year, or 1.65 billion IVDs, are offered as LDTs, based on publicly available data from Grand View Research, which states that "LDTs constitute about 50% of total in-vitro diagnostics devices that are used in some laboratories" (Ref. [3]). We request comments on this estimate.

E. Benefits of the Proposed Rule

Benefits of this proposed rule, if finalized, would include the forgone costs incurred by patients from problematic IVDs offered as LDTs. We consider current (known and unknown) problems associated with such IVDs as defining baseline risks from the use of IVDs offered as LDTs. The problems caused by problematic IVDs also vary in severity according to the type of error associated with the test and the consequences the error may have for patient care.

We expect the following health and non-health benefits from this rule:

Health Benefits

1. Public health benefits from averted misdiagnosis (for purposes of this discussion, a misdiagnosis includes a missed diagnosis and an inaccurate diagnosis) and incorrect treatment: An overall increase in the accuracy of laboratory test results and decrease in false or misleading labeling may reduce the incidence of patient misdiagnosis, resulting in appropriate treatments or interventions, improved health outcomes, and reduction in transmission of infectious diseases.
2. More timely diagnosis: An increase in accurate laboratory test results may prevent unnecessary delays for a correct diagnosis, which may lead to a faster improvement of a patient's condition thus reducing the need for more invasive or costly treatments. In some cases, timely diagnosis may determine whether a disease or condition is treatable or terminal.

Non-Health Benefits

3. Reduced healthcare costs to patients and healthcare systems: Accurate laboratory test results can reduce the need for additional tests, procedures, and treatments, which can reduce healthcare costs to healthcare systems.
4. ~~Increased public trust in healthcare systems: Improving the frequency of accurate laboratory test results can improve public trust in healthcare systems and bolster the credibility of medical professionals.~~
5.4. Reduced legal costs: Phasing out the general enforcement discretion approach would reduce the prevalence of problematic IVDs and thus may reduce the incidence of litigation over alleged harms caused by problematic IVDs.

1. Baseline Risk of Problematic IVDs

The baseline is a description of the world without the rule. In this case the baseline risk of problematic IVDs offered as LDTs represents the point of departure from which we measure benefits of this rule. Given the lack of available information due to the current general enforcement discretion approach for LDTs, it is difficult to estimate the population baseline risk of exposure to a problematic IVD offered as an LDT. As a general approach, we rely on a variety of sources of information regarding reportedly problematic IVDs offered as LDTs, including but not limited to ~~medical device reports (MDRs) / allegations of inaccurate results/harm, FDA's review of submissions for IVDs offered as LDTs[40], and publications and lawsuits against laboratories, to estimate the probability of population exposure to problematic IVDs offered as LDTs.~~publications and press reports. The types of risks covered in these sources may not necessarily reflect the types of risks that may be present in the future; for example, it is possible that the types of risks covered in sources involving COVID-19 may not be present in the future. However, these sources include many types of tests covering a range of diseases/conditions, which we generally expect will be present in the future, such as cancer and coronary artery disease. Even in the case of COVID-19, some studies predict that the frequency of future

[40] ~~Although FDA generally has not enforced requirements for LDTs, it has received premarket submissions from some laboratories seeking authorization for their tests. FDA began tracking submissions identified by the applicant as LDTs in 2017.~~

pandemics of the same magnitude as COVID-19 is increasing (Ref. [22]). Others estimate that the probability of a future pandemic is between 2.5% to 3.3% annually.[41, 42] (Refs. [23] [24]).Therefore, our estimates of the benefits of this rule are based on the reduction of future risks that are similar to past risks.

These sources do not represent the totality of problematic IVDs offered as LDTs. The number of reportedly problematic IVDs offered as LDTs identified in these sources likely represents just the tip of the iceberg.

2. Health Benefits

The public health benefits associated with a reduction in population exposure to problematic IVDs offered as LDTs arise from non-events. That is, the public health benefits arise due to improved safety/effectiveness of IVDs offered as LDTs. To assess these benefits, we must therefore place a value on risk reduction (from exposure) and health-related costs for health outcomes that we anticipate will no longer take place. The conjectural nature of the risk reduction suggests that any estimate of preventing exposure to a problematic IVD offered as an LDT is uncertain. Health benefits of this proposed rule, if finalized, would be the foregoneavoided costs associated with the reduction of baseline risks of known and unknown cases of problematic IVDs offered as LDTs.

We are aware that the New York State Department of Health (NYSDOH) reviews IVDs offered as LDTs for use on New York patient samples, and that this review is in some ways similar to what the proposed rule aims to achieve. To aid estimating the benefits of the rule, we

[41] Bloomberg News. World Has 28% Risk of New Covid-Like Pandemic Within 10 Years. https://www.bloomberg.com/news/articles/2023-04-14/another-covid-like-pandemic-could-hit-the-world-within-10-years#xj4y7vzkg

[42] Center for Global Development: What's Next? Predicting The Frequency and Scale of Future Pandemics https://www.cgdev.org/event/whats-next-predicting-frequency-and-scale-future-pandemics#:~:text=In%20other%20words%2C%20there%20is,within%20the%20next%2025%20years.

request information via public comment on any studies or evaluations of health or longevity improvements attributable to NYSDOH review of IVDs offered as LDTs, and relatedly request comment on extrapolating from such experience for the purpose of estimating incremental effects of this FDA proposal.

In this analysis, we ~~address health benefits only for the following diseases/conditions: Cancer, COVID-19, and coronary artery disease. We are~~ are able to quantify ~~aggregate *recurring*~~ health benefits of the reduction in current mortality risk ~~only from cancer~~ resulting from improvements in health outcomes from a reduction of problematic IVDs offered as LDTs. We are able to partially quantify ~~aggregated *one-time*~~ benefits ~~from case studies for~~related to COVID-19 and coronary artery disease from case studies.

~~We would expect additional benefits associated with foregone costs from the use of problematic IVDs offered as LDTs for other diseases/conditions not included in this analysis. Therefore, this analysis reflects an underestimate of anticipated benefits.~~

a. Cancer Extrapolations

We quantify health benefits in the form of reduced baseline mortality risk ~~from cancer~~ based on expected reduction of misdiagnosis with problematic IVDs offered as LDTs. Based on the data available to us, this analysis focuses specifically on benefits in the form of reduced mortality risk (i.e., benefits associated with reducing false negative diagnoses). However, we anticipate that the proposed rule would lead to other benefits as well, such as reduced risk of undergoing potentially harmful treatments based on false positive diagnoses.[43]

[43] For example, Cheng et. al. addresses the importance of identifying epidermal growth factor receptor (EGFR) mutation testing for therapy selection of tyrosine kinase inhibitor (TKI) therapies for newly diagnosed patients with metastatic non-small cell lung cancer (NSCLC). First and second generation anti- EGFR TKIs are first line therapies for patients with positive EGFR mutation diagnosed with (NSCLC), while conventional chemotherapy is the recommended treatment for patients who are EGFR wild type. The clinical and economic consequences of incorrect

~~Accurate~~Our overall benefits estimate depends on the estimated probability of preventable misdiagnosis from false negative test results from a problematic IVD, which will be explained later in the analysis.

We also present these estimates with the caveat that the estimated probability of misdiagnosis-related harm depends on the manner of attribution of harm to diagnostic delays, and therefore our estimates might imply a number of cases bearing mortality risk consequences that differs from certain available estimates of the number of deaths attributable to misdiagnosis (Ref. [25]).[44] With a correct diagnosis, death can be delayed to a later date than one following an incorrect diagnosis. However, depending on when a misdiagnosis occurs, death might still be delayed to a degree depending on how soon a patient seeks follow-up and receives a correct diagnosis at a later time. Life expectancy in this case would still be shortened compared to if the initial diagnosis had been correct, but this would not necessarily be counted as a death due to misdiagnosis[45]. It is also possible that the differences in risk of death from a delayed diagnosis could be attributable to treatment differences such as fewer effective therapies for later-stage lung cancers contributing to the adverse impact of diagnostic delays (Ref. [26]).

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false positive and false negative molecular diagnostic test results can be significant. Consequences of false positive EGFR results would be from the additional costs of TKI treatment plus side effects without any additional survival benefits. Consequences of false negative results would be from costs of chemotherapy treatment and side effects while denying survival benefit associated with TKI. The authors found that IVDs offered as LDTs in this study were twice as likely as FDA approved tests to result in EGFR misclassification and that "aggregate treatment costs for patients tested with LDTs were approximately $7.3 million more than with the FDA-approved test, due to higher drug and adverse event costs among patients incorrectly treated with targeted therapy or chemotherapy, respectively" (Ref. [2]).

[44] From Newman-Toker (2023), annual US incidence was 6.0 M vascular events, 6.2 M infections and 1.5 M cancers. Per 'Big Three' dangerous disease case, weighted mean error and serious harm rates were 11.1% and 4.4%, respectively. Extrapolating to all diseases (including non-'Big Three' dangerous disease categories), the authors estimated 795 000 total serious harms annually in the USA (plausible range 598 000–1 023 000). Sensitivity analyses using more conservative assumptions estimated 549 000 serious harms. Results were compatible with setting-specific serious harm estimates from inpatient, emergency department and ambulatory care (Ref. [25]).

[45] In general, this rule may reduce the risk of dying earlier or at a certain age (also referred to as the hazard function). This change in the hazard function can be expressed as a reduction in the expected number of deaths in a specified time period (less than one for an individual) or as an increase in the expected number of years lived (Ref. [69]).

Although we do not estimate the benefits from avoiding false positives, accurate testing for patients ~~with cancer~~ can help maximize the benefits of certain therapies that ~~cancer~~ patients need to treat or manage their condition. False ~~teststest~~ results may result in some treatments being denied to eligible patients, which may worsen their health outcomes.

A 2022 study by Pfeifer et al., published in the American Journal of Clinical Pathology, reported that certain oncology IVDs offered as LDTs for the same intended use as an FDA-approved companion diagnostic had significant variability in their performance. The analytical accuracy of 9 (47%) of 19 IVDs offered as LDTs that were evaluated was significantly lower than that of the FDA-approved companion diagnostic (Ref. [1]).

~~In a study of 60,502 newly diagnosed metastatic non-small cell lung cancer (NSCLC) patients, Cheng, et al. 2017 estimated that 2% (1,422) of patients would be misclassified with (IVDs offered as) LDTs versus 1% (577) with an FDA-approved test (Ref. [2]). Hence, IVDs offered as LDTs in this study were twice as likely as FDA approved tests to result in misclassification.~~

~~The authors also found that "aggregate treatment costs for patients tested with LDTs were approximately $7.3 million more than with the FDA-approved test, due to higher drug and adverse event costs among patients incorrectly treated with targeted therapy or chemotherapy, respectively" (Ref. [2]). The impact of inaccurate testing estimated in individual analyses is not generalizable across all IVDs offered as LDTs, because the consequences of patient misclassification or misdiagnosis depend in most part on the differential safety and efficacy of the indicated treatment regimens, and on the size of the population afflicted (Ref. [2]).~~

Value of Reduced Mortality Risk

~~As a first step in valuing reduced cancer mortality risk from this rule, we collected~~As a first step in valuing reduced mortality risk from this rule, we estimate the gain in life expectancy

associated with a correct diagnosis for someone who has cancer. As noted elsewhere in this regulatory impact analysis, Newman-Toker et al. (Ref. [25]) describe cancer as one of the "Big Three" categories of conditions for which misdiagnosis is prevalent, so a cancer focus represents a reasonable analytic starting point. However, we request comment on data and methods that would allow for a refined analysis to reflect life expectancy changes associated with other medical conditions.

First, we collect 2023 data on estimated new cancer cases along with the five-year relative survival rate covering 2012-2018.[46] (Ref. [27]). The five-year relative survival rate (RSR) in column B of Table 65, represents the percentage of individuals surviving their cancer diagnosis 5 years after diagnosis compared to individuals who are cancer free.[47][48] We then use the RSR to estimate the absolute survival rate (of individuals with cancer who are diagnosed) further down below.

At the bottom of column D, we obtain the average five-year RSR across cancer sites, weighting by percent of total new cancer cases. For example, the weight on the RSR for breast cancer is the number of breast cancers divided by the sum of all new cancer cases (290,560 / 1,818,030 = 16%). The estimated five-year weighted average RSR for all new cancer cases is the sum of column D, 68.6%.

[46] Surveillance, Epidemiology and End Results Program (SEER) program for the National Cancer Institute at NIH https://seer.cancer.gov/statfacts/html/common.html

[47] Relative survival is a net survival measure representing cancer survival in the absence of other causes of death. Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals. The formulation is based on the assumption of independent competing causes of death. The relative survival adjusts for the general survival of the U.S. population for that race, sex, age, and date at which the age was coded.

[48] Relative survival is a net survival measure representing cancer survival in the absence of other causes of death. Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals. The formulation is based on the assumption of independent competing causes of death. The relative survival adjusts for the general survival of the U.S. population for that race, sex, age, and date at which the age was coded.

Table 5. Calculating the Weighted Average Relative Survival Rate (RSR) for New Cancer Cases

Site	Estimated New Cases (2022) A	Relative Survival (%) (2012–2018) B	% New Cases C	RSR x Percent weight D (=B*C/100)
Breast	290,560	90.5	16%	14.46
Prostate	268,490	96.8	15%	14.30
Lung and Bronchus	236,740	22.9	13%	2.98
Colon and Rectum	151,030	65.1	8%	5.41
Melanoma of the Skin	99,780	93.7	5%	5.14
Bladder	81,180	77.1	4%	3.44
Non-Hodgkin Lymphoma	80,470	73.8	4%	3.27
Kidney and Renal Pelvis	79,000	76.5	4%	3.32
Uterus	65,950	81.3	4%	2.95
Pancreas	62,210	11.5	3%	0.39
Leukemia	60,650	65.7	3%	2.19
Oral Cavity and Pharynx	54,000	68	3%	2.02
Thyroid	43,800	98.4	2%	2.37
Liver and Intrahepatic Bile Duct	41,260	20.8	2%	0.47
Myeloma	34,470	57.9	2%	1.10
Other	168,440	60.35	9%	4.78
Sum	**1,818,030**		100%	**68.60%**

Note: Product across table may not be exact due to rounding.

~~Thus, on average, a person with cancer who is diagnosed has a 68.6% chance of living at least five more years compared to individuals who are cancer free.[59] We assume that the difference between correct diagnosis and misdiagnosis is this relative 68.6% chance of living five more years. On the one hand, it is unlikely in reality that someone with cancer who is misdiagnosed succumbs immediately. On the other hand, a person who is accurately diagnosed might also live longer than five more years. We welcome public comment on valuing accurate diagnosis.~~

~~We value mortality risk reductions~~Thus, on average, a person with cancer who is diagnosed has 68.6% of the chance of living another five years that a person has who is cancer

free. According to the National Cancer Institute, the median age of a cancer diagnosis is 66 years (Ref. [28]). Per CDC life tables, the 5-year survival rate for all age-66 individuals is approximately 91.13%.[49] To estimate the absolute 5-year survival of persons with cancer who receive a correct diagnosis from diagnostic testing, we multiply the RSR of 68.60% by 91.13%, thereby obtaining 62.52%. This estimate is likely lower than the true 5-year survival of persons with cancer who receive a correct diagnosis from diagnostic testing for the following reasons: 1) 91.13% does not in fact represent the 5-year survival rate of cancer-free individuals aged 66, but instead the 5-year survival rate of all age-66 individuals, including those with cancer, and 2) the SEER data attempts to represent all cases, which would thus include some that are missed upon initial diagnostic testing and only detected later. Based on the above, and the fact that the 5-year survival rate of 62.52% is more than half, or 50%, the median remaining life expectancy of someone with cancer who is correctly diagnosed by diagnostic testing is at least 5 years.

Next, based on survival of untreated individuals, we estimate the median remaining life expectancy of someone with cancer who is not diagnosed as such. The median survival time for untreated individuals is 2.3 years in cases of breast cancer (Ref. [29]) and 11.94 months, or 0.995 years, in cases of lung cancer (Ref. [30]). We average these two survival times, weighting by the numbers of new cases of breast and lung cancer, respectively, from Table 5 above, and thus obtain a survival time for untreated cancer patients of about 1.71 years. We acknowledge the uncertainty introduced by assuming that lung and breast cancers are representative of all cancers and request comment on refining this aspect of the analysis.

We therefore estimate the gain in life expectancy from appropriate treatment upon diagnostic testing to be about 3.29 years (= 5 – 1.71). Thus, for an age-66 person with cancer

[49] Calculated from Table 1 "Life table for the total population: United States, 2020" in the report "United States Life Tables, 2020," available at: https://www.cdc.gov/nchs/data/nvsr/nvsr71/nvsr71-01.pdf

who has just been tested, treating the cancer is worth about 3.29 more years of life starting about 1.71 years from the time of testing. Table 6 shows these life years discounted to the time of the diagnostic test at rates of three and seven percent.

Table 6. Life Years Due to Treatment of Cancer

Time from treatment (years)	treatment	Discounted to time of treatment (3%)	Discounted to time of treatment (7%)
1.714	1	0.951	0.890
2.714	1	0.923	0.832
3.714	1	0.896	0.778
4.714	0.286	0.249	0.208
Total	3.286	3.018	2.708

Untreated and undiagnosed cancers may not have the same average prognosis. A patient diagnosed with cancer may go untreated for various reasons—including, in some cases, because no effective treatment exists. Ward et al. (2013) analyze data on nontreatment of cancer from the National Cancer Data Base and the Iowa Cancer Registry, which show that between roughly 8 and 12 percent of newly diagnosed cancer patients in Iowa did not receive a first course of treatment (Ref. [31]). This indicates that between 88% and 92% of these patients received a first course of treatment. Extrapolating from that range, we present estimates using adjustments in which life-years gained due to correct diagnosis are 88%, 90% or 92% of the life-years gained due to appropriate treatment. We request comment on additional literature, data or analyses regarding the range of diagnosed patients that receive treatment. Such additional estimates would allow for refinement of the range used in this proposed rule for our quantitative approach.

Finally, we value these mortality risk reductions (at the time of the diagnostic test) using estimates of the value per statistical life year (VSLY), which is the rate at which a consumer or patient substitutes money for gains in life expectancy. A reduction in current mortality risk

implies a corresponding increase in life expectancy. We ~~thus estimate~~ use VSLYs derived from the value of ~~five-year RSR after diagnosis as VSLY x 5 years x 68.6% (weighted average RSR across cancers) (Ref. [11]). The value~~a statistical life (VSL) under assumptions of ~~five-year RSR after diagnosis in~~three and seven percent discounting.[50,51] Table 7**Error! Reference source not found.** below represents our ~~estimate~~estimates of the value (at the time of ~~reduced mortality risk from~~ the diagnostic test), of the additional expected life years from an accurate diagnosis.[52,53]

Table 7. Estimated Value Per Case of ~~Five-~~Accurate~~Year RSR After~~ Diagnosis (2022$)

	~~VSLY (undiscounted)~~(a) VSLY (3% discounting) x Diagnosis-to-Treatment Ratio	(b) Value ~~of 5-year survival with no disease~~Per Case (VSLY 3%) (= a * 3.018)	(c) VSLY (7% discounting) x Diagnosis-to-Treatment Ratio	(d) Value ~~of 5-year RSR after diagnosis~~Per Case (VSLY 7%) (= c * 2.708)
Low ~~estimate~~	~~$144,306~~$251,109 x 88%	$~~721,529~~0.67 million	~~$494,959~~$420,449 x 88%	$1.00 million
Central ~~estimate~~	~~$309,227~~$538,091 x 90%	$1~~,546,134~~.46 million	~~$1,060,627~~$900,962 x 90%	$2.2 million
High ~~estimate~~	~~$470,712~~$819,095 x 92%	$2~~,353,559~~.27 million	$1,~~614,511~~371,464 x 92%	$3.42 million

Note: Product across table may not be exact due to rounding.

Expected Reduction in Misdiagnosis

~~We assume that the number of new cancer cases would represent all known new cancer cases today, including cases that in the past could have been diagnosed but instead went undetected. Assuming that cases that went undetected in the past are equal to cases currently~~

[50] The approach for valuing mortality risk reductions is generally based on estimates of the value per statistical life (VSL), from which a value per statistical life year (VSLY) is derived. The VSLY values presented are updated to 2022 dollars per HHS guidance (Ref. [32]).

[51] We note that VSLY depends on the choice of discount rate per OMB Circular A-4 (2003).

[52] ~~The approach for valuing mortality risk reductions is generally based on estimates of the value per statistical life (VSL), from which a value per statistical life year (VSLY) is derived. The VSLY values presented are updated to 2022 dollars per HHS guidance (Ref. [11]). https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis~~

[53] ~~We note that VSLY depends on the choice of discount rate per OMB Circular A-4 (2003). In our current approach for estimating benefits, we use an undiscounted VSLY (meaning future life years and survival probabilities are not discounted). We also note that our health benefits estimates are biased toward a lower value compared to using either a discounted 3% or 7% VSLY.~~

~~going undetected, which this count naturally omits, we take this count of 1.8 million as our estimate of baseline total new cancers per year. Therefore, we estimate the probability of misdiagnosis due to a problematic IVD offered as an LDT and apply that probability to 1.8 million baseline yearly new cancer cases to obtain the expected reduction in misdiagnosis.~~

To estimate the probability of misdiagnosis from problematic IVDs offered as LDTs, we take into account four probabilities: the probability of misdiagnosis ~~of a person who has cancer~~being associated with a fatality; the probability that a misdiagnosis occurs after testing with an IVD (as opposed to another method of diagnosis); the probability that an IVD is an IVD offered as an LDT (as opposed to another IVD); and, finally, the probability that an IVD offered as an LDT and associated with a misdiagnosis is a problematic IVD. With respect to this last probability, we note that an IVD that yields a false result in an individual case is not necessarily a problematic IVD (indeed, no test is perfect 100% of the time). As described in section I.B, we use the term "problematic IVDs" in this document to refer to IVDs that, on the whole, are unsafe or ineffective. It is exposure to ~~these~~problematic IVDs offered as LDTs that this proposed rule seeks to prevent.

~~To estimate the probability of misdiagnosis of a person who has cancer, we use a low estimate of 10%, a primary estimate of 28% based on~~ Newman-Toker et al. ~~2020~~2021 (Ref. [26]~~), and a high estimate of 46% based on Aaronson et al. 2019 (Ref. [13]).~~) state that "of the 2.7 million deaths annually in the [United States]… attributable to diagnostic error… multiple systematic reviews of autopsy studies indicate that the proportion is likely close[] to 5–10%"—or between 0.135 million and 0.27 million fatalities across all misdiagnosed conditions. Because heart disease will be assessed in a separate section of this regulatory impact analysis, we exclude 22% of these cases (range: 11% to 33%), reflecting an assumption that 50% of vascular events

are heart disease (range: 25% to 75%) and 44% (= 6.0M / 13.7M) of misdiagnosis-related fatalities are associated with vascular events.[54] The resulting estimates of annual misdiagnosis-related fatalities associated with conditions other than heart disease are 0.09 million, 0.16 million and 0.24 million.

We then assume that 50% of misdiagnoses occur after testing with an IVD (whether an IVD offered as an LDT or another IVD), as opposed to other methods of diagnosis, in the absence of specific information on these relative probabilities. We welcome public comment providing additional sources of data for this calculation.

We then estimate that 50% of IVDs are IVDs offered as LDTs. We base this estimate on publicly available data from Grand View Research, which states that "LDTs constitute about 50% of total in-vitro diagnostics devices that are used in some laboratories" (Ref. [3]).[55]

Finally, among IVDs offered as LDTs, we estimate that about 47% are problematic IVDs offered as LDTs. We base this estimate on Pfeifer et al. 2022, who report that the analytical accuracy of 9 (47.37%) of 19 evaluated oncology IVDs offered as LDTs was significantly lower than that of the FDA-approved companion diagnostic (Ref. [1]).[56] We include a low estimate of about 12% (= 0.4737 * 0.25) and a high estimate of about 59% (= 0.4737 * 1.25).

Thus, in Table 8, we estimate a baseline probabilityannual total of about 3.3% that a cancer case would0.019 million fatal cases receive a misdiagnosis due to testing with a

[54] As noted above, per Newman-Toker et al. (2023), annual US incidence was 6.0 M vascular events, 6.2 M infections and 1.5 M cancers.

[55] https://www.grandviewresearch.com/industry-analysis/laboratory-developed-tests-market-report. Viewed on July 6, 2023

[56] As with other steps in this analysis in which we have extrapolated from cancer to other conditions, we request comment on data and methods that would allow for a more refined analysis.

problematic IVD offered as an LDT, which would thus be preventable by the rule (0.~~033~~019 million = 0.~~28~~16 * 0.50 * 0.50 * 0.474).[57]

Table 8.- ~~Probability of~~Fatalities Associated with Preventable Misdiagnosis

	Low	Primary	High
a) ~~Probability of~~ Annual fatalities due to misdiagnosis~~, given cancer~~ of conditions other than heart disease (millions)	0.~~1~~009	0.~~28~~16	0.~~46~~24
b) Probability that misdiagnosis follows testing with an IVD, as opposed to some other method of diagnosis	0.50	0.50	0.50
c) Probability that an IVD is an LDT*	0.50	0.50	0.50
d) Probability that an LDT* is a problematic LDT*	0.1184	0.4737	0.5921
e) ~~Probability that a cancer case would result at baseline in a~~Annual fatalities due to misdiagnosis (of conditions other than heart disease) preventable by the rule (= a * b * c *d) (millions)	0.~~0030~~0026	0.~~0332~~019	~~.0681~~0.036

*LDT refers to IVD offered as an LDT

As a final step in Table 9, to obtain estimated aggregated benefits, we multiply the estimated reduction of inaccurate diagnoses times the benefits per case from Table 7 and times the portion of relevant risk not already internalized in decision-making by medical providers and patients, by 90%, 95% and 100%. The non-internalization percentage is unlikely to be zero because medical providers who frequently order tests may eventually be able to observe quality trends across various labs and because patients sometimes seek second opinions, but the percentage is unlikely to be high because without deliberate study of records aided by statistical tools, internalization of the risks of different tests would depend on provider recall and coincident identification of an association from the noise of a provider's experiences. Because higher-magnitude baseline risk

[57] We note that this analysis does not consider that a problematic IVD offered as an LDT is more likely to yield a misdiagnosis than is a non-problematic IVD offered as an LDT. We lack the data necessary to quantify the greater probability that a problematic IVD offered as an LDT will yield a misdiagnosis as compared to the probability that a non-problematic IVD offered as an LDT will yield a misdiagnosis. ~~We lack the data necessary to quantify this probability.~~ This analysis therefore likely underestimates the overall probability that a cancer case would receive a misdiagnosis due to testing with a problematic IVD offered as an LDT, and thus likely underestimates the overall probability that a cancer case would ~~thus~~ be preventable by this rule.

may be likely to prompt more medical provider attention to quality trends across various labs, the high estimates yielded by earlier portions of this mortality risk analysis are multiplied by the low non-internalization percentage, and vice versa**Error! Reference source not found.**. Given the lack of specific data on the extent to which medical providers may internalize some of the risks of such tests, we request public comment and any data, studies or analyses that estimate the extent to which such risks may be internalized in this context.

Table 9. Recurring (Annual) Benefits from Improved Testing ~~In Table 9, we multiply this probability by the total number of baseline yearly new cancers from Table 6. The estimated number of inaccurate diagnoses ranges between 5,382 to 123,793 with a central estimate of 60,282 patients.~~

~~Table 9. Estimated Annual Number of Inaccurate Diagnoses From IVDs Offered as LDTs~~

Estimate	~~New cancer cases from SEER data~~Total Benefits (VSLY 3%)	~~Probability of patient misdiagnoses from testing with problematic IVD offered as LDT~~Total Benefits (VSLY 3%) with Adjustment for Baseline Internalization	~~Estimated reduction of inaccurate diagnoses~~Total Benefits (VSLY 7%)	Total Benefits (VSLY 7%) with Adjustment for Baseline Internalization
Low	$1~~,818,030~~.78 billion	~~0.30%~~$1.78 billion	~~5,382~~ $2.67 billion	$2.67 billion
Central	~~1,818,030~~$27.7 billion	~~3.32%~~$26.31 billion	~~60,282~~ $41.61 billion	$39.53 billion
High	~~1,818,030~~$80.8 billion	~~6.81%~~$72.72 billion	~~123,793~~ $121.4 billion	$109.26 billion

~~Note: Product across table may not be exact due to rounding.~~

As a final step in Table 10, to obtain estimated aggregated benefits, we multiply the estimated reduction of inaccurate diagnoses times the benefits per case (which is equal to the value of five-year chance of survival after diagnosis in Table 7).

Table 10. Recurring (Annual) Benefits from Improved Testing in Oncology

Estimate	Estimated reduction of inaccurate diagnoses	Benefits per case	Aggregated Benefits
Low	5,382	$494,959	$2,664,032,959
Central	60,282	$1,060,627	$63,936,791,013
High	123,793	$1,614,511	$199,865,901,271

Note: Product across table may not be exact due to rounding.

b. COVID-19

During the COVID-19 pandemic, FDA has reviewed emergency use authorization (EUA) requests for COVID-19 tests from laboratories. FDAFDA's analysis of the first 125 EUA requests for COVID-19 molecular diagnostic tests from laboratories found that 82 (66%) were not designed or validated appropriately (Ref. [34]).

Additionally, press reports indicated problematic tests beyond those in FDA's analysis. For example, one Chicago laboratory contracted with the University of Nevada Reno and Washoe County School district to conduct COVID-19 testing using a test they offered without an EUA from FDA. A ProPublica investigation of the laboratory's operations in Nevada led to findings that the Chicago laboratory offered a test that was unreliable. According to ProPublica, the Chicago laboratory's test missed 96% of the positive cases from the university campus. The test's errors routinely sent people infected with COVID-19 back into the community.[58] (Ref. [35]). Despite growing evidence of the laboratory telling infected people they had tested negative, "government managers in Nevada ignored their own scientists' warnings and expanded

[58] Anjeanette Damon, The COVID Testing Company That Missed 96% of Cases; ProPublica; May 16, 2022. https://www.propublica.org/article/covid-testing-nevada-false-negatives-northshore

the lab's testing beyond schools to the general public."[59] The laboratory ceased commercial operations in the state before the investigation could be completed.

Use of the test in this case study increased the public's risk of contracting COVID-19 by falsely assuring individuals that they were not infected. This false assurance might have also interfered with care that individuals with COVID-19 would have otherwise obtained if they had a true positive test. We estimate benefits as if this laboratory offered a test after obtaining emergency use authorization from FDA (i.e., after an FDA determination that the EUA standard was met), potentially preventing the outcome that later developed.

To estimate the number of people affected by this problematic IVD, we rely on an analytic model described in a study by Paltiel, Zheng, & Walensky (2020) (Ref. [36]). The purpose of the model was to assess isolation and screening programs to help decide a level of isolation and screening that would keep students at residential colleges safe from contracting COVID-19. The authors adapted a simple compartmental epidemic model to capture features of a situation facing university decision-makers that included the epidemiology of COVID-19; the natural history of COVID-19 illness; and regular mass screening to detect, isolate, and contain the presence of COVID-19 in a residential college setting. A spreadsheet implementation of the model allows the user to vary critical epidemic parameters and to examine how different test performance attributes such as frequency, sensitivity, specificity, and cost would translate to outcomes. The default model input data the authors used were obtained from a variety of published sources, adhering whenever possible to the data guidance for modelers issued by the U.S. Centers for Disease Control and Prevention and the Office of the Assistant Secretary for Preparedness and Response. For purposes of this analysis, we defined the already known

[59] *Ibid.*

epidemic ~~scenario~~scenario[60] given the known false negative testing rate of 96% as an input to estimate test sensitivity. The estimated cumulative outcomes depend on the input data for the number of tests administered, number of true-positive and false-positive results, number of new infections, and person-days requiring isolation. The model estimates economic performance such as cost of initial and confirmatory tests and incremental cost-effectiveness, and budget impacts are assumed to occur during an abbreviated 80-day semester, running from Labor Day through Thanksgiving. The description of our input parameters can be found in Table ~~11~~10.

Table 10. Description and Value of Input Parameters

Description Input Parameters	Value
Tests sold between October 2021 and October 2022	1,738,~~443~~443[61]
Initial Susceptible	232,000
Initial Infected (1.5%)	3,450
Days **	80
False negative rate (FN)	96%
True negative rate (TN)	~~4~~96%
True positive rate (TP~~)*~~)	~~50~~4%
False positive rate (FP~~)*~~)	~~50~~4%
Sensitivity = TP/(TP + FN)	~~34.2~~4.0%
Specificity = TN/(TN + FP)	~~7.4~~96.0%
Rate at which infected individuals recover from disease and are removed (ρ)**	2.5
Cost per test	$25
Cost per confirmatory test	$100
Days to incubation~~***~~	3
Time to recovery~~***~~	14
Symptom case fatality rate~~***~~	0.05%
Probability that infection will lead to symptoms	30%

~~* We assume 50% for both TP and FP~~

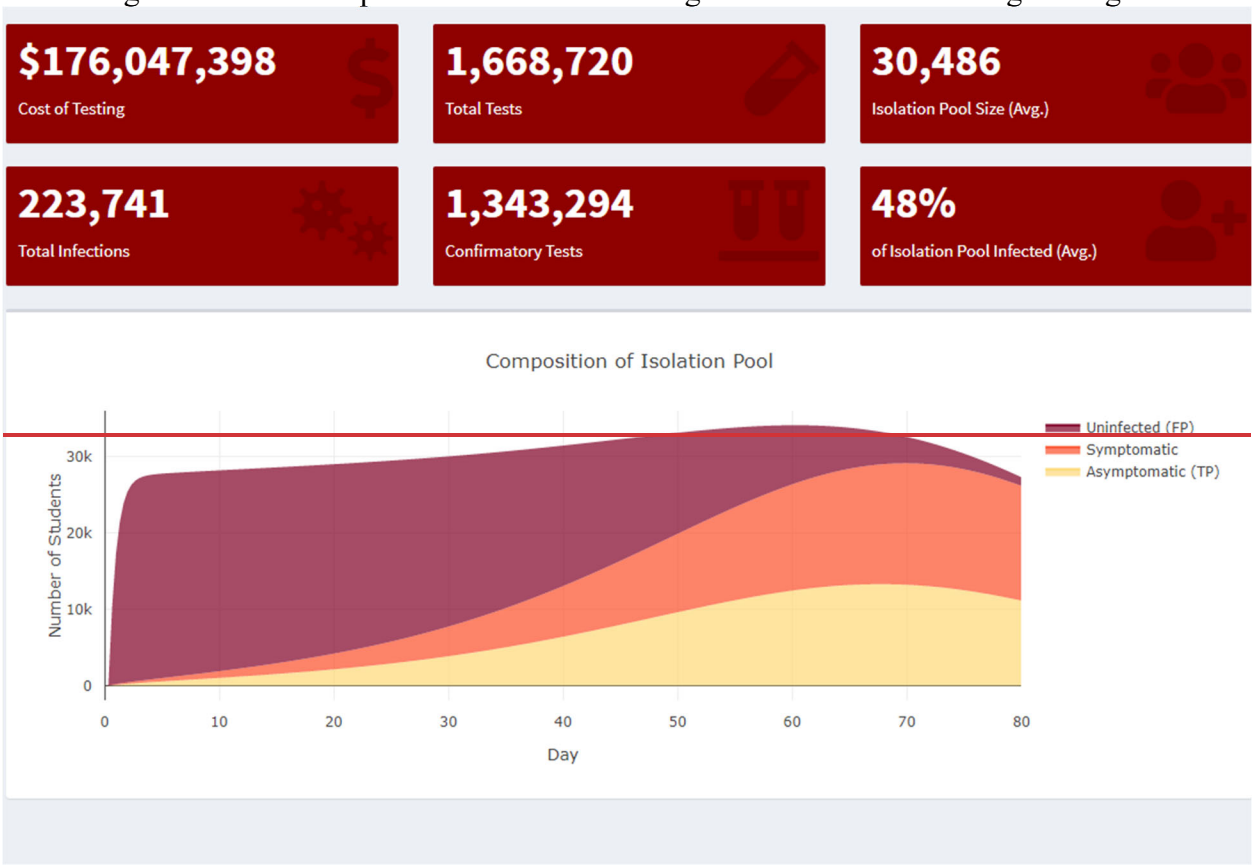
~~***~~ Model default setting

[60] This is dependent on the level of isolation and screening scenario that would keep students at residential colleges safe from contracting SARS-Cov-2.

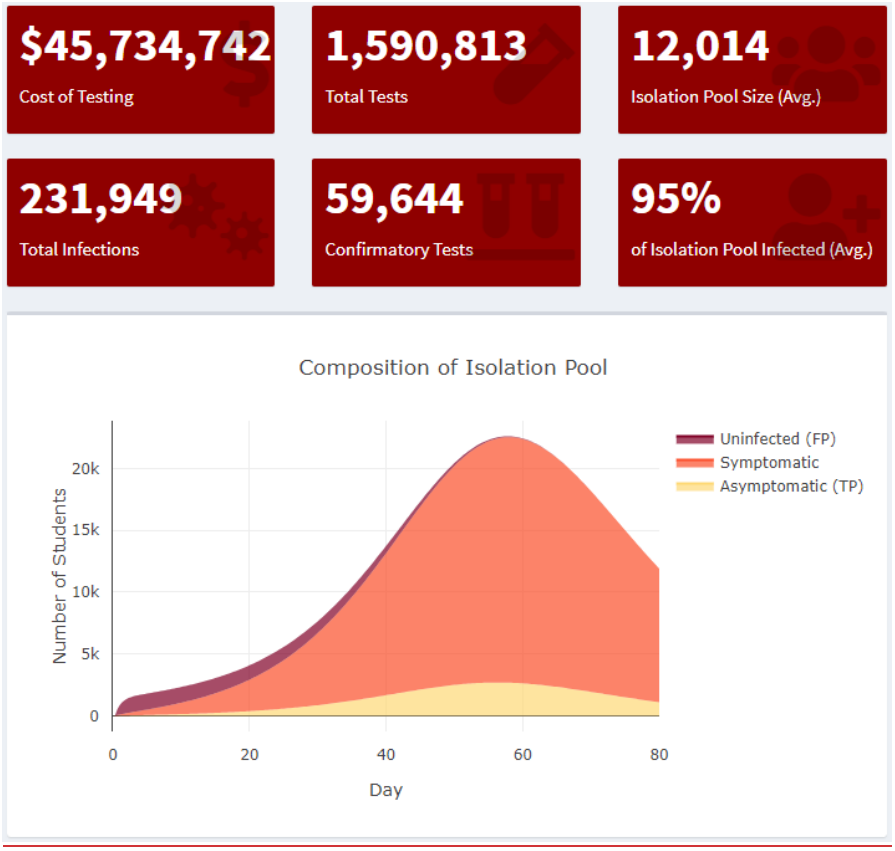
[61] A CMS "Statement of Deficiencies" for this laboratory reported that 1,738,443 tests were administered between May 1, 2021, and December 30, 2021. CMS, Statement of ~~Deficiences~~Deficiencies and Plan of Correction (Dec. 29, 2021), available at https://s3.documentcloud.org/documents/21872905/northshore-clinical-labs-14d0426602-form-cms-2567-12292021.pdf. Thus, this number is likely an underestimate for a full year of testing.

Figure 1 below shows how cases and testing costs can grow from use of problematic IVDs. At the end of 80 days, the model shows ~~223,741~~231,949 cases which is essentially ~~96~~99.9% of the initial susceptible population estimate with the total costs of the testing program reaching $~~176~~45 million.[62]

Figure 1. Model Output Results from assessing SARS-CoV-2 Screening Strategies



[62] The public version of the 2020 Paltiel, Zheng, & Walensky, model can be accessed at https://data-viz.it.wisc.edu/covid-19-screening/



We use the case fatality rate of 0.05~~%~~%, but instead of assuming death ultimately occurs, apply this percentage to ~~measure~~estimate critical cases,[63] and of the 30% probability that infection would eventually lead to observable COVID-19 symptoms, we assume that half of the 30% would be mild cases and the other half severe. We roughly reach a cumulative estimate of ~~223,741~~231,949 cases with visible symptoms, of which ~~112~~116 are critical, ~~111,815~~115,917 are with severe symptoms and ~~111,815~~115,917 are cases with mild symptoms.

The final step in estimating benefits from this particular case study requires estimating the gains from averting COVID-19 morbidity. The gains are first estimated as Quality Adjusted Life Years (QALYs): about 0.01 per mild case averted, 0.02 QALY per severe case, and 3.15 QALYs per critical case. ~~These~~When deriving the value per QALY (VQALY) from a VSLY that

[63] We assume no death associated with this cohort because the test was offered at schools and universities and death is rarely associated with the age-cohort being tested.

assumes a 3% discount rate, these gains translate into monetary values of about $5,3006,390 per mild case, $11,00012,779 per severe case, and $1.82.0 million per critical case. Using a VSLY that assumes a 7% discount rate, these gains translate into monetary values of about $10,532 per mild case, $21,065 per severe case and $3.3 million per critical case using a (Ref. [37]). We modify several inputs used in the report, including to incorporateincorporating HHS's current estimates of the value per statistical life and value per quality-adjusted life (QALY) year,VSL and to reviseVQALY, and revising the QALY losses to match estimates contained in more recent research. TheWe present the updated undiscounted values per mild, severe and critical cases are in Table 13in Table 11 for VQALYs derived from VSLYs that assume three and seven percent discount rates (Ref. [38]).

The potential one-time benefit in this one case study underscores the magnitude of the problem brought about by problematic IVDs offered as LDTs. While this case study may be considered a worst-case example, it estimates that the one-time benefit from preventing an extremely unreliable and high-volume test from being offered is about $1.4 billion dollars (In Table 1211).

., we estimate that the benefit from avoiding the use of this particular high-volume test would have been about $2.5 billion using a VSLY based on a 3% discount rate and about $4 billion using a VSLY based on a 7% discount rate.

Table 11.. Case Study (One-time) Benefits from AvertedAverting COVID-19 Cases Due to a Certain Problematic IVD ($2022) (1)

Level	Cases	QALYs	Value /case		Total Benefit	
Level	Cases	QALYs	3% VQALY	7% VQALY	3% VQALY	7% VQALY
Critical (0.05%)	112 116	3.15	$1,177,2902,012,694	$131,703,9863,317,716	$233,421,215	$384,770,450
Severe (49%)	111,815 115,917	0.02	$7,47512,779	$835,797,6752 1,065	$1,481,298,442	$2,441,765,489

Mild (49%)	~~111,815~~ 115,917	0.01	$~~3,737~~6,390	$~~417,898,838~~1 0,532	$740,649,221	$1,220,882,745
Sum	~~223,741~~ 231,949		-	~~$1,385,400,499~~	$2,455,368,878	$4,047,418,684

(1) Undiscounted, 3% and 7% discounted 2022 primary estimate for value per QALY ~~is~~are 373,743, $638,951 and $1,053,243 respectively per (Ref. 10).

We use the above result to estimate a recurring benefit based on the annual likelihood of a pandemic similar to COVID-19. While other unknown incidents due to other unreliable tests during the COVID-19 pandemic might also have been preventable by the proposed rule, we include only one such instance, similar in scope and impacts as analyzed above, per future pandemic. According to a report from the Center for Global Development, the annual probability of a future pandemic of similar magnitude to COVID-19 is between 2.5% to 3.3% (Ref. [23]). We thus estimate the central annual likelihood of 2.9% as the midpoint between 2.5% and 3.3%. In Table 12 below, we estimate the annual benefit from preventing the use, during a pandemic, of a problematic IVD such as analyzed above by multiplying this range of annual likelihood estimates by the total benefits from Table 11. Annual estimated benefits from averted cases of a COVID-like pandemic are $81 million using a VQALY based on a 3% discount rate and $133.6 million using a VQALY based on a 7% discount rate.

Table 12. Case Study: Recurring Annual Benefits from Averted COVID Cases Due to Faulty Testing

	Annual likelihood	Non-health (testing cost)	Health (by VQALY assumption)		
			0% discounting	3% discounting	7% discounting
Low	0.025	$1,143,369	$35,905,607	$61,384,222	$101,185,467
Central	0.029	$1,326,308	$41,650,505	$71,205,697	$117,375,142
High	0.033	$1,509,246	$47,395,402	$81,027,173	$133,564,817

c. Heart Disease

Between 2008 and early 2011, one laboratory sold over 160,000 StatinCheck tests designed to determine an individual's KIF6 genotype. This test was marketed as a way to

determine a patient's response to statin drugs, based on the idea that patients with the Trp719Arg polymorphism of the KIF6 protein would have a greater reduction in cardiovascular disease (CVD) events when on statin therapy~~.~~ than patients without this polymorphism. However, in April 2011, FDA denied premarket approval of this test, citing lack of sufficient evidence of the safety and efficacy of the test~~.~~ based in particular on clinical validity concerns.

Approximately 35% of patients in studies on CVD have the Trp719Arg polymorphism (Refs. [39, 40]). If 35% of the StatinCheck test recipients were identified as having the Trp719Arg polymorphism, then 56,000 patients may have been informed that they would respond better to statin therapy than other patients. If these patients received lower-potency statin treatment than is standard, a loss of quality adjusted life years (QALY) likely occurred, though medical expenditures were likely reduced. The use of high-potency statins results in an increase of 0.13 QALYs relative to the use of low-potency statins; the use of high-potency statins costs $1,069 more than low-potency statins (Ref. [41]).~~-~~ Using ~~$309,227 as the value of~~ a ~~statistical life year (~~VSLY of $538,091 (the central VSLY that assumes three percent discounting), the value of lost ~~benefits~~health from using low-potency statins instead of high-potency statins is $~~40,199 (=$309,227~~69,952 (= $538,091 x 0.13). ~~-~~The net ~~welfare loss or~~ lost benefit for each person using low-potency statins is $~~39,130 (= $40,199~~68,883 (= $69,952 - $1,069~~);~~), and the estimated total welfare losses are ~~$2.4~~thus about $3.9 billion (= $~~39,130~~68,883 x 56,000). Using a VSLY of $900,962 (the central VSLY that assumes seven percent discounting), the value of lost health from using low-potency statins instead of high-potency statins is $117,125 (= $900,962 x 0.13). The net lost benefit for each person using low-potency statins is $116,056 (= $117,125 - $1,069), and the estimated total welfare losses are thus about $6.5 billion (= $116,056 x 56,000).

3. Non-Health Benefits

a. ~~Cost-Saving~~ Benefits from Avoiding Future Overpayment for Problematic IVDs

When patients pay for healthcare resources, including IVDs offered as LDTs to diagnose or make decisions about treating a particular health state, the value of said resource is determined by its most productive or beneficial use. ~~An inaccurate test result produces the least productive use, and at a minimum, the cost is based on the price paid for the test alone (notwithstanding the health consequences that may follow).~~ When patients pay the price for a test expecting a certain degree of performance, but instead receive a lower degree of performance, they will have essentially overpaid for the test and as a result experience a loss in income. ~~We estimate the potential loss in income to patients who paid for a problematic IVD, as a fraction of the market revenues for IVDs offered as LDTs.~~ [64]

~~To estimate the share of problematic IVDs offered as LDTs by health concern, we use a sample of 70 sources of information regarding reportedly problematic IVDs offered as LDTs and categorize them by the type of disease or condition for which the IVD described therein is intended to be used (listed in the first column of Table 13). These sources are discussed in more detail in the proposed rule in section III.B. We count these sources by type to estimate the percent share of IVD offered as LDT by disease, as shown in column A of Table 13. We treat these percentages as a proxy for estimating market share of IVDs offered as LDTs by type of disease or condition.~~

[64] There might be some tests that can only be obtained if the patient deliberately seeks them out themselves. In this case, the patient is likely aware that these are not FDA approved since they would come with a warning. A patient who understands that an IVD is problematic and is willing to pay for it does not realize cost savings by being prevented from buying that problematic IVD.

~~We next use the primary, low and high estimates in Column B of the probability of patient misdiagnoses from testing with problematic IVD offered as LDT obtained from Table 9 in section 2.a.~~

~~Table 13 Estimated share of problematic IVDs offered as LDTs by health concern~~

We estimate the potential loss in income to patients who paid for a problematic IVD offered as an LDT as a fraction of the market revenues for IVDs offered as LDTs. First, to estimate the probability of misdiagnosis, we use a range of estimates based on table 3 in Newman-Toker et al. 2021 (Ref. [26]). To obtain low, high, and primary estimates, we take the averages, respectively, of the lower bounds, upper bounds, and point estimates presented by Newman-Toker et al. across lung, breast, colorectal, and prostate cancer and melanoma, weighting by the numbers of new cases of those cancers in Table 5. We thus obtain a low estimate of 7.21%, a primary estimate of 10.86%, and a high estimate of 28.66%. As in section II.E.2.a, we then assume that 50% of misdiagnoses occur after testing with an IVD (whether an IVD offered as an LDT or another IVD), that 50% of IVDs are IVDs offered as LDTs, and that about 47% are problematic IVDs offered as LDTs. We thus estimate that 0.21% to 4.24% of spending on IVDs offered as LDTs is essentially wasted, with a central estimate of 1.29%.

Multiplying these percentages by the range of estimated market revenues for IVDs offered as LDTs—in Table 3 (section D.3)—the estimated annual benefit from wasted spending avoided by patients from this rule would range from about $58 million to $1.3 billion with a primary estimate of $368 million (Table 13).

Table 13: Annual Avoidance of Wasted Spending on Problematic IVDs Offered as LDTs

	Primary	**Low**	**High**
Annual revenue from IVDs offered as LDTs	$28,626,626	$27,157,057	$30,096,195

Probability of misdiagnosis due to problematic IVD offered as LDT~~LDT TYPE by disease/condition~~	~~Share of LDT tests by type (A)~~ 1.29%	0.21%~~Probability of misdiagnosis due to problematic IVD offered as LDT (B)~~			~~Probability of misdiagnosis due to problematic IVD offered as LDT, by Type (C)~~ 4.24%		
		~~Primary~~	~~Low~~	~~High~~	~~Primary~~	~~Low~~	~~High~~
~~Cancer~~ **Wasted spending avoided**	~~34.21%~~**$368,083**	~~3.32%~~**$57,987**	~~0.30%~~	~~6.81%~~	**$1**~~.13%~~**,276,757**	~~0.10%~~	~~2.33%~~
~~COVID-19~~	~~14.47%~~	~~3.32%~~	~~0.30%~~	~~6.81%~~	~~0.48%~~	~~0.04%~~	~~0.99%~~
~~NIPS~~	~~13.16%~~	~~3.32%~~	~~0.30%~~	~~6.81%~~	~~0.44%~~	~~0.04%~~	~~0.90%~~
~~Alzheimers~~	~~2.63%~~	~~3.32%~~	~~0.30%~~	~~6.81%~~	~~0.09%~~	~~0.01%~~	~~0.18%~~
~~Heavy metals~~	~~2.63%~~	~~3.32%~~	~~0.30%~~	~~6.81%~~	~~0.09%~~	~~0.01%~~	~~0.18%~~
~~Coronary Artery Disease~~	~~2.63%~~	~~3.32%~~	~~0.30%~~	~~6.81%~~	~~0.09%~~	~~0.01%~~	~~0.18%~~
~~Other~~	~~30.26%~~	~~3.32%~~	~~0.30%~~	~~6.81%~~	~~1.00%~~	~~0.09%~~	~~2.06%~~
~~Sum~~	~~100.00%~~	-	-	-	-	-	-

~~Applying the estimated share of problematic IVDs offered as LDTs by type in Table 13 (columns C) and multiplying them by the estimated market revenue of $28,626,626,000 for IVDs offered as LDTs in Table 3 (section D.3), the estimated undiscounted recurring annual benefit from costs avoided by patients from this rule would range between $80.5 million to $2 billion with a primary estimate of $950 million (Table 14).~~

~~Table 14: Annual Cost-Saving Benefits from Avoiding Future Overpayment for Problematic IVDs Offered as LDTs~~

~~Test Type by Diseases/Condition~~	~~Cost of Problematic IVDs Offered as LDTs ($1,000)~~		
	~~Primary~~	~~Low~~	~~High~~
~~Cancer~~	~~$324,726~~	~~$27,505~~	~~$701,081~~
~~COVID-19~~	~~$137,384~~	~~$11,637~~	~~$296,611~~
~~NIPS~~	~~$124,895~~	~~$10,579~~	~~$269,646~~
~~Alzheimer's~~	~~$24,979~~	~~$2,116~~	~~$53,929~~
~~Heavy metal toxicity~~	~~$24,979~~	~~$2,116~~	~~$53,929~~

~~Coronary Artery Disease~~	~~$24,979~~	~~$2,116~~	~~$53,929~~
~~Other~~	~~$287,257~~	~~$24,331~~	~~$620,187~~
~~**Sum**~~	~~**$949,199**~~	~~**$80,399**~~	~~**$2,049,313**~~

Note: Product may not be exact due to rounding.

We request comment on whether the cost section of this regulatory impact analysis appropriately captures costs (analogous to the cost savings estimated above) that are associated with the diagnostic tests that would *replace* problematic IVDs offered as LDTs.

b. Non-invasive Prenatal Screening (NIPS) Tests

The NIPS testing industry has grown significantly in the last decade due to advances in medical technology and an increasing demand for information about fetal status. NIPS tests can provide information about the possibility of a fetus having certain genetic abnormalities that could result in a child being born with a serious health condition. That said, these screening tests only provide the risk of a fetus having certain genetic abnormalities and require diagnostic confirmatory testing to confirm or rule out such suspected genetic abnormalities. NIPS results should not be used by themselves to make critical healthcare decisions and should be discussed with a healthcare provider. NIPS testing has become more widely available and accessible, making it easier for pregnant individuals to access this testing. This has also led to a proliferation of NIPS testing options and an increase in the marketing of these tests, creating a very competitive environment for this industry.

After the success for conditions like Down syndrome, manufacturers started to suggest to doctors (some with aggressive marketing) that they should order additional screenings for far less common conditions, such as DiGeorge syndrome. The problem with this new development

was that the accuracy of testing for rare conditions can be wrong up to 83 to 91 percent of the time~~,~~[65] (Ref. [5]), which is why the test results should not be used on their own for diagnosis.

Adding screening tests for rarer conditions caused by genetic microdeletions—tiny pieces of missing DNA at the sub-chromosomal level—have helped companies competing in the market to grow. As the New York Times reported, "As companies began looking for ways to differentiate their products, many decided to start screening for more and rarer disorders. All the screenings could run on the same blood draw, and doctors already order many tests during short prenatal care visits, meaning some probably thought little of tacking on a few more."[66]

The upside for testing companies was significant: "adding microdeletions can double what an insurer pays — from an average of $695 for the basic tests to $1,349 for the expanded panel, according to the health data company Concert Genetics."[67]

When patients, private insurers or government programs pay for healthcare resources (including IVDs offered as LDTs to screen for a particular condition that have potentially unreliable, inaccurate, or misinterpreted results and require confirmatory diagnostic testing), the value of said resource is determined by its most productive or beneficial use. ~~The resource loss is a loss to society whether it was paid directly by the patient or through a private insurer or a government program on behalf of the patient.~~ If private insurance pays for too many problematic tests, costs most likely will be passed on to patients in the form of higher premiums or denial of coverage. If the tests are paid by government programs, the costs are passed on to taxpayers. More generally, the resource loss is a loss to society whether it was paid directly by the patient or

~~[65] Kliff, S., and A. Bhatia, "When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong," New York Times, January 1, 2022. Available at https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html.~~

[66] Ibid.

[67] Ibid.

through a private insurer or a government program on behalf of the patient. An unreliable, inaccurate, or misleading test result produces ~~the least productive use, and,~~ at a minimum, ~~the~~a cost that is based on the price paid for the test alone (notwithstanding the health consequences that may follow). For purposes of this analysis, the costs ~~to~~most directly experienced by patients represent the cost to society regardless of whether the cost of the test is offset by private insurers or government programs.

We estimate the potential loss in income to patients or consumers who paid for a problematic test, using information from the NY Times article.[68] The number of screening tests for microdeletions sold in 2020 was above 400,000, and consumers paid approximately an additional $654 for each inaccurate expanded test. The product of 400,000 and $654 gives us an estimated $262 million in cost saving benefits from averting future over payment.

c. Reduction in Costs from Lawsuits.

Compliance with applicable legal requirements for IVDs offered as LDTs may reduce the incidence of litigation over alleged harms caused by problematic IVDs. In this case ex ante compliance can prevent some sellers of IVDs offered as LDTs from widespread marketing of problematic IVDs before they become the subject of litigation. We do not quantify the overall welfare losses due to tort costs but provide one case study concerning a COVID-19 test offered without emergency use authorization from FDA, to highlight the magnitude of the problem.

On March 1st, 2022, Blue Cross and Blue Shield of Minnesota (Blue Cross or BCBSM) took legal action against COVID-19 testing laboratory GS Labs, LLC (GS Labs) to recover more than $10 million in overpayments made since the start of the pandemic.~~[69]~~ (Ref. [42]). Blue Cross

[68] Ibid.

~~[69] Blue Cross and Blue Shield of Minnesota Files Lawsuit Against GS Labs, Mar. 2, 2022, https://www.bluecrossmn.com/about-us/newsroom/news-releases/blue-cross-and-blue-shield-minnesota-files-lawsuit-against-gs-labs.~~

sued GS Labs for violations of Minnesota consumer protection law, fraud, and ERISA violations. BCBSM alleged that GS Labs charged unreasonably high prices for unnecessary, problematic IVDs ~~and~~. They also described endemic problems with GS Labs' testing, including a Nebraska Department of Health and Human Services order for remedial measures in March 2021~~. The~~(the Department found that GS Labs' facilities had failed to meet the standards necessary to perform clinical testing under CLIA~~.~~). GS Labs also sent correspondence to patients that it had identified a lapse in its "quality control process" for certain of its PCR testing. The incident caused it to "deviate[ ] from applicable laboratory standards for testing facilities" during a period of several weeks. GS Labs stated that this lapse in quality control "may have impacted [patients'] test results." The case is currently ongoing~~.[70,71]~~ (Refs. [42] and [43]).

In a 2022 report from the U.S. Chamber of Commerce Institute for Legal Reform (ILR), high costs from the tort system lead to higher prices for other things in the economy. Compensation to claimants (when they win a case) only represents 53 percent of the total size of the tort system, while the remaining litigation and risk transfer costs make up about 47 percent of expenses in the system. In other words, for every $1.00 received by claimants, $0.88 was paid in legal and other costs ($1 / $1.88 =53~~%).~~[72]%) (Ref. [44]). Assuming total litigation and risk transfer costs would be the opportunity costs of having the problem dealt with *ex-ante* via compliance with applicable requirements instead of *ex-post* via litigation, a $10 million dollar case litigation and risk transfer costs would be 47 percent of $10 million dollars or $4.7 million. For an aggregate $100 million award, litigation and risk transfer costs would be $47 million.

d. Reduction in Costs to Healthcare Systems

~~[70] https://www.mprnews.org/story/2022/07/28/gs-labs-covid-testing-minnesota~~
~~[71] https://www.bluecrossmn.com/about-us/newsroom/news-releases/blue-cross-and-blue-shield-minnesota-files-lawsuit-against-gs-labs~~
~~[72] https://instituteforlegalreform.com/research/tort-costs-in-america-an-empirical-analysis-of-costs-and-compensation-of-the-u-s-tort-system/~~

When laboratories make decisions about the use of IVDs offered as LDTs, some of their choices may rest on the potentially lower costs of product adoption, which generally favor IVDs offered as LDTs. However, there are potential costs to patients and the broader health ~~system~~system[73] when the IVDs offered as LDTs are less safe or effective relative to other IVDs. From a holistic cost of care point of view, costs saving in the laboratory budget may result in more spending elsewhere in the system, such as by pharmacies or hospitals (Ref. [8]). For example, when many patients receive a false positive result from a problematic IVD offered as an LDT, and receive treatment like surgery for a disease or condition they do not have, the resources used for their surgery may be diverted from patients who actually might need surgery. To meet the increased demand for surgical rooms, hospitals may divert resources from one area to invest more in surgery capacity when they otherwise would not have to.

In a 2015 study by Vyberg, et al., the authors compared false negative (FN) and false positive (FP) rates between IVDs offered as LDTs (FN 35%, FP 5%) and other IVDs (FN 11%, FP 0%) intended to test for human epidermal growth factor receptor 2 (HER2), for a total of 1,703 tests (Ref. [45]). The authors ran these IVDs through their economic models and found that other IVDs would result in better clinical outcomes, less disease progression and lower costs, versus the IVDs offered as LDTs. The authors also noted that every $1 saved by laboratories by using cheaper reagents, could potentially result in approximately $6 additional costs to the healthcare system. We are unable to extrapolate this ratio to the rest of the market

[73] The Compendium of U.S. Health Systems, 2016, defines a health system as an organization that includes at least one hospital and at least one group of physicians that provides comprehensive care (including primary and specialty care) who are connected with each other and with the hospital through common ownership or joint management. Under this definition, foundation models are considered a form of joint management, while joint participation among providers in an accountable care organization is not, by itself, indicative of joint management. Source: https://www.ahrq.gov/chsp/defining-health-systems/index.html. Viewed on June 28, 2023.

because: the difference in prices among currently marketed IVDs offered as LDTs and comparable other IVDs is not known.[74]

4. Summary of Benefits

Quantified health benefits include the sum of ~~one-time~~ benefits derived from two selected case studies (COVID-19 and heart disease) aggregated at a case study level and annual or recurring health benefits from a reduction in problematic IVDs offered as LDTs for ~~oncology~~other applications. The case studies represent selected cases that occurred in the past that FDA ~~premarket review~~oversight may have prevented, and therefore quantified (undiscounted) health benefits represent ~~a~~ minimum ~~estimate of $4 billion. Recurring (undiscounted) health benefits from a reduction in problematic IVDs offered as LDTs for oncology applications range from $2.74 billion to $200 billion (Table 15).~~ estimates.

Non-health benefits are the sum of one time and recurring costs savings from avoiding payment for problematic IVDs. The one-time (non-health) benefit estimate of $~~438~~262 million is based on two case studies (COVID-19 and NIPS) and should be considered a minimum estimate. Total undiscounted recurring non-health benefits range from ~~$3.71 billion~~59 million to $~~20.57~~1.3 billion with a primary estimate of ~~$15.65 billion~~369 million (Table ~~15~~14).

Unquantified benefits would include the reduction in costs from lawsuits and reduction in costs to healthcare systems.

Due to limited resources, we are unable to produce generalized estimates for benefits from individual case studies except for recurring health benefits from a reduction in problematic

[74] Vyberg et al.'s cost calculator is not explained in sufficient detail for us to confirm their claim that a societal perspective is reflected in the study (see Kim et al. (Ref. [64]) and Sanders et al. (Ref. [65]) for discussion of widespread errors in cost perspective identification); and such practices as adding productivity estimates to QALYs has noteworthy potential to generate double-counting, thus raising general questions about the soundness of Vyberg et al.'s quantitative methods.

IVDs offered as LDTs ~~for oncology applications and cost saving (non-health) benefits from avoiding future payment for problematic IVDs. The total one-time benefit is the sum of benefits from selected case studies that we were able to aggregate at a case study level. The case studies represent selected cases that occurred in the past that FDA premarket review may have prevented and therefore the one-time benefit estimate represents a minimum estimate. The total recurring annual benefit is the sum of all generalized estimates. The estimated benefits associated with COVID-19 are based on both generalized (recurring) and case study (one-time) estimates~~and non-health benefits from avoiding future wasted spending on problematic IVDs.

We present total benefits ~~estimates~~ and ~~the sum of~~subtotal health and non-health benefits in Table ~~15~~14.

Table 14. Total Minimum Undiscounted Benefits (millions 2022$)

Health Benefits (VSLY – 3%)			**Recurring Annual Benefits**		
Type	**Level**	**One Time Benefits (minimum)**	Low	Central	High
~~Cancer~~Conditions other than COVID-19 or Heart Disease	Generalized	-	$~~2,664~~1,777	$~~63,937~~26,310	$~~199,867~~72,723
COVID-19	Case study	~~$1,385~~	-~~$61~~	-$	-$

				71	81
Heart Disease	Case study	$~~2,191~~ 3,857	-	-	-
~~Subtotal~~ Health Benefits (VSLY – 3%)		***~~$3,857~~***	$1,838	$266,381	$722,804
~~Subtotal~~ Health Benefits (VSLY – 7%)		***~~$3,577~~*****One Time Benefits (minimum)**	***~~$2,664~~*****Recurring Annual Benefits**	~~$633,937~~	~~$1,999,866~~
Type	**Level**		***Type***	***Level***	
Conditions other than COVID-19 or Heart Disease	Generalized		$2,670	$39,530	$1,092,263
COVID-19	Case study		$101	$117	$1134
Heart Disease	Case study	$6,499			
Subtotal Health Benefits (VSLY – 7%)		***$6,499***	$2,771	$39,647	$1,093,396
Non health Benefits					
Reduced Overpayment	Generalized	-	$~~80~~58	$~~9~~4	$~~2~~,

				~~9~~ 368	~~0~~ 4~~9~~1,277
COVID-19	Case Study	~~$176~~	$1	$1	$2
NIPS	Case Study	$262			
Subtotal Non-Health Benefits		***$~~438~~262***	$~~80~~59	$ ~~9~~ ~~4~~ ~~9~~ 369	$ ~~2~~,~~0~~ ~~4~~ ~~9~~1,278
Total Sum of Benefits (VSLY – 3%)		**$4,~~01~~4119**	**$~~2,744~~1,898**	**$ ~~6~~ ~~4~~,~~8~~ ~~8~~ ~~6~~ 2~~6~~,751**	**$ ~~2~~ ~~0~~ ~~1~~,~~9~~ ~~1~~ ~~5~~ 7~~4~~,082**
Total Sum of Benefits (VSLY – 7%)		**$6,761**	**$2,830**	**$ 40,017**	**$ 110,674**

~~We~~ Generally speaking, we expect benefits to begin to accrue ~~one year~~two years after ~~Stage 1~~publication of the ~~proposed~~final phaseout policy ~~described in the rule is in effect (on year 2),~~ though we do not expect all estimated benefits to take place all at once. Instead, we assume that one-time benefits will occur evenly over Stages 1 to 5 of the ~~first four years~~final phaseout policy (year ~~2~~3 to year 5). We also expect recurring benefits to begin to accrue at an incremental rate of ~~25~~0%, 50%, 75%, and 100% for the first four years (Table ~~16~~15). The ~~present~~annualized value ~~sum of benefits~~ is estimated as $~~549~~22.3 billion using a 7 percent discount rate and $~~816~~31.4 billion using a 3 percent discount rate. ~~The annualized present value sum is estimated as $51.78 billion using a 7 percent discount rate and $54.85 billion using a 3 percent discount rate.~~

Table 15. Undiscounted ~~and Discounted~~ Benefits Stream (Primary Estimate in Millions 2022$, 20 years, 3% and 7%)

	Rate		Year	If VSLY based on 3% discounting			If VSLY based on 7% discounting		
~~Stage~~	~~Rate (~~One-time~~)~~	~~Rate (~~Recurring~~)~~	~~Year~~	~~(A)~~ One-time ~~Undiscounted~~	~~(B)~~ Recurring ~~Undiscounted~~	~~Sum (A+B) Discounted at 3%~~ Total	~~Sum (A+B) Discounted at 7%~~One-time	Recurring	Total
			1	$0	$0	$0	$0	$0	$0
~~Stage~~ 1	0~~.25~~	0~~.25~~	2	$~~1,004~~0	$~~16,221~~0	$~~16,236~~0	$~~15,045~~0	$0	$0
~~Stage~~ 2	0.~~25~~33	0.5	3	$1,~~004~~359	$~~32,443~~13,375	$~~30,608~~14,735	$~~27,302~~2,231	$20,008	$22,239
~~Stages~~ 3 & 4	0.~~25~~33	0.75	4	$1,~~004~~359	$~~48,664~~20,063	$~~44,129~~21,422	$~~37,892~~2,231	$30,013	$32,244
~~Stages~~ 4 & 5	0.~~25~~33	1	5	$1,~~004~~359	$~~64,886~~26,751	$~~56,837~~28,110	$~~46,978~~2,231	$40,017	$42,248

	0	÷1	6	$0	$64,88626,751	$54,34126,751	$43,2360	$40,017	$40,017
	0:	:	:	:	-:	:-	-:	:	:
	0	÷	÷	÷	-÷	÷	-÷		
	0	÷	÷	÷	-÷	÷	-÷		
	0	1	20	$0	$64,88626,751	$35,92626,751	$16,7680	$40,017	$40,017
Sum				$4,014078	$1,135,505461,453	$815,992465,531	$548,5756,693	$690,292	$696,985
Annualized Present Value					-	$54,84722,332	$51,782		$31,408

F. Costs of the Proposed Rule

The proposed rule (if finalized) would not establish any new requirements. FDA is proposing to phase out its general enforcement discretion approach so that IVDs generally would be expected to meet existing medical device requirements, regardless of whether the IVDs have been manufactured by a laboratory or other manufacturer.

FDA has structured the phaseout policy to contain five key stages. In each stage, the general enforcement discretion approach would be phased out with respect to certain requirements for most IVDs that are offered as LDTs by laboratories that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing[75], such that, upon completion of the phaseout, these IVDs manufactured by laboratories would generally fall under the same enforcement approach as other IVDs.

- Stage 1: End the general enforcement discretion approach with respect to MDR and correction and removal reporting requirements one year after FDA publishes the final phaseout policy, which FDA intends to issue in the preamble of the final rule.

[75] Other laboratories would be out of compliance with CLIA regulations if they were developing and performing tests that are not FDA authorized, and such tests have never fallen within FDA's general enforcement discretion approach.

- Stage 2: End the general enforcement discretion approach with respect to requirements not covered during other stages of the phaseout policy, including registration and listing, labeling, and investigational use requirements two years after FDA publishes the final phaseout policy.
- Stage 3: End the general enforcement discretion approach with respect to quality system (QS) requirements three years after FDA publishes the final phaseout policy.
- Stage 4: End the general enforcement discretion approach with respect to premarket ~~approval~~review requirements ~~(~~for high-risk IVDs~~)~~ three and a half years after FDA publishes the final phaseout policy, but not before October 1, 2027.
- Stage 5: End the general enforcement discretion approach with respect to premarket ~~submission~~review requirements for moderate risk and low risk IVDs that require premarket submissions four years after FDA publishes the final phaseout policy, but not before April 1, 2028.

When calculating the costs for each stage of the phaseout policy described in the proposed rule, we use wage information from the Bureau of Labor Statistics Occupational Employment and Wage Statistics.[76] Specifically, we use wage information for a specific industry: medical and diagnostic laboratories.[77]

The remainder of this section discusses the estimated cost of the proposed rule by stage of the phaseout policy. Section II.F.~~5~~6 discusses additional cost considerations that we do not quantify.

1. Costs Under Stage 1

[76] https://www.bls.gov/oes/current/naics4_621500.htm
[77] NAICS code: 621500

Under Stage 1, FDA would expect ~~laboratories~~laboratories[78] to comply with MDR requirements (requirements for adverse event reporting) under 21 U.S.C. 360i(a)-(c) and 21 CFR part 803 and correction and removal reporting requirements under 21 U.S.C. 360i(g) and 21 CFR part 806 one year after FDA publishes a final phaseout policy. During the first year following the proposed rule (if finalized), laboratories would face costs associated with compliance with Stage 1, as well as costs associated with reading and understanding the rule in its entirety.

a. Costs To Read and Understand The Rule

We expect that laboratories affected by this rule will incur costs to read and understand the rule. We assume an average of one medical laboratory manager and one attorney at each entity will read the rule. Consistent with guidelines from the Department of Health and Human ~~Services~~Services[79], we assume that the reading speed of regulation reviewers ranges from 200 to 250 words per minute. The proposed rule has approximately 24,500 words. The overall burden in hours (per reader) to read the rule ranges from 1.63 hours (= (24,500 words / 250 words per minute) / 60 mins per hour) to 2.04 hours (= (24,500 words / 200 words per minute) / 60 mins per hour). The mean hourly wages for managers and lawyers in this industry are $57.28 and $78.93, respectively.[80] Fully loaded wage rates are $114.56 an hour for managers and $157.86 an hour for lawyers (average: $136.21).[81] We assume that one to three employees will read the rule. The estimated learning costs per entity would range from $222.48 (=1.63 hours x $136.21 per hour x 1 employee) to $834.29 (=2.04 hours x $136.21 per hour x 3 employees), with a primary

[78] In this section, when we use the word "laboratories," we refer to manufacturers who offer IVDs as LDTs that are within the scope of the proposed phaseout policy.
[79] https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis
[80] NAICS code 621500, occupation codes 11-1021 for general and operations managers and 23-1011 for lawyers. Available from: https://www.bls.gov/oes/current/naics4_621500.htm
[81] Fully-loaded wages account for employee benefits and overhead on top of the hourly wage, calculated by doubling the published wage rate.

cost of $494.39 (=1.81 hours x $136.21 per hour x 2 employees). Multiplying this estimate by the total numbers of affected laboratories per year yields a total one-time cost for reading the rule between $0.13 million and $2.00 million, with a primary estimate of $0.59 million. The estimated total recurring cost ranges from $0.01 million to $0.16 million, with a primary estimate of $0.05 million (see Table ~~17~~16).

Table 16. Costs of Reading and Understanding the Rule

	Primary	Low	High
Average reading speed (words/minute)	225	250	200
Length of proposed preamble & codified (words)	24,500	24,500	24,500
Hours	1.81	1.63	2.04
Number of employees to read rule	2	1	3
Labor cost of hourly employee	$136.21	$136.21	$136.21
Per-laboratory cost	$494.39	$222.48	$834.29
Number of affected laboratories	1,200	600	2,400
Number of new laboratories per year	96	48	192
Total One-time Costs (millions)	**$0.59**	**$0.13**	**$2.00**
Total Recurring Costs (millions)	**$0.05**	**$0.01**	**$0.16**

Note: Product across table may not be exact due to rounding.

b. Costs of Medical Device Reporting

Under Stage 1, FDA would expect laboratories to comply with MDR requirements under 21 U.S.C. 360i(a)-(c) and 21 CFR part 803. In estimating the costs of compliance for laboratories, we use a similar approach to the *Medical Device Reporting: Electronic Submission Requirements* final regulatory impact analysis (Ref. [46]). We expect that ~~the majority of MDR costs~~laboratories will ~~be~~face one-time costs associated with establishing a reporting system for laboratories for which, at baseline, the requirement to have such systems generally has not been enforced. We also expect new laboratories to enter the market each

year, so we assume that the new entities will incur recurring costs associated with establishing a reporting system.

We expect laboratories to modify standard operating procedures (SOPs) in response to the MDR requirements. We estimate it will take 1 – 3 management employees with an hourly wage of $60.55 ($121.10 fully-loaded) 8 – 12 hours each to modify a laboratory's SOP. Multiplying these estimates, we estimate the one-time costs of modifying SOPs to be between $0.58 million and $10.46 million, with a primary estimate of $2.91 million. We estimate the recurring costs to range from $0.05 million to $0.84 million, with a primary estimate of $0.23 million. See Table ~~18~~17.

We expect laboratories to install and validate e-Submitter software for the purposes of complying with MDR requirements. We expect this task to take a single computer and information system manager 48 to 56 hours, working at an hourly wage of $73.25 ($146.50 fully loaded). Multiplying by the number of affected entities, we estimate the one-time costs of installing and validating e-Submitter software to be between $4.22 million and $19.69 million, with a primary estimate of $9.14 million. We estimate the recurring costs to be between $0.34 million to $1.58 million, with a primary estimate of $0.73 million.

We expect 0.6% of covered laboratories to establish Health Level Seven (HL7) Individual Case Study Report (ICSR) capability. We expect this task to take a single computer and information system manager 48 to 52 hours, working at an hourly wage of $73.25 ($146.50 fully loaded). Multiplying by the small fraction of laboratories that we expect to establish such capabilities, we estimate the one-time costs to range between $0.03 million to $0.11 million, with a primary estimate of $0.05 million. We estimate the recurring costs to be between $0.002 million to $0.01 million, with a primary estimate of $0.004 million.

We expect laboratories to acquire an e-certificate from a third-party system to commence medical device reporting. We estimate that there is a small one-time search cost of acquiring the e-certificate of $20. Multiplied by the number of affected entities, we estimate the one-time costs of acquiring an e-certificate to range from $0.01 million to $0.05 million, with a primary estimate of $0.02 million. We estimate the recurring costs to range from $0.001 million to $0.004 million, with a primary estimate of $0.002 million.

We also expect a small recurring cost associated with the payment of an annual fee to maintain e-certification in the reporting system. We anticipate an annual $10 search cost that applies to each affected laboratory. Multiplying by the number of total laboratories, we estimate this recurring cost to range from $0.01 million to $0.02 million, with a primary estimate of $0.01 million.

Finally, we expect ~~an~~a recurring cost associated with filing and submitting MDRs. We estimate it will take computer and information system managers 430 ~~hours~~hours[82], working with an hourly wage of $73.25 ($146.50 fully loaded). Multiplying by the number of affected entities, we estimate this recurring cost to range from $37.79 million to $151.16 million, with a primary estimate of $75.58 million.

Overall, we expect the total one-time costs for complying with MDR requirements in Stage 1 of the proposed rule to range from $4.84 million to $30.31 million, with a primary estimate of $12.12 million. The estimated total recurring costs range from $38.18 million to $153.61 million, with a primary estimate of $76.56 million. See Table ~~18~~17.

[82] We use annual reporting and ~~recording~~record keeping burdens from a prior analysis of medical device reporting. In particular, we use the average number of hours associated with creating a medical device report, multiplied by the average number of reports per respondent~~. See https://www.federalregister.gov/documents/2014/02/14/2014-03279/medical-device-reporting-electronic-submission-requirements~~ (Ref. [46]).

Table 17: Costs of Medical Device Reporting

		Primary	Low	High
One-time/Annual				
Modifying SOPs	Hours	10	8	12
	Wage	$121.10	$121.10	$121.10
	Employees	2	1	3
	Entities affected	1,200	600	2,400
	New entities per year	96	48	192
	One-time Subtotal (millions)	*$2.91*	*$0.58*	*$10.46*
	Recurring Subtotal (millions)	*$0.23*	*$0.05*	*$0.84*
Install and Validate e-Submitter Software	Hours	52	48	56
	Wage	$146.50	$146.50	$146.50
	Employees	1	1	1
	Entities affected	1,200	600	2,400
	New entities per year	96	48	192
	One-time Subtotal (millions)	*$9.14*	*$4.22*	*$19.69*
	Recurring Subtotal (millions)	*$0.73*	*$0.34*	*$1.58*
Establish HL7ICSR capability	Hours	50	48	52
	Wage	$146.50	$146.50	$146.50
	Employees	1	1	1
	Entities affected	7	4	14
	New entities per year	1	0	1
	One-time Subtotal (millions)	*$0.05*	*$0.03*	*$0.11*
	Recurring Subtotal (millions)	*$0.004*	*$0.002*	*$0.01*
Acquiring e-Certificate	Search cost	$20.00	$20.00	$20.00
	Entities affected	1,200	600	2,400
	New entities per year	96	48	192
	One-time Subtotal (millions)	*$0.02*	*$0.01*	*$0.05*
	Recurring Subtotal (millions)	*$0.002*	*$0.001*	*$0.004*
Recurring Annual				
Maintaining Certificates	Search cost	$10.00	$10.00	$10.00
	Entities affected	*1,200*	*600*	*2,400*
	Recurring Subtotal (millions)	*$0.01*	*$0.01*	*$0.02*
Filing and submitting MDRs	Hours	430	430	430
	Wage	$146.50	$146.50	$146.50
	Entities affected	1,200	600	2,400

	Recurring Subtotal (millions)	*$75.58*	*$37.79*	*$151.16*
Total One-time Costs (millions)		**$12.12**	**$4.84**	**$30.31**
Total Recurring Costs (millions)		**$76.56**	**$38.18**	**$153.61**

c. Costs of Correction and Removal Reporting

Under Stage 1, FDA would expect laboratories to comply with correction and removal reporting under 21 U.S.C. 360i(g) and 21 CFR part 806. In estimating the costs of compliance for laboratories, we use information from the 2020 FDA notice: *Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals* (Ref. [47]). We expect that the majority of correction and removal reporting costs will be recurring costs associated with creating correction and removal reports. At baseline, the requirement to create such reports generally has not been enforced.

We expect 50% of laboratories to purchase a digital verification certificate to assist with correction and removal reporting. We expect this certificate to cost $50. Multiplying by the number of affected entities, we expect a one-time cost of purchasing a digital verification certificate to range from $0.02 million to $0.06 million, with a primary estimate of $0.03 million. Multiplying by the number of new entities per year, we expect ~~an~~a recurring cost of purchasing a digital verification certificate to range from $1,200 to $4,800, with a primary estimate of $2,400.

We expect laboratories to incur a recurring cost associated with correction and removal reporting requirements. We assume it will take a single general/operations manager working at an hourly wage of $57.28 ($114.56 fully-loaded) 10 hours to create a single correction and removal report. The 2020 FDA notice *Agency Information Collection Activities; Submission*

for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals acknowledged 1,033 correction and removal reports~~.~~ per year per entity. In the same year (2020), the U.S. Census Statistics of U.S. Businesses (SUSB) estimated there were approximately 9,338 medical device manufacturing establishments in the U.S.[83] These numbers suggest that there are approximately 0.11 correction and removal reports per year per entity. We assume that ratio is the same for laboratories and apply the ratio to the total number of affected entities. Multiplying all elements together, we estimate the recurring cost of correction and removal reporting to range between $0.08 million to $0.30 million, with a primary estimate of $0.15 million.

Overall, we expect the total one-time costs for correction and removal reporting in Stage 1 of the proposed rule to range between $0.02 million to $0.06 million, with a primary estimate of $0.03 million. The estimated total recurring costs range from $0.08 million to $0.31 million, with a primary estimate of $0.15 million. See Table ~~19~~18.

Table 18~~:~~. Costs of Correction and Removal Reporting

		Primary	Low	High
One-time/Annual				
Digital Verification Certificate	Flat fee	$50.00	$50.00	$50.00
	Entities affected	600	300	1,200
	New entities per year	48	24	96
	One-time Subtotal (millions)	*$0.03*	*$0.02*	*$0.06*
	Recurring Subtotal	*$2,400*	*$1,200*	*$4,800*
Recurring Annual				
Reporting	Hours per report	10	10	10
	Number of reports per entity	0.11	0.11	0.11
	Wage	$114.56	$114.56	$114.56
	Entities affected	1,200	600	2,400
	Recurring Subtotal (millions)	*$0.15*	*$0.08*	*$0.30*

[83] We select NAICS code 33911: Medical Equipment and Supplies Manufacturing from the full dataset available at: https://www.census.gov/data/datasets/2020/econ/susb/2020-susb.html

Total One-time Costs (millions)	**$0.03**	**$0.02**	**$0.06**
Total Recurring Costs (millions)	**$0.15**	**$0.08**	**$0.31**

2. Costs Under Stage 2

Under Stage 2, FDA would expect that laboratories comply with requirements not covered during other stages of the phaseout policy two years after FDA publishes a final phaseout policy. These requirements include registration and listing requirements (21 U.S.C. 360 and 21 CFR part 807, excluding subpart E), labeling requirements (21 U.S.C. 352 and 21 CFR parts 801 and 809, subpart B), and investigational use requirements (21 U.S.C. 360j(g) and 21 CFR part 812).[84]

a. Costs of Registration and Listing

Under Stage 2, FDA would expect laboratories to comply with registration and listing requirements under 21 U.S.C. 360 and 21 CFR part 807 (excluding subpart E). In estimating the costs of compliance for laboratories, we use a similar approach to the 2016 *Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs That Are Regulated Under a Biologics License Application, and Animal Drugs* final regulatory impact analysis (Ref. [48]). We anticipate one-time costs associated with registration and listing requirements and recurring costs associated with re-registration.

[84] We anticipate that costs for compliance with any other requirements under Stage 2 such as mandatory recall orders under section 518(e) of the FD&C Act, or notification orders under section 518(a) of the FD&C Act because these requirements would only be triggered under certain circumstances. Therefore, the costs would be minimal compared to the costs for compliance with the requirements listed ~~here and described below.~~below. In addition, if requirements listed below are appropriately satisfied, these other requirements generally should not become applicable.

We expect the registration and listing would take a general/operations manager 3 hours, working at a wage of $57.28 ($114.56 fully loaded), to complete registration for a single establishment and to list that establishment's IVDs offered as LDTs.[85] We also expect that annual re-registration and listing updates would take a general/operations manager 1 hour. Multiplying by the numbers of affected entities per year, we expect total one-time costs for registration and listing requirements to range between $0.21 million and $0.82 million, with a primary estimate of $0.17 million. The estimated total recurring costs range from $0.09 million to $0.34 million, with a primary estimate of $0.17 million. See Table ~~20~~19.

Table 19~~:~~. Costs of Registration and Listing

		Primary	Low	High
One-time/Annual				
Initial registration and listing of IVDs offered as LDTs	Hours	3	3	3
	Wage	$114.56	$114.56	$114.56
	Entities affected	1,200	600	2,400
	New entities per year	96	48	192
	One-time Subtotal (millions)	*$0.41*	*$0.21*	*$0.82*
	Recurring Subtotal (millions)	*$0.03*	*$0.02*	*$0.07*
Recurring Annual				
Re-registration	Hours	1	1	1
	Wage	$114.56	$114.56	$114.56
	Entities affected	1,200	600	2,400
	Recurring Subtotal (millions)	*$0.14*	*$0.07*	*$0.27*
Total One-time Costs (millions)		**$0.41**	**$0.21**	**$0.82**
Total Recurring Costs (millions)		**$0.17**	**$0.09**	**$0.34**

b. Costs of Labeling

[85] We assume that each affected laboratory will list an average number of 67 product listings and an average number of 6 new product listings per year, based on our estimates discussed in section II.D.1.

Under Stage 2, FDA would expect laboratories to comply with labeling requirements under 21 U.S.C. 352, 21 CFR part 801, and 21 CFR part 809, subpart B. We anticipate one-time and recurring costs associated with revising existing labeling.

We expect it will take a general/operations manager, working at a wage of $57.28 ($114.56 fully-loaded), [86] 4 to 34 hours (with a primary estimate of 20 hours) to redesign existing labeling for IVDs offered as LDTs to comply with labeling requirements. (Ref. [49]). Multiplying by the number of expected entities, we expect the one-time cost of revising existing labeling to range between $0.27 million and $9.35 million, with a primary estimate of $2.75 million.[87] Multiplying the estimates by the number of new entities per year, we expect the recurring cost to range between $0.02 million to $0.75 million, with a primary estimate of $0.22 million.

We estimate the total one-time costs of labeling to range between $0.27 million and $9.35 million, with a primary estimate of $2.75 million. The estimated total recurring costs range from $0.02 million to $0.75 million, with a primary estimate of $0.22 million. See Table 2120.

Table 20. Costs of Labeling

		Primary	Low	High
Revise existing labeling	Hours	20	4	34
	Wage	$114.56	$114.56	$114.56
	Entities affected	1,200	600	2,400
	New entities per year	96	48	192
	One-time Subtotal (millions)	*$2.75*	*$0.27*	*$9.35*
	Recurring Subtotal (millions)	*$0.22*	*$0.02*	*$0.75*

[86] NAICS code 621500, occupation codes 11-1021 for general and operations managers. Available from: https://www.bls.gov/oes/current/naics4_621500.htm

[87] As discussed in section II.D.1, we assume each affected laboratory would offer 67 IVDs offered as LDTs and 6 new IVDs offered as LDTs per year.

Total One-time Costs (millions)	**$2.75**	**$0.27**	**$9.35**
Total Recurring Costs (millions)	**$0.22**	**$0.02**	**$0.75**

c. Costs of Complying with Investigational Use Requirements

Under Stage 2, FDA would expect laboratories to comply with investigational use requirements under 21 U.S.C. 360j(g) and 21 CFR part 812. Medical devices that are used for investigational purposes (i.e., that are the object of a clinical investigation or research involving one or more subjects to determine device safety and/or effectiveness) and have an investigational device exemption (IDE) application approved or considered approved under 21 CFR part 812, or are exempt from the requirements under that part, are exempted from various other requirements under the FD&C Act and FDA's regulations, such as premarket approval. These devices are subject to other requirements, outlined in 21 CFR part 812. We anticipate one-time and annual costs associated with complying with investigational device exemption requirements under 21 U.S.C. 360j(g) and 21 CFR part 812.

We use two estimates from existing literature as our low and high estimates of the cost of ~~compliance~~complying with IDE application requirements (Refs. [50, 51]).[88] We use a primary estimate as the median between the low and high estimates. Overall, we expect the cost of developing an IDE application for an IVD offered as an LDT to range between $5,265 and $48,000, with a primary estimate of $26,633.[89]

[88] IDE requirements in 21 CFR part 812 include certain requirements distinct from the requirement for approval of an IDE application, such as certain recordkeeping and labeling requirements. We anticipate that costs for compliance with these other requirements, where applicable, would be minimal compared to the costs discussed in this subsection for preparing and submitting an IDE application.

~~[89] IDE requirements in 21 CFR part 812 include certain requirements in addition to the requirement for approval of an IDE application, such as certain recordkeeping and labeling requirements. We anticipate that costs for compliance with these other requirements, where applicable, would be minimal compared to the costs discussed in this subsection for preparing and submitting an IDE application.~~

We assume two percent of the existing IVDs offered as LDTs are investigational, based on extrapolation of internal information from NYSDOH regarding the percent of IVD submissions they receive that are for investigational IVDs offered as LDTs. (Ref. [14]). NYSDOH receives IVD submission packages for IVDs offered as LDTs that are not "designated as FDA-cleared, approved, or exempt,"[90] (Ref. [15]) and these submission packages include clinical trial tests as well as high, moderate, and low risk tests offered for clinical use, based on NYSDOH criteria. Over a two-year period, approximately two percent of IVD submission packages received by NYSDOH were for clinical trial IVDs per NYSDOH criteria.

Not all investigational IVDs require an IDE application.[91] Based on the number of IVD IDE submissions and the number of IVD premarket submissions that FDA received over a four-year period, we estimate that we receive about 13.5 IVD IDE submissions for every 100 premarket submissions. Therefore, we estimate that about 13.5% of investigational IVDs offered as LDTs that would later be subject to premarket review would first submit an IDE application. As described in section II.F.4, we estimate that 50% of IVDs require a premarket submission. Applying these factors, we estimate that 6.75% (which represents 50% x 13.5%) of investigational IVDs would require an IDE application.

The number of IDE applications for IVDs currently offered as an LDT can be estimated by multiplying the percent of investigational IVDs currently offered as an LDT (2%) by the percent of investigational IVDs that would require an IDE application (6.75%) by the number of affected IVDs offered as LDTs.

[90] https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval

[91] IDE requirements in 21 CFR part 812 do not apply to investigations of certain types of devices. See 21 CFR 812.2(c). Moreover, certain categories of investigations are considered to have an approved IDE application. See 21 CFR 812.2(b).

We also expect there would be new investigational IVDs introduced every year, at a rate of anywhere between 1% and 100% of new IVDs. To account for our uncertainty, we assume that the mean value between 1% and 100% or 50% of the new IVDs would be investigational. As described above, we estimate that 6.75% of investigational IVDs would require an IDE.

Multiplying the cost estimates from literature by the relevant percentages and number of affected IVDs offered as LDTs, we expect the total one-time costs of preparing and submitting IDE applications for the existing IVDs offered as LDTs to range between $0.29 million and $10.42 million, with a primary estimate of $2.89 million. The estimated total annual costs range from $0.69 million to $25.19 million, with a primary estimate of $6.99 million. See Table ~~22~~21.

Table 21~~:~~. Costs of Complying with Investigational Use Requirements

		Primary	Low	High
One-time				
Total cost of preparing/ submitting IDE	Inflation-adjusted estimate from literature	$26,633	$5,265	$48,000
	Percent of IVDs offered as LDTs that are investigational	2	2	2
	Percent of investigational IVDs offered as LDTs that require submission of IDE application	6.75	6.75	6.75
	IVDs currently offered as LDTs affected	80,400	40,200	160,800
	One-time Subtotal (millions)	*$2.89*	*$0.29*	*$10.42*
Annual				
Total cost of preparing/ submitting IDE	Inflation-adjusted estimate from literature	$26,633	$5,265	$48,000
	Percent of IVDs offered as LDTs that are investigational	50	50	50
	Percent of investigational IVDs offered as LDTs that require submission of IDE application	6.75	6.75	6.75

	New IVDs offered as LDTs per year	7,776	3,888	15,552
	Annual Subtotal (millions)	*$6.99*	*$0.69*	*$25.19*
Total One-time Costs (millions)		**$2.89**	**$0.29**	**$10.42**
Total Annual Costs (millions)		**$6.99**	**$0.69**	**$25.19**

3. Costs Under Stage 3

Under Stage 3, at the three-year mark, FDA would expect compliance with the QS requirements under 21 U.S.C. 360j(f) and 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 with some, but not all, of the QS requirements. As described in section VI.B.3 of the proposed rule, for these IVDs, FDA would expect compliance with 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 21 CFR part 820, subpart M. As further described in section VI.B.3 of the proposed rule, for any IVDs that are within the scope of the proposed phaseout policy but for which all manufacturing activities do not occur within a single laboratory, and/or which are distributed outside of that single laboratory, FDA would also expect compliance with the other QS requirements under 21 U.S.C. 360j(f) and 21 CFR part 820 ~~3~~three years after finalizing the phaseout policy. We lack the evidence to quantify the numbers of IVDs that are within the scope of the proposed phaseout policy but for which all manufacturing activities do not occur within a single laboratory, and/or which are distributed outside of that single laboratory. To

account for uncertainty, we consider different assumptions for low, primary, and high estimates. We first assume that for all IVDs within the scope of the proposed phaseout policy, all manufacturing activities occur within a single laboratory to estimate a lower bound estimate. For an upper bound estimate, we assume that all manufacturing activities do not occur within a single laboratory for any IVD within the scope of the proposed phaseout policy. We use an average of the lower and upper bound estimates for our primary estimate. We request comment on this assumption or sources of data to better analyze the cost of Stage 3.

In estimating the costs of compliance for laboratories, we use number of annual labor hours and proportion of types of labor (from vice president to clerical staff) needed to comply with each relevant provision of 21 CFR part 820. We also use wage rates to estimate costs of complying with these provisions for affected entities (see Table ~~23~~22).[92] Table ~~24~~23 shows the number of labor hours for compliance with each provision of Part 820~~.~~ (Refs. [52] [53]). We multiply the labor hours by appropriate wage rates and number of affected entities to estimate costs of compliance with the QS requirements under this stage.[93]

We expect the total one-time costs for compliance with the QS requirements in Stage 3 of the proposed rule to range from $6.19 million to $408.37 million, with a primary estimate of $72.56 million. The total recurring costs are estimated to range from $30.26 million to $1,869.50 million, with a primary estimate of $378.97 million. See Table ~~24~~23.

Table 22~~:~~. Medical and Diagnostic Laboratories Industry Wage Rates for Selected Labor Categories

Labor Category	Wages (/hour)	NAICS	OCC Code
Vice president	$60.92	621500	11-1000

[92] All wage rates are doubled to account for overhead costs. Available from: https://www.bls.gov/oes/current/naics4_621500.htm

[93] As discussed in section II.D.1, we assume each affected laboratory would offer 67 IVDs offered as LDTs and 6 new IVDs offered as LDTs per year.

Upper management	$73.25	621500	11-2000
Middle management	$61.74	621500	11-3000
Technical	$29.26	621500	29-0000
Admin support	$29.55	621500	43-6011
Clerical	$17.92	621500	43-4000

Table 23~~:~~. Costs of Compliance with Quality System Requirements

		Primary	Low	High
One-time/Annual				
820.20(a) Quality Policy	Hours	8	0	24
820.20(b) Organization	Hours	6	0	20
820.20(d) Quality Planning	Hours	14	0	40
820.20(e) Quality System Procedures	Hours	14	0	40
820.22 Quality Audit	Hours	8	0	24
820.25 Personnel, establish procedures for identifying training needs	Hours	8	0	24
820.25 Personnel, train in CGMP revisions	Hours	50	0	290
820.40 Document Controls	Hours	14	0	40
820.60 Identification and Traceability	Hours	8	0	24
820.72, 820.75 Inspection, measuring, and test equipment, process validation	Hours	23	0	72
820.70(i) Automated Processes	Hours	14	0	40
820.90 Nonconforming Product	Hours	14	0	40
820.140 Handling	Hours	8	0	24
820.200 Servicing	Hours	14	0	40
820.30(a) General	Hours	200	30	560
820.50(a) Assessment of Suppliers and Contractors	Hours	75	25	125
820.100 Corrective and Preventive Action	Hours	28	16	40
820.150 Storage	Hours	15	8	24
820.198 Records	Hours	28	16	40
Entities affected		1,200	600	2,400
New entities per year		96	48	192
Recurring Annual				
820.20(a) Quality Policy	Hours	1	0	2
820.20(b) Organization	Hours	1	0	2
820.20(c) Management Review	Hours	8	0	24
820.20(d) Quality Planning	Hours	4	0	10
820.20(e) Quality System Procedures	Hours	4	0	10
820.22 Quality Audit	Hours	1	0	2

820.25 Personnel, maintain procedures	Hours	1	0	2
820.40 Document Controls	Hours	2	0	4
820.60 Identification and Traceability	Hours	1	0	2
820.72, 820.75 Inspection, measuring, and test equipment, process validation	Hours	4	0	13
820.70(i) Automated Processes	Hours	2	0	4
820.90 Nonconforming Product	Hours	2	0	4
820.140 Handling	Hours	1	0	2
820.200 Servicing	Hours	2	0	4
820.30(a) General	Hours	20	3	56
820.30(b) Design and Development Planning	Hours	216	32	520
820.30(e) Design Review	Hours	942	82	2,574
820.30(f) Design Verification	Hours	1,681	249	4,047
820.30(h) Design Transfer	Hours	43	6	104
820.30(i) Design Changes	Hours	378	56	910
820.30(j) Design History File	Hours	22	3	52
820.50(a) and (b) Purchasing control	Hours	159	98	233
820.100 Corrective and Preventive Action	Hours	3	2	4
820.150 Storage	Hours	2	1	2
820.198 Records	Hours	3	2	4
Entities affected		1,200	600	2,400
Total One-time Costs (millions)		**$72.56**	**$6.19**	**$408.37**
Total Recurring Costs (millions)		**$378.97**	**$30.26**	**$1,869.50**

We note 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). Specifically, FDA proposed to withdraw the majority of the current requirements in part 820 and instead incorporate by reference the 2016 edition of the International Organization for Standardization (ISO) 13485, Medical devices – Quality management systems for regulatory purposes, in part 820. As stated in that proposed rule, the requirements in ISO 13485 are, when taken in totality, 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 the 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~~regulatory text 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~~regulatory text 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. We note that to the extent amended QS requirements are in effect, we do not expect the total costs for compliance with QS requirements in Stage 3 ~~of the proposed rule may~~to substantially change.

4. Costs Under Stages 4 and 5

Under Stage 4, FDA would expect laboratories to comply with premarket ~~approval~~review requirements for high-risk IVDs (21 U.S.C. 360e and 21 CFR part 814) beginning three and a half years after the publication of the final phaseout policy. Laboratories would face one-time costs of preparing and submitting premarket approval (PMA) applications

and PMA supplements as well as greater annual reporting burdens associated with premarket approval. FDA would also face additional costs of reviewing the applications. We quantify these costs in the following sections.

Additionally, 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 would be expected to comply with 510(k) requirements or de novo requirements four years after the final rule. Under this stage, we anticipate costs associated with preparing and submitting 510(k) premarket notifications or de novo classification requests, and FDA review costs.

a. Number of Submissions to FDA

Due to the variations in the size of laboratories, business models, and types of IVDs, there is no comprehensive database or repository from which we can definitively calculate the number of IVDs offered as LDTs currently available or the rate at which new IVDs offered as LDTs are introduced. Likewise, there is insufficient data to definitively determine what percentage of IVDs offered as LDTs are likely to be in each class of devices. We rely on New York State Department of Health internal data to estimate the number of affected IVDs offered as LDTs (see section II.D.1 and Table 2).

As discussed in section II.D.1, we assume one laboratory would offer 67 IVDs offered as LDTs and 6 new IVDs offered as LDTs per year. Multiplying 67 IVDs per lab by the number of affected laboratories, it is estimated that the number of affected IVDs would range from 40,200 to 160,800, with a primary estimate of 80,400. Multiplying 6 new IVDs per lab per year by the number of affected laboratories and new laboratories entering the market per year, it is estimated

that the number of new IVDs per year would range from 3,888 to 15,552, with a primary estimate of 7,776.

We further break down these estimates by type of FDA submission to estimate compliance costs. ~~Currently 40% of IVDs~~As mentioned in section II.F.2, we estimate that approximately 50% of IVDs currently undergo premarket review. Of these, about 40% are offered after 510(k) clearance, 5% after de novo classification, and 5% after premarket approval. For those offered after 510(k) clearance, we assume that about 60% may be supported by a method comparison study and about 40% may be supported by a moderately complex clinical study. We apply these shares to the estimated total number of submissions to estimate the number of IVDs by submission type (Table ~~25~~24). We request comment on the assumptions.

Table 24~~:~~. Number of Affected IVDs by Submission Type

	Primary	Low	High
Existing IVDs offered as LDTs currently on the market			
Total affected PMA, 510(k), de novo tests	*40,200*	*20,100*	*80,400*
PMA	4,020	2,010	8,040
510(k) Total	32,160	16,080	64,320
510(k) with method comparison study	18,974	9,487	37,949
510(k) with moderately complex clinical study	13,186	6,593	26,371
de novo	4,020	2,010	8,040
Total number of 510(k) exempt devices	*40,200*	*20,100*	*80,400*
Total number of existing IVDs offered as LDTs	**80,400**	**40,200**	**160,800**
New IVDs offered as LDTs per year			
Total affected PMA, 510(k), de novo tests	*3,888*	*1,944*	*7,776*
PMA	389	194	778
510(k) Total	3,110	1,555	6,221
510(k) with method comparison study	1,835	918	3,670
510(k) with moderately complex clinical study	1,275	638	2,551
de novo	389	194	778
Total number of 510(k) exempt devices	*3,888*	*1,944*	*7,776*

Total number of new tests per year	**7,776**	**3,888**	**15,552**

Note: The number of new tests per year include new tests from both affected labs and new labs entering the market per year.

d. Costs of PMA, 510(k), and de novo requirements

In estimating the costs of compliance for laboratories, we use estimates for the 510(k) and the premarket approval processes derived by ~~Easton~~Eastern Research Group (ERG) (Ref. [54]). The estimates by ERG present the representative costs of regulatory-related activities based on semi-structured discussions with project consultants and other information and knowledge about the development process.

Devices subject to premarket approval typically require pre-market and post-market procedures that are not typically associated with 510(k) clearance, such as pre-market manufacturing site and clinical site inspections and annual report submissions. In addition, the requirements relating to submissions for device modifications are generally different for devices that have received PMAs as compared with other devices. For example, supplements must be approved for ~~modifications to a manufacturing procedure or method of manufacturing,~~ such as the use of a different facility or establishment to manufacture, process, or package the device. We have excluded costs that would already be part of compliance with the QS requirements under Stage 3, including costs of developing design controls, acquiring GMP-compliant manufacture capability, and developing a risk management system.

To estimate cost for submission and preparation of the PMA, IVDs are broken out by complexity of the clinical trial supporting IVD safety and effectiveness due to the different costs. We use the ERG estimates of the PMAs with complex clinical trials for lower bound estimates (Ref. [54]). For upper bound estimates, we use the ERG estimates of the PMAs with complex, extensive clinical trials. We updated the ERG estimates to account for inflation. We

expect that most of the PMAs will involve complex clinical trials. We assume that of the PMAs, 95% are complex clinical trials and 5% are complex, extensive clinical trials. We take 95% of the low and 5% of the high estimates to calculate primary estimates. The total cost of submission and preparation per PMA is estimated to range from $4.12 million to $9.33 million, with a primary estimate of $4.38 million. Multiplying the estimates by the number of affected IVDs currently on the market, we expect one-time cost of submission and preparation for PMAs to range from $8.28 billion to $74.98 billion, with a primary estimate of $17.60 billion. Multiplying the estimates by the numbers of new IVDs per year and IVDs from new entities per year, we expect recurring cost of submission and preparation for PMAs to range from $0.80 billion to $7.25 billion, with a primary estimate of $1.70 billion.

PMA holders are also subject to annual reporting requirements, which impose preparation costs on PMA holders and review costs on FDA. We use a prior estimate from the Microbiology Devices; Reclassification of Nucleic Acid-Based Systems for *Mycobacterium tuberculosis* complex final regulatory impact analysis (Ref. [55]) to estimate the recurring preparation cost. The current estimate after adjustment for inflation is $11,798 per PMA. Multiplying the estimates by the numbers of affected IVDs and IVDs from new entities per year, we expect total recurring cost of PMA annual reporting requirements to range from $26.01 million to $104.03 million, with a primary estimate of $52.02 million.

Overall, we estimate the total one-time costs to industry of PMA requirements in Stage 4 to range between $8.28 billion and $74.98 billion, with a primary estimate of $17.60 billion. The total recurring costs are estimated to range between $0.83 billion and $7.36 billion, with a primary estimate of $1.75 billion. See Table ~~26~~25.

Table 25~~:~~. Costs of Premarket Approval Application

	Primary	Low	High
Cost of Submission and Preparation			
Develop necessary SOPs	$39,572	$37,688	$75,376
Hold pre-submission meeting with FDA	$2,513	$2,513	$2,513
Prepare indications for use	$25,125	$25,125	$25,125
Complete electrical tests and EMC testing	$18,593	$17,588	$37,688
Perform clinical trials	$2,832,871	$2,638,150	$6,532,562
Preparing labeling	$25,125	$25,125	$25,125
Pre-approval inspection	$115,576	$115,576	$115,576
Prepare regulatory submission	$1,319,075	$1,256,262	$2,512,524
Subtotal cost per submission	*$4,378,450*	*$4,118,026*	*$9,326,488*
IVDs currently offered as LDTs affected	4,020	2,010	8,040
*One-time Subtotal (millions)**	*$17,601.37*	*$8,277.23*	*$74,984.97*
New IVDs offered as LDTs per year	389	194	778
*Recurring Subtotal (millions)**	*$1,702.34*	*$800.54*	*$7,252.28*
Recurring Annual			
Annual Report preparation for existing PMAs	$11,798	$11,798	$11,798
IVDs currently offered as LDTs affected	4,020	2,010	8,040
New IVDs offered as LDTs per year	389	194	778
*Recurring Subtotal (millions)**	*$52.02*	*$26.01*	*$104.03*
Total One-time Costs (billions)	**$17.60**	**$8.28**	**$74.98**
Total Recurring Costs (billions)	**$1.75**	**$0.83**	**$7.36**

Notes:
Unless otherwise specified, line-item estimates are inflation-adjusted estimates from Eastern Research Group, Inc. 2012: Economic Analysis of CDRH Submission Requirements. Totals may not add due to rounding. The number of new IVDs per year include new tests from both affected entities currently on the market and new entities entering the market per year.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

Some IVDs with approved PMAs may require a PMA supplement as required under 21 CFR 814.39.[94] There are several types of PMA supplements (see Table ~~27~~26Table 26; each row is a type of PMA supplement). We first estimate the expected number of PMA supplements by supplement type by multiplying the number of expected PMAs by the number of expected PMA

[94] See the following page for a list of changes that would require a PMA supplement: https://www.fda.gov/medical-devices/premarket-approval-pma/pma-supplements-and-amendments.

supplements per ~~PMA~~PMA[95] and the share of supplements by supplement ~~type~~type[96]. We assume that entities would submit PMA supplements in year 4. We also assume that the number of PMA supplements from existing IVDs currently offered as LDTs will spread over 10 years (year 4 to year 13). See Table ~~27~~26 for the expected number of annual ~~(new IVDs offered as LDTs)~~ PMA supplements.

Next, to estimate the total costs to industry of PMA supplement preparation, we multiply the number of PMA supplements by an estimated full-time equivalent (FTE) ~~cost~~cost[97] associated with each supplement type and the cost of preparing a PMA from the previous section. This approach assumes the cost of preparing a PMA supplement for a laboratory is proportional to the FTE required for FDA to review the supplement type. Overall, we estimate the total recurring costs to industry of PMA supplements to range from $125.19 million to $1.13 billion, with a primary estimate of $266.21 million. See Table ~~28~~27.

We request comment on the number of PMA supplements or costs to laboratories to develop PMA supplements, by supplement type.

Table 26~~:~~. Number of PMA Supplements by Submission Type

	Cumulative share of supplements by type	Primary	Low	High
135 Review Track	0.053	30	15	59
Normal 180-day track	0.205	115	57	229
Normal 180-day track - No user fee	0.128	72	36	144

[95] As of June 2023, the estimated number of active PMAs for all IVDs is 187 and total number of supplements over 7 years is 928. We divide the total number of supplements by the number of active PMAs and 7 years to calculate the number of PMA supplement per active PMA per year, which is 0.71 (= 928 supplements / 187 active PMAs / 7 years). We assume that the same rates for IVDs overall will apply to IVDs offered as LDTs.

[96] We use the FDA internal information on the total number of ~~FDA reviews~~ supplement submissions received by FDA from 2017 to 2023, as of July 2023.

[97] This cost reflects hours spent in CDRH substantive review of devices, required to determine whether they meet the standard to be approved~~, cleared, or authorized.~~. It does not include some of the steps required to complete review of a submission, such as management or time spent on such reviews by staff outside CDRH.

Panel-Track	0.067	37	19	75
Real-Time Process	0.374	210	105	420
Special CBE	0.095	53	27	107

Note: This table reports the number of annual PMA supplements for years 4 to 13.

Table 27~~:~~. Costs of PMA Supplements

	Adjusted FTE weights over PMA	Primary	Low	High
Annual				
135 Review Track	0.033	$5.37	$2.52	$22.87
Normal 180-day track	0.033	$20.87	$9.81	$88.90
Normal 180-day track - No user fee	0.033	$13.07	$6.15	$55.67
Panel Track	1.000	$205.17	$96.48	$874.07
Real Time Process	0.010	$12.00	$5.64	$51.14
Special CBE	0.033	$9.73	$4.57	$41.43
Total Recurring Costs (millions)		**$266.21**	**$125.19**	**$1,134.09**

Note: This table reports the costs of PMA supplements for years 4 to 13.

Similar to the PMA, we use the ERG estimates of the 510(k) process to estimate the one-time submission and preparation cost of 510(k)s, adjusting for inflation. We use the ERG estimates of 510(k) with small or simple clinical trials for 510(k) submissions with method comparison studies (see Table ~~29~~28) (Ref. [54]). We use the ERG estimates of 510(k) with moderately complex clinical trials for 510(k) submissions with moderately complex clinical studies (see Table ~~30~~29).[98]

For any 510(k) submission (or de novo ~~request~~request[99]), we expect it will take one operations specialist manager, working at a wage of $61.74 ($123.48 fully loaded), 1 to 2 hours (with a primary estimate of 1.5 hours) to identify a predicate device (or determine that no predicate device exists, in the case of a de novo). The other one-time submission and preparation

[98] Distinctions of the estimates used in ~~Tables 29~~ and ~~Table 30~~ are based on the type of study supporting clinical validation of these tests due to differing costs.

[99] In the absence of more detailed information on De Novo costs, we extrapolate 510(k) costs to estimate De Novo costs. We request comment on this assumption and the estimates.

costs are derived from the ERG estimates. The total cost of submission and preparation per 510(k) with method comparison studies is estimated to range from $233,034 to $316,825, with a primary estimate of $274,930. Multiplying these by the number of expected IVDs currently on the market, the one-time submission and preparation costs for 510(k)s with method comparison studies, is estimated between $2.21 billion and $12.02 billion, with a primary estimate of $5.22 billion. Multiplying by the numbers of new IVDs per year and IVDs from new entities per year yields the recurring cost between $213.82 million and $1.16 billion, with a primary estimate of $504.53 million.

Overall, we estimate the total one-time costs to industry of 510(k)s with method comparison studies in Stage 5 to range between $2.21 billion and $12.01 billion, with a primary estimate of $5.22 billion. The estimated total recurring costs range from $0.21 billion to $1.16 billion, with a primary estimate of $0.50 billion. See Table ~~29~~28.

Table 28: Costs of 510(k)s (Method Comparison Study)

	Primary	Low	High
Cost of Submission and Preparation			
Identify predicate device			
Hours	1.5	1	2
Wage	$123.48	$123.48	$123.48
Develop necessary SOPs	$37,688	$37,688	$37,688
Hold pre-submission meeting with FDA	$2,136	$1,759	$2,513
Prepare indications for use	$25,125	$25,125	$25,125
Complete electrical tests and EMC testing	$27,638	$17,588	$37,688
Perform method comparison	$62,813	$62,813	$62,813
Preparing labeling	$25,125	$25,125	$25,125
Prepare regulatory submission	$94,220	$62,813	$125,626
Subtotal cost per submission	*$274,930*	*$233,034*	*$316,825*
IVDs currently offered as LDTs affected	18,974	9,487	37,949
*One-time Subtotal (millions)**	*$5,216.63*	*$2,210.84*	*$12,023.13*
New IVDs offered as LDTs per year	1,835	918	3,670
*Recurring Subtotal (millions)**	*$504.53*	*$213.82*	*$1,162.83*

Total One-time Costs (billions)	**$5.22**	**$2.21**	**$12.02**
Total Recurring Costs (billions)	**$0.50**	**$0.21**	**$1.16**

Notes:
Unless otherwise specified, line-item estimates are inflation-adjusted estimates from Eastern Research Group, Inc. 2012: Economic Analysis of CDRH Submission Requirements. Totals may not add due to rounding. The number of new IVDs per year include new tests from both affected entities currently on the market and new entities entering the market per year.
**We calculate subtotals by multiplying the subtotal cost per submission by the number of affected IVDs.*

~~Table 30~~Table 29 presents costs of 510(k) submissions with a moderately complex clinical study. We calculate the costs using the exact same methods as in Table ~~29~~28. The estimated subtotal cost of submission and preparation per submission ranges from $484,287 to $568,077, with a primary estimate of $526,182. Multiplying the estimates by the number of affected IVDs currently on the market, we expect one-time submission and preparation cost to range from $3.19 billion to $14.98 billion, with a primary estimate of $6.94 billion. Multiplying the estimates by the numbers of new IVDs per year and IVDs from new entities per year, we expect recurring submission and preparation cost to range from $308.80 million to $1.45 billion, with a primary estimate of $671.02 million. Overall, we estimate the total one-time costs to industry of 510(k)s with a moderately complex clinical study under Stage 5 to range between $3.19 billion and $14.98 billion, with a primary estimate of $6.94 billion. The estimated recurring costs range from $0.31 billion to $1.45 billion, with a primary estimate of $0.67 billion.

Table 29~~:~~. Costs of 510(k)s (Moderately Complex Clinical Study)

	Primary	Low	High
Cost of Submission and Preparation			
Identify predicate device			
Hours	1.5	1	2
Wage	$123.48	$123.48	$123.48
Develop necessary SOPs	$37,688	$37,688	$37,688
Hold pre-submission meeting with FDA	$2,136	$1,759	$2,513
Prepare indications for use	$25,125	$25,125	$25,125

Complete electrical tests and EMC testing	$27,638	$17,588	$37,688
Perform clinical study	$314,065	$314,065	$314,065
Preparing labeling	$25,125	$25,125	$25,125
Prepare regulatory submission	$94,220	$62,813	$125,626
Subtotal cost per submission	*$526,182*	*$484,287*	*$568,077*
IVDs currently offered as LDTs affected	13,186	6,593	26,371
*One-time Subtotal (millions)**	*$6,938.03*	*$3,192.81*	*$14,980.88*
New IVDs offered as LDTs per year	1,275	638	2,551
*Recurring Subtotal (millions)**	*$671.02*	*$308.80*	*$1,448.90*
Total One-time Costs (billions)	**$6.94**	**$3.19**	**$14.98**
Total Recurring Costs (billions)	**$0.67**	**$0.31**	**$1.45**

Notes:
Unless otherwise specified, line-item estimates are inflation-adjusted estimates from Eastern Research Group, Inc. 2012: Economic Analysis of CDRH Submission Requirements. Totals may not add due to rounding. The number of new IVDs per year include new tests from both affected entities currently on the market and new entities entering the market per year.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

Table ~~31~~30 shows costs of a de novo classification request. We use the ERG estimates of 510(k) with moderately complex clinical trial for upper bound and use the ERG estimates of 510(k) with a method comparison study for lower bound estimates (Ref. [54]).[100] We assume that most de novo requests would have data from clinical trials. We take 99% of the high and 1% of the low estimates to calculate primary estimates. We calculate costs of de novo classification requests using the exact same methods as in ~~Table 30.~~Table 29. The estimated subtotal cost of submission and preparation per submission ranges from $233,788 to $568,077, with a primary estimate of $564,674. Multiplying the estimates by the number of affected IVDs currently on the market, we expect one-time submission and preparation cost to range from $469.91 million to $4.57 billion, with a primary estimate of $2.27 billion. Multiplying the estimates by the numbers of new IVDs per year and IVDs from new entities per year, we expect recurring submission and preparation cost to range from $45.45 million to $441.74

[100] In the absence of more detailed information on De Novo costs, we extrapolate 510(k) costs to estimate De Novo costs, noting however that De Novo costs are likely higher than 510(k) costs. We request comment on this assumption and the estimates.

million, with a primary estimate of $219.55 million. Overall, we estimate the total costs to industry of de novo classification requests to range between $0.47 billion and $4.57 billion, with a primary estimate of $2.27 billion. The estimated total recurring costs range from $0.05 billion to $0.44 billion, with a primary estimate of $0.22 billion.

Table 30~~:~~. Costs of De Novo Classification Request

	Primary	Low	High
Cost of Submission and Preparation			
Determine that no predicate devices exist			
Hours	1.50	1.00	2.00
Wage	$123.48	$123.48	$123.48
Develop necessary SOPs	$37,688	$37,688	$37,688
Hold pre-submission meeting with FDA	$2,513	$2,513	$2,513
Prepare indications for use	$25,125	$25,125	$25,125
Complete electrical tests and EMC testing	$37,487	$17,588	$37,688
Perform method comparison or clinical study	$311,553	$62,813	$314,065
Preparing labeling	$25,125	$25,125	$25,125
Prepare regulatory submission	$124,998	$62,813	$125,626
Subtotal cost per submission	*$564,674*	*$233,788*	*$568,077*
IVDs currently offered as LDTs affected	4,020	2,010	8,040
*One-time Subtotal (millions)**	*$2,269.99*	*$469.91*	*$4,567.34*
New IVDs offered as LDTs per year	389	194	778
*Recurring Subtotal (millions)**	*$219.55*	*$45.45*	*$441.74*
Total One-time Costs (billions)	**$2.27**	**$0.47**	**$4.57**
Total Recurring Costs (billions)	**$0.22**	**$0.05**	**$0.44**

Notes:
Unless otherwise specified, line-item estimates are inflation-adjusted estimates from Eastern Research Group, Inc. 2012: Economic Analysis of CDRH Submission Requirements. Totals may not add due to rounding. The number of new IVDs per year include new tests from both affected entities currently on the market and new entities entering the market per year.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

~~5. Costs to FDA~~

~~In addition to the cost to industry of preparing and submitting PMAs, PMA supplements, 510(k)s, and de novo requests, there would be incremental review costs on FDA. To estimate the review costs, we first use average costs per page based on submission type used in a prior estimate from the Microbiology Devices; Reclassification of Nucleic Acid-Based~~

Systems for *Mycobacterium tuberculosis* complex final regulatory impact analysis (Ref. [27]). The current estimate after adjustment for inflation is $864,057 per PMA and $20,565 per 510(k) (or de novo).[101] We also use labor costs from estimated FTEs for FDA review of different submission types.[102] The 3-year average cost of all personnel compensation and benefits paid per FTE at FDA is $296,450.[103] We then multiply this by the estimated FTEs by submission type to estimate the review cost per submission. We use an average of the two estimates for the review cost per submission.

Multiplying the review cost per submission by the total number of affected IVDs yields a total one-time review cost of PMAs between $1.18 billion and $4.73 billion, with a primary estimate of $2.37 billion. Multiplying the estimate by the numbers of new IVDs per year and tests from new entities per year yields a total recurring review cost of PMAs between $0.11 billion to $0.46 billion, with a primary estimate of $0.23 billion. The total recurring review cost of PMA supplements is estimated to range between $14.25 million and $57.003 million, with a primary estimate of $28.50 million.[104] The total one-time review cost of 510(k)s is estimated to range from $315.50 million to $1.26 billion, with a primary estimate of $631.00 million. The total recurring review cost of 510(k)s is estimated to range from $30.51 million to $122.06 million, with a primary estimate of $61.03 million. The total one-time review cost of

[101] We extrapolate 510(k) costs to estimate De Novo costs, noting however that De Novo costs are likely higher than 510(k) costs. However, in the absence of more detailed information, we sometimes rely on such extrapolations to arrive at estimates due to uncertainty.

[102] This cost reflects hours spent in CDRH substantive review of devices, required to determine whether they meet the standard to be approved, cleared, or authorized. It does not include some of the steps required to complete review of a submission, such as management or time spent on such reviews by staff outside CDRH.

[103] Federal Register :: Food Safety Modernization Act Domestic and Foreign Facility Reinspection, Recall, and Importer Reinspection Fee Rates for Fiscal Year 2022 Available at: https://www.federalregister.gov/documents/2021/07/28/2021-16056/food-safety-modernization-act-domestic-and-foreign-facility-reinspection-recall-and-importer

[104] Table 32 reports an average review cost of PMA supplements and recurring costs of PMA supplements for year 4 to year 13.

de novo classification requests is estimated between $212.24 million and $848.95 million, with a primary estimate of $424.48 million. The recurring review cost of de novo classification requests is estimated to range from $20.53 million to $82.11 million, with a primary estimate of $41.05 million.

Overall, we estimate the total one-time FDA review costs to range between $1.71 billion and $6.85 billion, with a primary estimate of $3.42 billion. We estimate the total recurring FDA review costs to range between $179.76million and $719.05 million, with a primary estimate of $359.53 million. See Table 32.[105]

Table 32: FDA Review Costs by Submission Type

		Primary	Low	High
PMA	FDA review costs using page numbers	$864,057	$864,057	$864,057
	FDA review costs using FTE	$313,644	$313,644	$313,644
	Average FDA review costs	*$588,850*	*$588,850*	*$588,850*
	IVDs currently offered as LDTs affected	4,020	2,010	8,040
	*Subtotal, one-time (millions)**	*$2,367.18*	*$1,183.59*	*$4,734.36*
	New IVDs offered as LDTs per year	389	194	778
	*Subtotal, recurring (millions)**	*$228.95*	*$114.47*	*$457.89*
PMA Supplements	*Average FDA review costs*	*$112,149*	*$112,149*	*$112,149*
	Supplements per year	517	258	1,033
	*Subtotal, recurring (millions)***	*$28.50*	*$14.25*	*$57.00*
510(k)	FDA review costs using page numbers	$20,565	$20,565	$20,565
	FDA review costs using FTE	$18,676	$18,676	$18,676
	Average FDA review costs	*$19,621*	*$19,621*	*$19,621*
	IVDs currently offered as LDTs affected	32,160	16,080	64,320
	*Subtotal, one-time (millions)**	*$631.00*	*$315.50*	*$1,262.01*
	New IVDs offered as LDTs per year	3,110	1,555	6,221
	*Subtotal, recurring (millions)**	*$61.03*	*$30.51*	*$122.06*

[105] The costs could spread over time depending on the time of submission and review.

De Novo	FDA review costs using page numbers	$20,565	$20,565	$20,565
	FDA review costs using FTE	$190,617	$190,617	$190,617
	Average FDA review costs	*$105,591*	*$105,591*	*$105,591*
	IVDs currently offered as LDTs affected	4,020	2,010	8,040
	*Subtotal, one-time (millions)**	*$424.48*	*$212.24*	*$848.95*
	New IVDs offered as LDTs per year	389	194	778
	*Subtotal, recurring (millions)**	*$41.05*	*$20.53*	*$82.11*
Total one-time costs (millions)		**$3,422.66**	**$1,711.33**	**$6,845.32**
Total recurring costs (millions)		**$359.53**	**$179.76**	**$719.05**

Notes: The number of new IVDs per year include new tests from both affected entities currently on the market and new entities entering the market per year.
**We calculate subtotals by multiplying average FDA review costs by the number of affected IVDs.*
***We multiply the average FDA review cost per PMA by the FTE weights to calculate the review cost per PMA supplement. This table reports the estimated review costs of PMA supplements for year 4 to year 13.*

6.5. Summary of Costs

Table 3331 summarizes our estimates of the one-time and recurring costs by stage of the proposed phaseout policy. We estimate the total one-time costs to range between $15.87 billion and $113.86 billion, with a primary estimate of $35.54 billion. We estimate the total recurring costs of the proposed rule to range between $1.77 billion and $14.31 billion, with a primary estimate of $4.24 billion.

Table 31: Total Costs (millions 2022$)

		Primary	Low	High
One-time				
Stage 1	Reading and Understanding the Rule	$0.64	$0.14	$2.16
	Medical Device Reporting	$12.12	$4.84	$30.31
	Correction and Removal Reporting	$0.03	$0.02	$0.06
Stage 2	Registration and Listing Requirements	$0.41	$0.21	$0.82
	Labeling Requirements	$2.75	$0.27	$9.35
	Investigational Use Requirements	$2.89	$0.29	$10.42

Stage 3	Quality System Requirements	$72.56	$6.19	$408.37
Stage 4	Premarket Approval Application	$19,968.55	$9,460.82	$79,719.32
Stage 5	510(k) Submission or De Novo Classification Request	$15,480.12	$6,401.30	$33,682.31
Total One-time Costs (billions)		**$35.54**	**$15.87**	**$113.86**
Recurring Annual				
Stage 1	Reading and Understanding the Rule	$0.05	$0.01	$0.16
	Medical Device Reporting	$76.56	$38.18	$153.61
	Correction and Removal Reporting	$0.15	$0.08	$0.31
Stage 2	Registration and Listing Requirements	$0.17	$0.09	$0.34
	Labeling Requirements	$0.22	$0.02	$0.75
	Investigational Use Requirements	$6.99	$0.69	$25.19
Stage 3	Quality System Requirements	$378.97	$30.26	$1,869.50
Stage 4	Premarket Approval Application	$1,983.30	$941.03	$7,814.20
	Premarket Approval Application Supplements*	$294.71	$139.44	$1,191.09
Stage 5	510(k) Submission or De Novo Classification Request	$1,497.18	$619.11	$3,257.63
Total Recurring Costs (billions)		**$4.24**	**$1.77**	**$14.31**

** This table reports the recurring costs of PMA supplements for year 4-13. The estimated recurring costs of PMA supplements for year 14-20 ranges from $68.55 million to $585.60 million, with a primary estimate of $144.89 million. The premarket review costs to FDA for stages 4 and 5 are reported in section G.*

Table ~~34~~32 presents a summary of the estimated twenty-year stream of costs. We expect that total costs for Stage 1 associated with reading and understanding the rule, medical device reporting, and correction and removal reporting would occur in the first year after publication of the final rule. In the first year after publication of the final rule, we estimate total costs to range from $43.27 million to $186.61 million, with a primary estimate of $89.56 million. We expect that total costs for Stage 2 associated with registration and listing requirements, labeling requirements, and investigational use requirements would occur in the second year after publication of the final rule. In year 2, total costs are estimated to range between $39.84 million to $200.95 million, with a primary estimate of $90.19 million. In the third year after publication of the final rule, we expect that costs for Stage 3 associated with Quality System requirements

would occur. We also expect that half of costs for Stage 4 associated with premarket approval applications would occur in year 3. Total costs in year 3 are estimated to range between $5.35 billion to $46.82 billion, with a primary estimate of $11.66 billion. In year 4, we assume half of costs associated with premarket approval applications would also occur. We expect that costs of PMA supplements would occur in year 4. We also expect that entities will face costs for Stage 5 associated with 510(k) submissions or de novo classification requests in year 4. Total costs in year 4 are estimated to range between $12.90 billion to $87.85 billion, with a primary estimate of $29.70 billion.

In subsequent years, the recurring cost for year 5 to year 13 is estimated to range between $1.77 billion and $14.31 billion, with a primary estimate of $4.24 billion. The recurring cost for year 14 to year 20 is estimated to range from $1.63 billion to $13.12 billion, with a primary estimate of $3.94 billion. We estimate the total costs over 20 years to range from $45.66 billion to $355.73 billion, with a primary estimate of $107.29 billion.

The present value of total estimated costs is $83.28 billion at a 3 percent discount rate and $62.23 billion at a 7 percent discount rate over 20 years. The annualized value of costs is $5.60 billion at a 3 percent discount rate and $5.87 billion at a 7 percent discount rate.

Table 32: Twenty-Year Timing of the Costs (millions 2022$)

	Primary	Low	High
Year 1	$89.56	$43.27	$186.61
Year 2	$90.19	$39.84	$200.95
Year 3	$11,658.95	$5,346.15	$46,820.53
Year 4	$29,702.70	$12,900.61	$87,854.75
Year 5-13 (costs for each year)	$4,238.30	$1,768.90	$14,312.78
Year 14-20 (costs for each year)	$3,943.60	$1,629.46	$13,121.69
Total Costs	$107,291.30	$45,656.19	$355,729.71
Present Value of Total Costs (3%)	$83,282.78	$35,584.08	$275,958.62
Present Value of Total Costs (7%)	$62,225.24	$26,717.37	$206,079.07

Annualized Value of Costs (3%)	**$5,597.91**	**$2,391.81**	**$18,548.75**
Annualized Value of Costs (7%)	**$5,873.62**	**$2,521.93**	**$19,452.41**

~~7.~~6. Other Unquantified Costs

Other unquantified social costs associated with this rule (or other manifestations of the costs that have been quantified) may include the impact on prices and access to diagnostics if many laboratories exit the market or discontinue offering certain ~~tests~~IVDs rather than incur the costs of compliance with FDA requirements. There may be instances in which a laboratory may choose to exit the market or discontinue certain IVDs offered as LDTs due to compliance costs. Without ~~cost~~information on the revenues or costs of production ~~or pricing information~~ of IVDs offered as LDTs, however, we are unable to estimate the impact associated with compliance costs on the prevalence of laboratories exiting the market or discontinuing manufacturing of certain IVDs offered as LDTs.

Therefore, we request public comment on the revenues generated by those IVDs offered as LDTs that would be at risk of discontinuation due to the costs of compliance with the proposed rule. Specifically, we seek data that would allow us to compare products' sales against minimum thresholds needed to cover the costs of undergoing the relevant reviews. For reference, our use of such data would be similar to the analysis done in section II.G.1 "Count of At-Risk Products" in the Preliminary Regulatory Impact Analysis of the proposed rule Medication Guides: Patient Medication Information.[106]

However, our analysis in section III (Initial small entity analysis) shows that 82% of annual receipts and 59% of IVDs offered as LDTs come from large laboratories (laboratories

[106] Available from: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/medication-guides-patient-medication-information-proposed-rule-preliminary-regulatory-impact

with annual receipts of $41,500,000 or greater), which may be unlikely to close as a result of compliance costs given how such costs compare to their overall revenues (see further discussion in section III). This means that 23% of receipts and 41% of IVDs offered as LDTs are estimated to come from small laboratories (laboratories with annual receipts of less than $41,500,000), which are more likely to reduce operations or exit the market than large laboratories. However, to the extent that some small laboratories may reduce operations or exit the market, it is possible that larger laboratories may take over the production of certain IVDs offered as LDTs, reducing potential impacts on IVD availability. This may have the effect of driving production concentration to a few large laboratories. Under this scenario, prices for certain IVDs offered as LDTs could increase, reducing overall net social benefits. According to economic theory, production concentration under a few laboratories could increase the risk of supply chain contractions, risking shortages for certain IVDs offered as LDTs and therefore affecting prices and access. Although under monopolistic competition, production of more IVDs offered as LDTs in large laboratories could also result in lower production costs due to the economies of scale associated with the operations of such laboratories, they do not produce at the minimum of their average costs curve and may charge prices higher than their marginal cost.

While we recognize that some laboratories may pass the costs of compliance to their customers by raising prices for IVDs offered as LDTs, increased FDA oversight may also help reduce social costs by helping to support coverage and reimbursement determinations and increasing patient accessibility to IVDs for which there is a reasonable assurance of safety and effectiveness. In addition, any price increases must be considered in the context of other costs that may be avoided as a result of a final phaseout policy. In particular, the phaseout policy is intended to address the risks associated with problematic ~~tests~~IVDs offered as LDTs, results

from which may cause patients to incur additional costs from inappropriate treatments, additional or repeat testing, unnecessary consultations with providers, or additional treatments that become necessary due to the progression or worsening of a disease or condition following misdiagnosis.

G. Budgetary Impacts

In addition to the cost to industry of preparing and submitting PMAs, PMA supplements, 510(k)s, and de novo requests, there would be incremental review costs for FDA. To estimate the review costs, we first use average costs per-page based on submission type used in a prior estimate from the Microbiology Devices; Reclassification of Nucleic Acid-Based Systems for *Mycobacterium tuberculosis* complex final regulatory impact analysis (Ref. [55]). The current estimate after adjustment for inflation is $864,057 per PMA and $20,565 per 510(k) (or de novo).[107] We also use labor costs from estimated FTEs for FDA review of different submission types.[108] The 3-year average cost of all personnel compensation and benefits paid per FTE at FDA is $296,450 (Ref. [56]). We then multiply this by the estimated FTEs by submission type to estimate the review cost per submission. We use an average of the two estimates for the review cost per submission.

Multiplying the review cost per submission by the total number of affected IVDs yields a total one-time review cost of PMAs between $1.18 billion and $4.73 billion, with a primary estimate of $2.37 billion. Multiplying the estimate by the numbers of new IVDs per year and tests from new entities per year yields a total recurring review cost of PMAs between $0.11 billion to $0.46 billion, with a primary estimate of $0.23 billion. The total recurring review

[107] We extrapolate 510(k) costs to estimate De Novo costs, noting however that De Novo costs are likely higher than 510(k) costs. However, in the absence of more detailed information, we sometimes rely on such extrapolations to arrive at estimates due to uncertainty.

[108] This cost reflects hours spent in CDRH substantive review of devices, required to determine whether they meet the standard to be approved, cleared, or authorized. It does not include some of the steps required to complete review of a submission, such as management or time spent on such reviews by staff outside CDRH.

cost of PMA supplements is estimated to range between $14.25 million and $57.00 million, with a primary estimate of $28.50 million.[109] The total one-time review cost of 510(k)s is estimated to range from $315.50 million to $1.26 billion, with a primary estimate of $631.00 million. The total recurring review cost of 510(k)s is estimated to range from $30.51 million to $122.06 million, with a primary estimate of $61.03 million. The total one-time review cost of de novo classification requests is estimated between $212.24 million and $848.95 million, with a primary estimate of $424.48 million. The recurring review cost of de novo classification requests is estimated to range from $20.53 million to $82.11 million, with a primary estimate of $41.05 million.

Overall, we estimate the total one-time FDA review costs to range between $1.71 billion and $6.85 billion, with a primary estimate of $3.42 billion. We estimate the total recurring FDA review costs to range between $179.76million and $719.05 million, with a primary estimate of $359.53 million. See Table 33.[110]

Table 33. FDA Review Costs by Submission Type

		Primary	Low	High
PMA	FDA review costs using page numbers	$864,057	$864,057	$864,057
	FDA review costs using FTE	$313,644	$313,644	$313,644
	Average FDA review costs	*$588,850*	*$588,850*	*$588,850*
	IVDs currently offered as LDTs affected	4,020	2,010	8,040
	*Subtotal, one-time (millions)**	*$2,367.18*	*$1,183.59*	*$4,734.36*
	New IVDs offered as LDTs per year	389	194	778
	*Subtotal, recurring (millions)**	*$228.95*	*$114.47*	*$457.89*
	Average FDA review costs	*$112,149*	*$112,149*	*$112,149*

[109] Table 33 reports an average review cost of PMA supplements and recurring costs of PMA supplements for year 4 to year 13.

[110] The costs could be spread over time depending on the time of submission and review. FDA review costs could also be reduced if third party review is utilized by industry as described in section II.J. under alternative five.

PMA Supplements	Supplements per year	517	258	1,033
	*Subtotal, recurring (millions)***	*$28.50*	*$14.25*	*$57.00*
510(k)	FDA review costs using page numbers	$20,565	$20,565	$20,565
	FDA review costs using FTE	$18,676	$18,676	$18,676
	Average FDA review costs	*$19,621*	*$19,621*	*$19,621*
	IVDs currently offered as LDTs affected	32,160	16,080	64,320
	*Subtotal, one-time (millions)**	*$631.00*	*$315.50*	*$1,262.01*
	New IVDs offered as LDTs per year	3,110	1,555	6,221
	*Subtotal, recurring (millions)**	*$61.03*	*$30.51*	*$122.06*
De Novo	FDA review costs using page numbers	$20,565	$20,565	$20,565
	FDA review costs using FTE	$190,617	$190,617	$190,617
	Average FDA review costs	*$105,591*	*$105,591*	*$105,591*
	IVDs currently offered as LDTs affected	4,020	2,010	8,040
	*Subtotal, one-time (millions)**	*$424.48*	*$212.24*	*$848.95*
	New IVDs offered as LDTs per year	389	194	778
	*Subtotal, recurring (millions)**	*$41.05*	*$20.53*	*$82.11*
Total one-time costs (millions)		**$3,422.66**	**$1,711.33**	**$6,845.32**
Total recurring costs (millions)		**$359.53**	**$179.76**	**$719.05**

Notes: The number of new IVDs per year include new tests from both affected entities currently on the market and new entities entering the market per year.
**We calculate subtotals by multiplying average FDA review costs by the number of affected IVDs.*
***We multiply the average FDA review cost per PMA by the FTE weights to calculate the review cost per PMA supplement. This table reports the estimated review costs of PMA supplements for year 4 to year 13.*

~~G.~~H. Transfers

If the proposed rule is finalized, laboratories would pay fees to FDA for establishment registration, premarket submissions (where applicable), and periodic reporting for IVDs with an approved PMA. While these fees are ~~costs for laboratories, they are revenue for FDA. The fees are therefore considered transfers since they do not affect net social benefits.~~paid by laboratories, they are revenue for FDA. The approach to estimating fee effects is distinct from the approaches for either benefits or costs, so they will be presented as transfers. Another perspective on the

user fees is that they indicate industry bearing costs that are otherwise more simplistically presented as being experienced by FDA; hypothetically adding the user fee estimates into the cost accounting would, however, be double-counting and thus misestimation of effects on net social benefits.[111]

See Table ~~35~~34 for the estimated transfers associated with the proposed rule. All anticipated fees are public information published by FDA.[112] Each laboratory is expected to pay an annual registration fee, at a cost of $6,493 per laboratory. Laboratories would also pay for submission of a report annually to FDA for each IVD that has received premarket approval, which costs $15,454 per report. Laboratories would pay $441,547 to FDA for each PMA they submit. For PMA supplements, they would pay $7,065 for each 30-day notice, $66,232 for each 180-day supplement, $353,238 for each panel-track supplement, and $30,908 for each real-time supplement they submit. They would pay $19,870 for each 510(k) they submit and $132,464 for each de novo request they submit. Small businesses that have gross receipts or sales of $100 million or less for the most recent tax year (including their affiliates) are eligible to pay a reduced fee for certain submissions, including 510(k) submissions ($4,967 per submission), de novo requests ($33,116 per submission), PMAs ($110,387 per submission), PMA supplements ($3,532 for each 30-day notice, $16,558 for each 180-day supplement, $88,309 for each panel-track supplement, and $7,727 for each real-time supplement), and PMA annual reports ($3,864 per submission). Small businesses with sales of $30 million or less are eligible to have the fee

[111] Net social benefits are the total benefits minus the total costs to society (industry, consumers, government, etc.). A transfer is a type of change where one member of society bears a cost that would simultaneously be a benefit to another member of society, resulting in a net effect of zero on social benefits. ~~In this case, industry is bearing a cost that is simultaneously a benefit for the government (FDA). Since industry~~Industry and the FDA are both members of society~~, the net effect on society of the fees paid by industry is zero~~.

[112] We cite FY23 fees; the fees are updated every summer for the upcoming fiscal year that they are likely to be updated when the final rule is published. https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa

waived on their first PMA. We assume 40 to 90 percent of the laboratories would have gross receipts or sales of $100 million or less, and we use 65 percent (average of 40% and 90%) to estimate the number of small business IVDs. Multiplying these fees by the relevant number of laboratories and IVDs, we expect total annual transfers to range from $93.48 million to $396.05 million, with a primary estimate of $198.03 million. We expect total one-time transfers to range from $0.61 billion to $3.02 billion, with a primary estimate of $1.51 billion.

Table 34~~: Cost.~~ Transfers

			Primary	Low	High
Recurring Annual	Registration Annual Fee	Fee	$6,493	$6,493	$6,493
		Entities affected	1,200	600	2,400
		Subtotal (millions)	*$7.79*	*$3.90*	*$15.58*
	Annual reporting on PMA	Fee (Adjusted fee for small entities)	$15,454 ($3,864)	$15,454 ($0)	$15,454 ($3,864)
		IVDs affected, non-small*	1,543	772	3,086
		IVDs affected, small*	2,866	1,433	5,731
		Subtotal (millions)	*$34.92*	*$11.92*	*$69.84*
One-time /Annual	PMA	MDUFA Review (Adjusted fee for small entities)	$441,547 ($110,387)	$441,547 ($110,387)	$441,547 ($110,387)
		IVDs affected, non-small*	1,543	772	3,086
		IVDs affected, small*	2,866	1,433	5,731
		Subtotal (millions)	*$997.68*	*$354.62*	*$1,995.36*
	PMA Supplements –180-day track	MDUFA Review (Adjusted fee for small entities)	$66,232 ($16,558)	$66,232 ($16,558)	$66,232 ($16,558)
		IVDs affected, non-small*	40	20	80
		IVDs affected, small*	75	37	149
		Subtotal (millions)	*$3.89*	*$1.95*	*$7.79*
	PMA Supplements – Panel-track	MDUFA Review (Adjusted fee for small entities)	$353,238 ($88,309)	$353,238 ($88,309)	$353,238 ($88,309)
		IVDs affected, non-small*	13	7	26
		IVDs affected, small*	24	12	48
		Subtotal (millions)	*$6.75*	*$3.38*	*$13.51*
	PMA Supplements – Real-Time	MDUFA Review (Adjusted fee for small entities)	$30,908 ($7,727)	$30,908 ($7,727)	$30,908 ($7,727)
		IVDs affected, non-small*	73	37	147
		IVDs affected, small*	136	68	273

		Subtotal (millions)	*$3.32*	*$1.66*	*$6.65*
	510(k)	MDUFA Review (Adjusted fee for small entities)	$19,870 ($4,967)	$19,870 ($4,967)	$19,870 ($4,967)
		IVDs Affected, non-small*	12,345	6,172	24,689
		IVDs affected, small*	22,926	11,463	45,852
		Subtotal (millions)	*$359.16*	*$179.58*	*$718.32*
	De Novo	MDUFA Review (Adjusted fee for small entities)	$132,464 ($33,116)	$132,464 ($33,116)	$132,464 ($33,116)
		IVDs affected, non-small*	1,543	772	3,086
		IVDs affected, small*	2,866	1,433	5,731
		Subtotal (millions)	*$299.30*	*$149.65*	*$598.61*
Total Recurring Transfers (millions)			**$198.03**	**$93.48**	**$396.05**
Total One-Time Transfers (millions)			**$1,510.09**	**$610.83**	**$3,020.19**

**The number of tests also includes tests from new entities per year.*

~~H.~~I. Stream of Benefits, Costs, and Transfers

We describe the details of how we estimate the benefits, costs, and transfers in sections II.E, II.F, II.G and II.~~G~~H, respectively. See Table ~~36~~35 for a summary of the timing of expected benefits, costs, and transfers over a twenty-year time frame, in millions of 2022 U.S. dollars. Only primary estimates are presented. For each year, we present the undiscounted benefits, costs to industry, costs to FDA, and transfers, as well as discounted estimates that account for inflation and the changing value of the dollar.

Table 35~~:~~. Undiscounted Twenty-year Flow of Benefits, Costs, and Transfers (millions 2022 USD)

Year	Benefits		Costs to Industry			Costs to FDA			Transfers						
~~Undiscounted~~	~~Discounted 3%~~VSLY based on 3% discounting	~~Discounted 7%~~VSLY based on 7% discounting	~~Undiscounted~~			~~Discounted 3%~~			~~Discounted 7%~~	~~Undiscounted~~	~~Discounted 3%~~	~~Discounted 7%~~	~~Undiscounted~~	~~Discounted 3%~~	~~Discounted 7%~~
1	$0.00	$0.00 ~~$0.00~~	$90	~~$87~~	~~$84~~	$0			$0	~~$0~~	~~$0~~	~~$0~~	~~$0~~		
2	$~~17,225~~0.00	$~~16,23~~60.00 ~~$15,045~~	$90	~~$85~~	~~$79~~	$0	~~$0~~	~~$0~~	$8	~~$7~~	~~$6~~				
3	$~~33,447~~14,735	$~~30,608~~22,239 ~~$27,302~~	$10,347	~~$9,469~~	~~$8,446~~	$1,312	~~$1,201~~	~~$1,071~~	$545	~~$499~~	~~$407~~				
4	$~~49,668~~21,422	$~~44,12~~932,244 ~~$37,892~~	$27,104	~~$24,082~~	~~$20,678~~	$2,599	~~$2,309~~	~~$1,982~~	$1,273	~~$1,131~~	~~$863~~				
5	$~~65,890~~28,110	$~~56,83~~742,248 ~~$46,978~~	$3,879	~~$3,346~~	~~$2,766~~	$360	~~$310~~	~~$256~~	$217	~~$187~~	~~$134~~				
6	$~~64,886~~26,751	$~~54,34~~140,017 ~~$43,236~~	$3,879	~~$3,248~~	~~$2,585~~	$360	~~$301~~	~~$240~~	$217	~~$182~~	~~$121~~				
7	$~~64,886~~626 ~~$52,~~	$40,~~408~~017	$3,879	~~$3,154~~	~~$2,416~~	$360	~~$292~~	~~$224~~	$217	~~$177~~	~~$110~~				

			,751	758										
8			$64,886 26,751		$51,22240,017	$37,764	$3,879	$3,062	$2,257	$360	$284	$209	$217	$172	$100
9			$64,886 26,751		$49,73040,017	$35,294	$3,879	$2,973	$2,110	$360	$276	$196	$217	$167	$91
10			$64,886 26,751		$48,28140,017	$32,985	$3,879	$2,886	$1,972	$360	$268	$183	$217	$162	$82
11			$64,886 26,751		$46,87540,017	$30,827	$3,879	$2,802	$1,843	$360	$260	$171	$217	$157	$75
12			$64,886 26,751		$45,51040,017	$28,810	$3,879	$2,720	$1,722	$360	$252	$160	$217	$152	$68
13	$64,886	$44,184	$26,925751		$40,017		$3,879	$2,641	$1,610	$360	$245	$149	$217	$148	$61
14			$64,886 26,751		$42,89740,017	$25,164	$3,599	$2,379	$1,396	$345	$228	$134	$203	$134	$52
15			$64,886 26,751		$41,64840	$23,518	$3,599	$2,310	$1,304	$345	$221	$125	$203	$130	$47

		,017										
16	$64,886 26,751	$40,435,017	$21,979	$3,599	$2,243	$1,219	$345	$215	$117	$203	$126	$43
17	$64,886 26,751	$39,257,401,017	$20,541	$3,599	$2,177	$1,139	$345	$209	$109	$203	$123	$39
18	$64,886 26,751	$38,114,401,017	$19,197	$3,599	$2,114	$1,065	$345			$203	$102	$203	$119	$35
19	$64,886 26,751	$37,004,401,017	$17,942	$3,599	$2,052	$995	$345	$197	$95	$203	$116	$32
20	$64,886 26,751	$35,926,401,017	$16,768	$3,599	$1,992	$930	$345	$191	$89	$203	$112	$29

Table ~~36~~35 shows that for most years in the twenty-year time horizon, FDA review costs are greater than transfers. The total one-time and recurring FDA review costs, transfers, and the resulting funding gap is presented in Table ~~37~~36.[113] These estimates are conducted using our current fiscal year 2023 Medical Device User Fee program (MDUFA) fee structure. We note that user fee payments are only intended to cover a portion of FDA review costs for premarket submissions.

Under the proposed phaseout timeline, FDA would not phase out the general enforcement discretion approach for premarket review requirements for high risk IVDs offered as LDTs (Stage 4) before October 1, 2027, or for other IVDs offered as LDTs that require a premarket submission (Stage 5) before April 1, 2028. These dates are significant, as October 1, 2027 is the end of MDUFA V and the start of the next medical device user fee program (i.e., MDUFA VI).[114]

Table 36~~:~~. Summary of FDA Review Costs and Transfers (in millions 2022$)

		Total One-time	Total Recurring (Year 4-13)	Total Recurring (Year 14-20)
FDA Review Costs	Primary	$3,422.66	$359.53	$345.04
	Low	$1,711.33	$179.76	$172.52
	High	$6,845.32	$719.05	$690.08
Transfers	Primary	$1,510.09	$160.02	$152.92
	Low	$610.83	$80.01	$76.46
	High	$3,020.19	$320.04	$305.84
Difference (=FDA Costs - Transfers)	Primary	$1,912.56	$199.50	$192.12
	Low	$1,100.50	$99.75	$96.06
	High	$3,825.13	$399.01	$384.24

[113] Distinctions of the annual costs and transfers estimated in year 4-13 and year 14-20 are based on the number of PMA supplements for IVDs currently offered as LDTs that would spread over 10 years (year 4 to year 13).
[114] Note that under the proposed phaseout policy, we anticipate that FDA would phase out the general enforcement discretion approach for establishment registration requirements during the current MDUFA V program, such that user fee payments for establishment registrations (which are distinct from user fee payments for premarket submissions) would be subject to the current MDUFA V fee structure.

After calculating the expected benefits, costs, and transfers for each year in a twenty-year time horizon, we calculate the present and annualized values using a 3% and 7% discount rate. See Table ~~38~~37.

Table 37~~:~~. Summary of Present and Annualized Values (in millions 2022$)

	Benefits	Costs	Transfers
Present Value 7%	$~~548,575.06~~332,737.25	$62,225.24	$2,394.44
Present Value 3%	$~~815,991.88~~332,240.55	$83,282.78	$4,000.27
Annualized Value 7%	$~~51,781.61~~31,408.04	$5,873.62	$226.02
Annualized Value 3%	$~~54,847.47~~22,331.78	$5,597.91	$268.88

~~I.~~J. Analysis of Regulatory Alternatives to the Proposed Rule

We considered five different regulatory alternatives as described below. In our analysis of alternatives, we compare total costs, benefits, and transfers with one option that would be more stringent and three options that would be less stringent. We also considered one alternative of taking no new action. Table ~~39~~38 summarizes our analysis of the alternatives of the proposed rule.

Table 38~~:~~. Summary of Discounted Regulatory Alternatives Over a 20 Year Period (in billions 2022$)

	Proposed Rule		**Alternative 2**		**Alternative 3**		**Alternative 4**	
	3%	**7%**	**3%**	**7%**	**3%**	**7%**	**3%**	**7%**
Annualized Total Benefits	$~~54.85~~2.33	$~~51.78~~3 1.41	$~~69.65~~2 1.93	$30.66~~.46~~	$~~62.51~~1 9.59	$~~57.81~~2 6.56	Discussed qualitatively	
Annualized Total Costs	$5.60	$5.87	$5.86	$6.26	$5.07	$5.~~07~~08	$~~1.75~~3.26	$~~1.62~~3.02
Annualized Net Benefits	$~~49.25~~1 6.73	$~~45.91~~2 5.53	$~~63.79~~1 6.06	$~~60.20~~2 4.40	$~~57.44~~1 4.52	$~~52.73~~2 1.49	Discussed qualitatively	
Annualized Transfers	$0.27	$0.23	$0.28	$0.~~28~~29	$0.24	$0.19	$0.09	$0.06

Present Value Total Benefits	$815.99	$548.58	$747.04	$508.51	$585.83	$391.10	Discussed qualitatively	
Present Value Total Costs	$83.28	$62.23	$87.24	$66.19	$75.44	$53.76	$26.02	$17.15
Present Value Net Benefits	$732.71	$486.35	$659.80	$442.32	$510.39	$337.34	Discussed qualitatively	
Present Value Transfers	$4.00	$2.39	$4.13	$2.97	$3.62	$1.99	$1.30	$0.66

Notes: We report primary estimates. There would be no additional costs or benefits under Alternative 1. For Alternative 4, we provide a qualitative discussion on the reduction of benefits. For Alternative 5, we are not able to quantify costs, benefits, and transfers due to lack of information.

1. We treat one alternative of taking no new action as the baseline for determining the costs and benefits of other alternatives. Under this option, there would be no additional costs or benefits relative to the status quo.
2. The second regulatory alternative reduces the phaseout period to three years following the ~~effective~~publication date of the final rule:
    - Stage 1: End the general enforcement discretion approach with respect to MDR and correction and removal reporting requirements, one year after FDA publishes the final phaseout policy.
    - Stage 2: End the general enforcement discretion approach with respect to requirements not covered during other stages of the phaseout policy, including registration and listing, labeling, investigational use requirements, and QS requirements, two years after FDA publishes the final phaseout policy.
    - Stage 3: End the general enforcement discretion approach with respect to premarket ~~approval~~review requirements ~~(~~for high-risk IVDs~~)~~ and other premarket ~~submission~~review requirements (for moderate-risk and low-risk IVDs that require premarket submissions), three years after FDA publishes the final phaseout policy.

Under this alternative, we assume that one-time and recurring costs of the QS requirements would occur in year 2 and costs of the PMA, 510(k), and de novo submissions would occur in

year 3. The estimated annualized costs of this alternative would be $6.26 billion, which is $388 million higher than the estimated costs associated with the proposed rule. The estimated annualized transfers of this alternative would be $294 million, which is $68 million higher than the estimated transfers associated with the proposed rule. The shorter phaseout period would result in higher annualized benefits because they would begin earlier than under the proposed rule. The estimated annualized benefits of this alternative would be $30.66~~.46~~ billion, which is $~~14.68~~0.75 billion higher than the benefits associated with the proposed rule. However, a shorter phaseout period means that, among other things, affected laboratories, including small ~~entities~~laboratories, would have less time to prepare and it might be less feasible for them to come into compliance. We request comments on the costs of compliance as a function of various compliance period lengths. We seek to know in what ways, if any, laboratories would approach compliance differently based on being afforded less time.

3. The third alternative extends the phaseout period to ten years for small entities (i.e., laboratories that have their annual receipts and sales less than $100 million) and six years for other entities:
    - Stage 1: End the general enforcement discretion approach with respect to MDR and correction and removal reporting requirements, one year after FDA publishes the final phaseout policy.
    - Stage 2: End the general enforcement discretion approach with respect to requirements not covered during other stages of the phaseout policy, including registration and listing, labeling, investigational use requirements, and QS requirements, four years after FDA publishes the final phaseout policy.

- Stage 3: End the general enforcement discretion approach with respect to premarket ~~approval~~review requirements ~~(~~for high-risk IVDs~~),,~~ five years (seven years for small ~~entities~~laboratories) after FDA publishes the final phaseout policy.
- Stage 4: End the general enforcement discretion approach with respect to premarket ~~submission~~review requirements for moderate risk and low risk IVDs that require premarket submissions, six years (ten years for small ~~entities~~laboratories) after FDA publishes the final phaseout policy.

Compared to the proposed rule, having a longer phaseout period would reduce the burden on the affected laboratories by shifting costs into the future. Costs for Stage 2 under the proposed rule (including compliance with registration and listing, labeling, and investigational use requirements) would occur in year 2, and costs for Stage 3 under the proposed rule (relating to compliance with QS requirements) would occur in year 3, but we assume that costs for Stage 2 under this alternative (which would include the costs for Stage 2 and Stage 3 under the proposed rule) would occur in year 4. We assume that costs for Stage 3 under this option would occur in year 5 (year 7 for small entities). We finally assume that costs for Stage 4 under this option would occur in year 6 (year 10 for small entities). The affected laboratories would thus have lower costs under Stages 2 to 4, except that the costs for Stage 1 would still occur in the first year after the final rule. The estimated annualized costs of this alternative would be approximately $5.08 billion, which is $798 million less than the estimated costs associated with the proposed rule. Out of the estimated annualized costs, the estimated annualized costs to FDA would be approximately $461 million under this alternative, which is $46 million less than the estimated FDA review costs with the proposed rule. In addition, the longer phaseout period for small laboratories would mean that these entities would have more time to prepare premarket

submissions, potentially making it more feasible for them to come into compliance. However, this option would also reduce annualized benefits by $6.034.84 billion because extending the phaseout period to six years (and ten years for small entitieslaboratories) would reduce the amount of avoided illnesses and death. We request comments on the costs of compliance as a function of various compliance period lengths. We seek to know in what ways, if any, laboratories would approach compliance differently based on being afforded more time.

4. In the fourth alternative, there would not be a phase out of the general enforcement discretion approach for QS requirements and premarket review requirements for IVDs that are offered as LDTs at the time of publication of the final rule. and have not been changed with respect to indications for use or performance after that date. Under this alternative, FDA would still phase out the general enforcement discretion approach with respect to registration and listing requirements, adverse event reporting requirements, and other requirements addressed in Stages 1 and 2 of the proposed phaseout policy for these IVDs.

We assume that there would be no one-time costs of the QS requirements and premarket review requirements. We also assume that there would be recurring costs for StageStages 3 through 5 for new IVDs offered as LDTs and IVDs offered as LDTs from new entities. The affected laboratories would thus have lower total costs. The estimated annualized costs of this alternative would be approximately $1,6193,019 million, which is $4.24 billion2,855 million less than the estimated costs associated with the proposed rule. Out of the estimated annualized costs, the estimated annualized costs to FDA would be approximately $277 million under this alternative, which is $252 million less than the estimated costs to FDA with the proposed rule. The estimated annualized transfers of this alternative would be approximately $62 million, which is $164 million less than the estimated transfers associated with the proposed rule.

However, this option would also reduce benefits, as discussed below. This option would also present a comparative barrier to laboratories with new IVDs offered as LDTs entering the market as they would still bear the costs of all stages (including Stages 3, 4 and 5) whereas laboratories with IVDs offered as LDTs on the market at the time of publication of the final rule would not bear the costs of Stages 3, 4 and 5.

Under this alternative, FDA would still phase out the general enforcement discretion approach for IVDs offered as LDTs on the market at the time of publication of the final rule with respect to registration and listing requirements, adverse event reporting requirements, and other requirements described in Stages 1 and 2. ~~This would provide FDA with more information than we have available today to identify problematic tests. Benefits that would result from this option would be associated with FDA's reactive enforcement (e.g., in response to MDRs) rather than proactive review of regulatory submissions.~~ In addition, the general enforcement discretion approach would be phased out with respect to all requirements described in Stages 1 through 5 (as described in the proposed phaseout policy) for IVDs offered as LDTs that are (1) not on the market at the time of publication of the final rule~~.~~ and (2) on the market at the time of publication but have been changed with respect to indications for use or performance after the date of publication. Overall, this alternative would ~~still address the public health concerns associated with problematic IVDs offered as LDTs, and would therefore~~ result in benefits, but to a lesser degree than the proposed phaseout policy.

While we expect a reduction in benefits under this alternative, we are unable to estimate the share of benefits that would be reduced under this option.[~~115~~116] We assume the number of

[~~115~~] ~~Our cost benefit model does not estimate marginal benefits compared to marginal costs associated with individual stages of this rule. Instead, our benefit estimate is estimated as a whole.~~

[116] Our cost benefit model does not estimate marginal benefits compared to marginal costs associated with individual stages of this rule. Instead, our benefit estimate is estimated as a whole.

IVDs offered as LDTs at the time of publication of the final rule would be significant. As discussed in section E.~~5~~4 Summary of Benefits, our estimates are based on the assumption that benefits would begin to accrue ~~one year~~two years after Stage 1 of the proposed phaseout policy (or year 2), though we do not expect all estimated benefits to take place all at once. Instead, we assume that one-time benefits will occur evenly (by 25%) over ~~the first four years~~Stages 1 to 5 (year ~~2~~3 to year 5) and that expected recurring benefits will begin to accrue at an incremental rate of ~~25~~0%, 50%, 75%, and 100% for the first four years (Table ~~16~~15).

~~We assume~~In the ~~number of IVDs offered as LDTs at the time of publication of the final rule would be significant. However, to the extent that laboratories modify such tests, they could be considered a new IVD offered as an LDT.~~

5. ~~The~~ fifth regulatory alternative ~~builds on the fourth regulatory alternative described above. Under this alternative, in addition to continuing~~ , FDA would continue the general enforcement discretion approach for ~~QS requirements and~~ premarket review requirements for IVDs that are offered as LDTs at the time of publication of the final rule, ~~FDA would seek to expand the Third Party review program such~~and would also leverage the New York State Department of Health (NYSDOH) Clinical Laboratory Evaluation Program (CLEP) by continuing enforcement discretion for premarket review requirements for tests that have obtained New York State approval. In this alternative, FDA further assumes that at least 50% of new IVDs offered as LDTs subject to 510(k) premarket notification requirements would be reviewed by an accredited Third Party review organization under FDA's Third Party review program.

Based on available information from the NYSDOH, we estimate that 11.4% (ranging from 5.7% to 22.8%) of IVDs offered as LDTs would not experience new costs associated with

submission preparation and review as a result of FDA leveraging the NYSDOH CLEP. In addition, 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. Manufacturers who submit to Third Party reviewers pay the Third Party but do not pay FDA user fees. Each Third Party sets their own rates which are generally comparable to FDA user fees. ~~in vitro diagnostic devices.~~ Under the MDUFA V agreement, FDA is currently working to enhance the program with the objective of eliminating routine re-review by FDA of Third Party reviews. Therefore, we estimate the cost to FDA of reviewing a 510(k) reviewed by a Third Party to be not more than one business day.

We have the same assumption as in alternative 4. We additionally assume that one-time and recurring costs of reviewing 510(k) submissions would be 50% of the proposed rule because they would be reviewed by Third Party reviewers. We also assume that one-time and recurring costs of reviewing premarket submissions would be 11.4% less than the proposed rule since they would be reviewed by NYSDOH. This alternative would thus lower total costs by lowering the FDA review costs. The estimated annualized costs to FDA would be approximately $225 million under this alternative, which is $304 million less than the estimated costs to FDA with the proposed rule. However, this option would also reduce benefits, as discussed in alternative 4.

~~Manufacturers who submit to Third Party reviewers pay the Third Party but do not pay FDA user fees. Each Third Party sets their own rates which are generally comparable to FDA user fees. Where existing programs are leveraged, such as the New York State Department of Health (NYSDOH) Clinical Laboratory Evaluation Program, there would be no new cost to the manufacturer for preparation of a submission or for its review. Based on available information~~

~~from the NYSDOH we estimate that 11.4% (ranging from 5.7% to 22.8%) of IVDs offered as LDTs would not experience new costs associated with submission preparation and review. Should the Third Party review program be expanded to include well-established tests subject to PMA requirements, some IVDs offered as LDTs would not experience new costs associated with submission preparation and review for these tests, as well.~~

~~J.~~K. Distributional Effects

The proposed rule (if finalized) may generate benefits and costs that accrue differentially to establishments and segments of society. In this section, we discuss differential health equity effects for populations on which IVDs offered as LDTs are used. We address differential effects for small entities in section III of this analysis.

As described in section II.E, we expect the proposed rule to result in an increase in the accuracy of laboratory test results, which may reduce the incidence of patient misdiagnosis resulting in more appropriate treatments and improved health outcomes, among other benefits. While we would not expect the benefits of the rule – in isolation – to differentially affect certain population segments, existing inequities in healthcare access may result in differential accrual of benefits across the general population. For example, there is evidence of disparities in access to testing (Ref. [57]) which may impact the patient populations that the benefits of this proposed rule would reach. 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 depend on the ability of tests to work as intended, and the harms of unsafe or ineffective IVDs offered as LDTs may be disproportionately realized among medically

underserved patient populations that such tests may aim to reach. Without appropriate oversight, IVDs offered as LDTs may actually exacerbate health disparities. There are reported concerns regarding higher rates of inaccurate results among underrepresented patient populations, particularly racial and ethnic minorities undergoing genetic testing (Refs. [58, 59, 60, 61, 62]). Additionally, 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 tests may be less accurate in underrepresented patient populations, which could contribute to health disparities (Ref. [63]). The role of IVDs offered as LDTs in either ameliorating or exacerbating existing health inequity ultimately depends on the safety and effectiveness of IVDs offered as LDTs, which this proposed rule is intended to help assure. By increasing its oversight, FDA may better prevent and mitigate harms disproportionately realized among underrepresented, medically underserved populations. As such, the benefits of this proposed rule may differentially reach these populations.

When IVDs are subject to increased FDA oversight, FDA would help 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 are generally 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 IVDs, FDA does not know whether diverse patient populations are being included in validation studies for these IVDs. FDA believes increased oversight for these IVDs will help ensure

adequate representation of the intended use population in validation studies and transparency regarding potential differential performance, helping to advance health equity. Nonetheless, while the proposed rule may help to advance health equity, we have no specific data showing that increased FDA oversight of IVDs offered as LDTs will necessarily reduce health disparities.

As described in section II.F.~~7~~6, there may be costs to society stemming from pass-throughs of costs for IVDs offered as LDTs. If laboratories pass-through the cost of compliance to the costs of IVDs offered as LDTs, testing frequency may decrease for areas that rely on IVDs offered as LDTs because of easy, rapid access.[117] If laboratories or healthcare facilities respond to increased compliance costs by increasing the price of IVDs offered as LDTs or reducing the availability of IVDs offered as LDTs, there may be an increase in health inequity. Vulnerable populations that rely on IVDs offered as LDTs for diagnostic testing may have less access to diagnostic tests in general after the implementation of the rule. However, in the absence of assurances about the safety and effectiveness of these tests, the value of access is uncertain. We further note that in the event any currently marketed tests for underserved populations are withdrawn from the market due to their inability to meet regulatory requirements, other manufacturers may fill the need with appropriately designed and validated tests, to patients' benefit. The effect of the rule on the price of IVDs offered as LDTs is unknown. The effect of price changes for IVDs offered as LDTs on diagnostic test usage is also unknown. We request comment on empirical data that links price changes in diagnostic tests to prevalence of use across populations.

We do not expect the proposed rule (if finalized) to result in an increase in health inequity in isolation. Though we do have evidence of existing health inequities in diagnostic testing and

[117] A 2021 Pew Charitable Trusts' survey of laboratory managers found that 'rapid access' and 'patient need' where top reasons why laboratory managers would choose to employ an LDT (Ref. [13]).

clinical trials across sociodemographic populations, we lack the evidence to quantify the effect of the rule on these existing health inequities, and thus cannot determine whether the rule will ameliorate or exacerbate health inequity. We request comment on sources of data we can use to better analyze the effect of the rule on health inequity.

~~K.~~L. International Effects

While the proposed rule (if finalized) will generate benefits that accrue to the domestic population, some laboratories that are located outside the United States would be expected to comply with applicable device requirements, as a result of this rule, if they offer IVDs as LDTs to patients within the United States. This section estimates the cost of compliance for international laboratories. These costs are not included in section II.F, which only assesses domestic costs.

As of March 2023, there are 64 international laboratories certified under CLIA to perform non-waived testing.[118] Using the same assumptions described in section II.D, we assume that 10% of CLIA certified laboratories make LDTs (64 x 0.10 = 6.4) and each laboratory would have 67 IVDs offered as LDTs, and thus we expect 429 (= 6.4 x 67) international IVDs offered as LDTs to be affected by this rule. We also assume 38 (6.4 x 6) new international IVDs offered as LDTs to be affected by this rule annually, consistent with assumptions in section II.D. We request comment on these estimates and assumptions.

We also adjust wages to reflect the fact that international laboratories may not offer the same wages as those in the United States. Specifically, we create a list of the unique countries that appear in our data on the 64 international laboratories, then search the National Bureau of

[118] https://qcor.cms.gov/advanced_find_provider.jsp?which=4&backReport=active_CLIA.jsp

Economic Research (NBER) Occupational Wages around the World (OWW) database for wage information for the relevant countries.[119] The most recent year with complete data is 2007. We observe the average hourly wage rate across all sectors for the relevant countries in U.S. dollars, then divide by the same measure for U.S. wages to get a relative measure of wages as percent deviation from the U.S. hourly wage rate for the same period. We then take the average percent deviation across the relevant countries and find that wages for the relevant international countries are 73% that of U.S. wages for the same time period. We therefore adjust the wages we use in the domestic cost analysis by 0.73 to assess international costs.

Aside from coverage and wage rates, the costs for international laboratories are calculated using the exact same methods as in section II.F. Because there are significantly fewer laboratories and tests, and wages are slightly lower, international costs are much lower than domestic costs of compliance. See Table ~~40~~39 for a summary of international costs, organized by stage and part of the proposed rule.

Table 39~~:~~. International Costs

		Primary	Low	High
One-time				
Stage 1	Reading and Understanding the Rule	$2,495	$1,123	$4,210
	Medical Device Reporting	$47,240	$37,705	$59,039
	Correction and Removal Reporting	$160	$160	$160
Stage 2	Registration and Listing Requirements	$1,606	$1,606	$1,606
	Labeling Requirements	$10,704	$2,141	$18,198
	Investigational Use Requirements	$15,417	$3,048	$27,786

[119] https://www.nber.org/research/data/occupational-wages-around-world-oww-database

Stage 3	Quality System Requirements	$282,496	$48,181	$794,952
Stage 4	Premarket Approval Application	$106,498,911	$100,915,440	$212,584,861
Stage 5	510(k) Submission or De Novo Classification Request	$82,550,998	$68,274,149	$89,806,626
Total One-time Costs		**$189,410,028**	**$169,283,553**	**$303,297,436**
Recurring Annual				
Stage 1	Reading and Understanding the Rule	$185	$83	$312
	Medical Device Reporting	$298,099	$297,336	$299,043
	Correction and Removal Reporting	$602	$602	$602
Stage 2	Re-registration	$664	$664	$664
	Labeling	$856	$171	$1,456
	Investigational Use Requirements	$34,516	$6,823	$62,208
Stage 3	Quality System Requirements	$1,452,853	$231,745	$3,575,696
Stage 4	Premarket Approval Application	$10,577,618	$10,037,605	$20,837,871
	Premarket Approval Application Supplements*	$1,571,768	$1,487,322	$3,176,240
Stage 5	510(k) Submission or De Novo Classification Request	$7,984,037	$6,603,231	$8,685,775
Total Recurring Costs		**$21,921,196**	**$18,665,582**	**$36,639,865**

** This table reports the recurring costs of PMA supplements for year 4-13. The estimated recurring costs of PMA supplements for year 14-20 ranges from $731,248 to $1,561,611, with a primary estimate of $772,766.*

See Table ~~41~~40 for a summary of the expected timing and annualized value of international costs. At a 3 percent discount rate, we expect the annualized value of international costs to range from $25.32 million to $48.10 million, with a primary estimate of $29.24 million. At a 7 percent discount rate, we expect the annualized value of international costs to range from $26.71 million to $50.56 million, with a primary estimate of $30.73 million.

Table 40-. Twenty-Year Timing of International Costs (millions 2022$)

	Primary	Low	High
Year 1	$0.35	$0.34	$0.36
Year 2	$0.36	$0.31	$0.41
Year 3	$61.39	$56.81	$123.03
Year 4	$157.72	$137.40	$232.74
Year 5-13 (costs for each year)	$21.92	$18.67	$36.64
Year 14-20 (costs for each year)	$20.35	$17.18	$33.46
Total Costs of the Proposed Rule	$559.56	$483.09	$920.55
Present Value of Total Costs (3%)	$434.98	$376.69	$715.56
Present Value of Total Costs (7%)	$325.55	$282.97	$535.64
Annualized Value of Costs (3%)	**$29.24**	**$25.32**	**$48.10**
Annualized Value of Costs (7%)	**$30.73**	**$26.71**	**$50.56**

III. Initial Small Entity Analysis

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 would 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 would have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document and the proposed rule, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

We used detailed data from 2017 Statistics of U.S. Businesses on U.S. 6-digit NAICS detailed employment sizes and revenues to analyze the potential impacts of this proposed rule on small entities. Since not all laboratories in this NAICS code offer IVDs as LDTs, we use the number of affected laboratories and distribute them proportionally across the revenue

distribution from the Economic Census to estimate breakdown of the laboratories by revenue size (see Table ~~42~~41). The Small Business Administration (SBA) considers Medical Laboratories (NAICS code 621511) to be small if their annual receipts are less than $41.5 million.[120] Of the 1,200 laboratories, 1,081 laboratories (the sum of all laboratories with less than $41.5 million in annual receipts), or 90 percent of the total, would be small according to the 2023 SBA size standard. We estimate that small businesses also ~~produce~~manufacture 46% of IVDs offered as LDTs currently on the market. We provide more detail on these estimates in Appendix A. We request comment on the estimates.

Table 41. Distribution of Revenues for Laboratories Offering IVDs as LDTs

Receipts Size ($1,000)	Number of Laboratories Under NAICS Code 621511	Number of Laboratories Offering IVDs as LDTs	Number of IVDs offered as LDTs
<$150	438	156	112
$150 - $999	933	333	1,258
$1,000 - $2,999	413	147	1,517
$3,000 - $4,999	481	172	3,921
$5,000 - $9,999	343	122	6,161
$10,000 - $14,999	146	52	4,327
$15,000 - $19,999	77	27	2,998
$20,000 - $29,999	115	41	6,267
$30,000 - $39,999	79	28	5,878
$40,000 - $44,999	21	7	1,913
$45,000 - $59,999	43	15	4,570
$60,000 - $69,999	15	5	2,318
$70,000 - $99,999	67	24	11,020
$100,000+	194	69	28,140
Total	3,365	1,200	80,400
<$41,500	3,031	1,081	33,014

[120] Small Business Association. Table of Size Standards. March 17, 2023. Available from: https://www.sba.gov/document/support-table-size-standards

B. Description of the Potential Impacts of the Rule on Small Entities

We compiled the costs and transfers associated with the proposed rule and compared them to the estimated share of annual receipts of the laboratories offering IVDs as LDTs. In Table ~~43~~42, we estimate the total annualized costs per entity at a 7 percent discount rate over 20 years and the costs as a percent of revenue by receipts size. The estimated annualized cost per small entity ranges from $26,255 to $9,332,409 per laboratory, depending on its size classification.[121] As shown in Table ~~43~~42, the annualized costs per entity are 22.9 percent of receipts for the small laboratories (with annual receipts of less than $41,500,000) making it likely that some small entities in this size category would exit the market or reduce operations as the burden is significant. We also estimate that small laboratories hold a 18% share of receipts while producing 41% of all IVDs offered as LDTs. For large laboratories (with annual receipts of $41,500,000 or greater), the annualized costs per entity estimated range is between 5.1 and 22.9 percent of receipts. These laboratories are less likely than the small laboratories to exit the market or reduce operations as a result of compliance costs, given how such costs compare to the laboratories' overall revenues.

Small businesses that have gross receipts or sales of $100 million or less for the most recent tax year (including their affiliates) are eligible to pay a reduced fee for certain submissions, including 510(k) submissions, de novo classification requests, PMAs, and PMA annual reports. Small businesses with sales of $30 million or less are eligible to have the fee waived on their first PMA. The estimated recurring transfer for small businesses is $10,739, $24,551, or $83,963 per laboratory, depending on its size classification. As seen in Table ~~43~~42,

[121] The estimated annualized cost per small entity ranges from $26,253 per laboratory with annual receipts that are less than $150,000 and to $9,331,689 per laboratory with annual receipts between $40 and $45 million.

the transfers associated with the rule are estimated to be 9.36% for 156 laboratories (14% of the small entities) with their annual receipts less than $150,000.

Table 42~~:~~. Small Business Costs and Transfers as a Percentage of Receipts

Receipts Size ($1,000)	~~LDT~~ Labs	Average Receipts	Total Costs per Lab	Costs as a % of Receipts	Total Transfers per Lab	Transfers as a % of Receipts
<$150	156	$114,693	$26,255	22.9%	$10,739	9.36%
$150 - $999	333	$603,539	$138,157	22.9%	$10,739	1.78%
$1,000 - $2,999	147	$1,643,710	$376,264	22.9%	$10,739	0.65%
$3,000 - $4,999	172	$3,647,332	$834,916	22.9%	$10,739	0.29%
$5,000 - $9,999	122	$8,037,357	$1,839,843	22.9%	$10,739	0.13%
$10,000 - $14,999	52	$13,260,631	$3,035,511	22.9%	$10,739	0.08%
$15,000 - $19,999	27	$17,419,278	$3,987,473	22.9%	$10,739	0.06%
$20,000 - $29,999	41	$24,386,024	$5,582,241	22.9%	$10,739	0.04%
$30,000 - $39,999	28	$33,294,914	$7,621,588	22.9%	$10,739	0.03%
$40,000 - $44,999	7	$40,768,634	$9,332,409	22.9%	$10,739	0.03%
$45,000 - $59,999	15	$47,556,757	$10,886,288	22.9%	$24,551	0.05%
$60,000 - $69,999	5	$69,135,779	$15,825,974	22.9%	$24,551	0.04%
$70,000 - $99,999	24	$73,594,799	$16,846,695	22.9%	$24,551	0.03%
$100,000+	69	$293,244,651	$14,857,515	5.1%	$83,963	0.03%
Total	1,200	$23,855,522	$2,447,343	10.3%	$15,474	0.00%
<$45.1 M	1,081	$4,873,251	$1,115,543	22.9%	$10,739	0.00%

C. Alternatives to Minimize the Burden on Small Entities

Regulatory alternatives 3 and 4, described in section II.~~I~~J, would reduce costs for all laboratories. Below we show how the reduction in cost under these alternatives would reduce the cost on small laboratories.

One alternative that could reduce the impact to small entities would be an extended phaseout policy from 4 years to 10 years for small laboratories as discussed in section II.~~I~~J.3 ("third alternative"). Compared with the proposed rule, small laboratories would have lower one-time and recurring costs for Stage 2 of the third alternative because they generally would have an additional one to two years before FDA would expect compliance with these requirements (e.g.,

labeling, registration and listing, investigational use, and QS requirements). There would also be an additional 3.5 years for the compliance expectations for PMA requirements and 6 years for the compliance expectations for 510(k) and de novo requirements. The costs associated with Stage 1 would be unimpacted by the extended phaseout policy as the costs would still occur in the first year after the final rule.

We estimate this option would reduce total costs by $3,569 to $2.29 million per small entity. However, some small laboratories (with annual receipts of less than $41,500,000) may still be likely to reduce operations or exit the market under this option, as the total recurring costs are estimated to be 19.8 percent of their receipts. This alternative would also reduce transfers for all laboratories offering IVDs as LDTs from $10,739 to $10,536 per entity for laboratories with their annual receipts below $30 million, which is $204 less than the estimated transfers of the rule. For the smallest laboratories, total transfers would be 9.19 percent of receipts. See Table 4443.

Table 43÷. Small Business Costs and Transfers as a Percentage of Receipts under Regulatory Alternative 3

Receipts Size ($1,000)	Labs	Average Receipts	Costs Per Lab (7%)	Costs as a % of Receipts	Transfers Per Lab (7%)	Transfers as a % of Receipts
< $100	156	$114,693	$22,686	19.8%	$10,536	9.19%
$100 - $499	333	$603,539	$119,377	19.8%	$10,536	1.75%
$599 - $999	147	$1,643,710	$325,117	19.8%	$10,536	0.64%
$1,000 - $2,999	172	$3,647,332	$721,423	19.8%	$10,536	0.29%
$3,000 - $5,999	122	$8,037,357	$1,589,746	19.8%	$10,536	0.13%
$6,000 - $9,999	52	$13,260,631	$2,622,881	19.8%	$10,536	0.08%
$10,000 - $14,999	27	$17,419,278	$3,445,439	19.8%	$10,536	0.06%
$15,000 - $19,999	41	$24,386,024	$4,823,424	19.8%	$10,536	0.04%
$20,000 - $24,999	28	$33,294,914	$6,585,555	19.8%	$10,536	0.03%
$25,000 - $29,999	7	$40,768,634	$8,063,816	19.8%	$10,536	0.03%
$30,000 - $39,999	15	$47,556,757	$9,406,470	19.8%	$17,294	0.04%
$40,000 - $49,999	5	$69,135,779	$13,674,685	19.8%	$20,692	0.03%

$50,000 - $99,999	24	$73,594,799	$14,555,655	19.8%	$20,692	0.03%
$100,000+	69	$293,244,651	$12,837,873	4.4%	$71,480	0.02%
Total	1,200	$23,855,522	$2,114,665	8.9%	$14,383	0.00%
<$41,500	1,081	$4,873,251	$963,903	19.8%	$10,536	0.00%

Alternative 4 could reduce the impact ~~to~~on small laboratories as there would not be a phaseout of the general enforcement discretion approach for QS requirements and premarket review requirements for IVDs offered as LDTs at the time of publication of the final rule. Compared with the proposed phaseout policy, laboratories would have lower costs because they would have no one-time costs for Stages 3 through 5 of the proposed phaseout policy. The costs associated with Stages 1 and 2 would be unimpacted by this alternative. We estimate this option would reduce total costs by $19,017 to $12.20 million per small entity and the total costs would be 6.3 percent of receipts. This alternative would also reduce transfers for all laboratories offering IVDs as LDTs from $10,739 to $4,588 per entity for laboratories with their annual receipts below $30 million, which is $6,152 less than the estimated transfers of the proposed phaseout policy. For the smallest laboratories, total transfers would be 6.3 percent of receipts. See Table ~~45~~44.

Table 44: Small Business Costs and Transfers as a Percentage of Receipts under Regulatory Alternative 4

Receipts Size ($1,000)	Labs	Average Receipts	Costs Per Lab (7%)	Costs as a % of Receipts	Transfers Per Lab (7%)	Transfers as a % of Receipts
< $100	156	$114,693	$7,238	6.3%	$4,588	4.00%
$100 - $499	333	$603,539	$38,088	6.3%	$4,588	0.76%
$599 - $999	147	$1,643,710	$103,731	6.3%	$4,588	0.28%
$1,000 - $2,999	172	$3,647,332	$230,175	6.3%	$4,588	0.13%
$3,000 - $5,999	122	$8,037,357	$507,219	6.3%	$4,588	0.06%
$6,000 - $9,999	52	$13,260,631	$836,848	6.3%	$4,588	0.03%
$10,000 - $14,999	27	$17,419,278	$1,099,291	6.3%	$4,588	0.03%

$15,000 - $19,999	41	$24,386,024	$1,538,946	6.3%	$4,588	0.02%
$20,000 - $24,999	28	$33,294,914	$2,101,166	6.3%	$4,588	0.01%
$25,000 - $29,999	7	$40,768,634	$2,572,815	6.3%	$4,588	0.01%
$30,000 - $39,999	15	$47,556,757	$3,001,198	6.3%	$6,882	0.01%
$40,000 - $49,999	5	$69,135,779	$4,363,000	6.3%	$6,882	0.01%
$50,000 - $99,999	24	$73,594,799	$4,644,399	6.3%	$6,882	0.01%
$100,000+	69	$293,244,651	$4,096,010	1.4%	$13,581	0.00%
Total	1,200	$23,855,522	$674,698	2.8%	$5,192	0.06%
<$41,500	1,081	$4,873,251	$307,540	6.3%	$4,588	0.00%

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Appendix A. Initial Small Entity Analysis Estimates

In Table 42 of Section III. Initial Small Entity Analysis, we used detailed data from 2017 Statistics of U.S. Businesses on U.S. 6-digit NAICS detailed employment sizes and revenues to analyze the potential impacts of this proposed rule on small entities. We initially use our estimated total market revenue for IVD's offered as LDTs of $28 billion in the bottom of column E in Table A.1 as our total annual receipts and extrapolate the share of annual receipt by enterprise size from the 2017 Census data corresponding to NAICS code 621511. This estimate is derived using the assumption that 50% of revenue for this NAICS category is from IVDs offered as LDTs.

Table A.1 Growth Adjusted Annual Receipts from LDTs by Enterprise Size (2022, U.S. Dollars)

Number of Firms and Receipts by Enterprise Receipt Size 2017				**Receipts Only LDTS ($1,000) in 2022 dollars adjusted for growth since 2017**	**Calculation**
i	**Enterprise Size ($1,000)**	**Firms**	**Receipts ($1,000) D**	**E**	
1	<100	438	22,315	$17,915	A * D1/D Total
2	100-499	933	250,134	$200,809	A * D2/D Total
3	500-999	413	301,551	$242,087	A * D3/D Total
4	1,000-2,499	481	779,302	$625,629	A * D1/D Total
5	2,500-4,999	343	1,224,596	$983,113	A * D1/D Total
6	5,000-7,499	146	860,008	$690,420	A * D1/D Total
7	7,500-9,999	77	595,808	$478,318	A * D1/D Total
8	10,000-14,999	115	1,245,731	$1,000,081	A * D1/D Total
9	15,000-19,999	43	609,900	$489,632	A * D1/D Total
10	20,000-24,999	36	558,497	$448,365	A * D1/D Total
11	25,000-29,999	31	654,966	$525,811	A * D1/D Total

12	30,000-34,999	21	380,304	$305,310	A * D1/D Total
13	35,000-39,999	12	253,411	$203,440	A * D1/D Total
14	40,000-49,999	17	559,107	$448,855	A * D1/D Total
15	50,000-74,999	50	1,631,212	$1,309,547	A * D1/D Total
16	75,000-99,999	15	460,659	$369,820	A * D1/D Total
17	100,000+	194	25,270,700	$20,287,475	A * D1/D Total
	Total	**3,365**	**35,658,201**	**$28,626,626**	

We estimate the number of labs by receipt size category by the same proportion as the number of firms by receipt category from the Census data. For example, for firms with annual receipts less than <$150,000 we divided 438 by 3,365 and multiply by 1,200 to obtain 156 (438/3,365*1,200 = 156). We repeat this calculation for the rest of the rows. We then estimate the average receipts per laboratory by receipt size category. We also re-classify enterprise size categories given our new estimated average receipts per lab (Table A.2).

Table A. 2 Estimated Number of LDT Laboratories and Average Annual Receipts per Laboratory (2022 U.S. dollars)

i	**Enterprise Size ($1,000)**	***Firms***	**Receipts ($1,000)**	**Receipts LDTS Only ($1,000) in 2022 dollars adjusted for growth since 2017**	**LDT Labs (1,200)**	Average Receipts per lab
1	<$150	438	$22,315	$17,915	156.20	$115
2	$150 - $999	933	$250,134	$200,809	332.72	$604
3	$1,000 - $2,999	413	$301,551	$242,087	147.28	$1,644
4	$3,000 - $4,999	481	$779,302	$625,629	171.53	$3,647
5	$5,000 - $9,999	343	$1,224,596	$983,113	122.32	$8,037
6	$10,000 - $14,999	146	$860,008	$690,420	52.07	$13,261
7	$15,000 - $19,999	77	$595,808	$478,318	27.46	$17,419

8	$20,000 - $29,999	115	$1,245,731	$1,000,081	41.01	$24,386
9	$30,000 - $39,999	79	$1,168,397	$937,996	28.17	$33,295
10	$40,000 - $44,999	21	$380,304	$305,310	7.49	$40,769
11	$45,000 - $59,999	43	$908,377	$729,251	15.33	$47,557
12	$60,000 - $69,999	15	$460,659	$369,820	5.35	$69,136
13	$70,000 - $99,999	67	$2,190,319	$1,758,402	23.89	$73,595
14	$100,000+	194	$25,270,700	$20,287,475	69.18	$293,245
	Total	3,365	$35,658,201	**$28,626,626**	1,200.00	$23,856

To estimate the number of LDTs per receipt category, we incorporate the assumption that on average 65% of submissions to FDA (LDTs) are from laboratories with less than $100 million in sales. Each row in Column B is divided by 100% and multiplied by 65% to obtain the LDT share by receipts size category (Column B_i /100% *65%). We obtain the number of LDTs per receipts size category in column D by multiplying column C time 80,400 (which is our estimated total number of LDTs). See Table A.3.

Table A.3 Share of LDTs and LDTs per Receipt Category

i	**Enterprise Size ($1,000)**	**Percent Firms by Receipt Size A**	**LDT LABS (A * 1,200)**	**Percent Receipts by Receipt Size B**	**LDT share by receipt category (adjusted for 65% Small)* C**	**LDTS per receipt category (65% Small)** D**
1	<$150	13%	156	0.06%	0.0014	112
2	$100 - $999	28%	333	0.70%	0.0157	1,258
3	$1,000 - $2,999	12%	147	0.85%	0.0189	1,517
4	$1,000 - $4,999	14%	172	2.19%	0.0488	3,921
5	$5,000 - $9,999	10%	122	3.43%	0.0766	6,161
6	$10.000 - $14,999	4%	52	2.41%	0.0538	4,327
7	$15,000 - $19,999	2%	27	1.67%	0.0373	2,998

8	$15,000 - $19,999	3%	41	3.49%	0.0780	6,267
9	$20,000 - $39,999	2%	28	3.28%	0.0731	5,878
10	$40,000 - $44,999	1%	7	1.07%	0.0238	1,913
11	$45,000 - $59,999	1%	15	2.55%	0.0568	4,570
12	$60,000 - $69,999	0%	5	1.29%	0.0288	2,318
13	$70,000 - $99,999	2%	24	6.14%	0.1371	11,020
14	$100,000+	6%	69	70.87%	0.3500	28,140
	Total	100%	**1,200**			**80,400**

*The sum of ratios in column B for labs with <100 million constitute 65% of LDTs and 35% LDTs correspond to labs with Receipts >= $100 Million

**Column D is the product of Column C and 80,400