DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Laboratory Developed Tests Final Rule

Docket No. FDA-2023-N-2177

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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Executive Summary

This final rule amends 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. In conjunction with this amendment, FDA is phasing out its general enforcement discretion approach for laboratory developed tests (LDTs) so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs, as discussed further in section V of the preamble to the rule.

We quantify benefits to patients from averted health losses due to problematic IVDs offered as LDTs.[1,2] We focus mainly on certain broad disease categories associated with the majority of misdiagnosis-related harms in the U.S. Additional benefits include averted non-health losses from reduced spending on problematic IVDs offered as LDTs and unquantified reduction in costs from lawsuits. We quantify costs to affected laboratories for complying with statutory and regulatory requirements, as described in the phaseout policy. Additional costs include costs to FDA, which we include in our estimates. We estimate that the annualized benefits over 20 years range from $0.99 billion to $11.1 billion at a seven percent discount rate, with a primary estimate of $3.51 billion, and from $1.24 billion to $13.62 billion at a three percent discount rate, with a primary estimate of $4.34 billion. The annualized costs range from $566 million to $3.56 billion at a seven percent discount rate, with a primary estimate of $1.29 billion, and from $603 million to $3.79 billion at a three percent discount rate, with a primary estimate of $1.37 billion.

[1] See discussion of "problematic IVDs" in section I.B below.
[2] See discussion of "IVDs offered as LDTs" in section V.A.1 of the preamble to the final rule and section II.D below.

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the final 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 final rule is a significant regulatory action under Executive Order 12866 Section 3(f)(1).

Because this rule is likely to result in an annual effect on the economy of $100 million or more or meets other criteria specified in the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act, OIRA has determined that this rule falls within the scope of 5 U.S.C. 804(2).

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because most facilities that will be affected by this rule are defined as small businesses and the final rule is likely to impose a

substantial burden on the affected small entities, we find that the rule will have a significant economic impact on a substantial number of small entities.

We prepared an analysis consistent with the Unfunded Mandates Reform Act of 1995 (section 202(a)), which requires to the preparation of a written statement that includes estimates of anticipated impacts before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $177 million, using the most current (2022) Implicit Price Deflator for the Gross Domestic Product. This final rule will result in an expenditure in at least one year that meets or exceeds this amount.

B. Overview of Benefits, Costs, and Transfers

This final rule amends 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 V of the preamble to the final rule, FDA is phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs.

We anticipate that the benefits of phasing out FDA's general enforcement discretion approach for LDTs includes a reduction in healthcare costs associated with unsafe or ineffective IVDs offered as LDTs (generally referred to in this document as "problematic IVDs"), including IVDs offered as LDTs that are promoted with false or misleading claims, and from therapeutic decisions based on unreliable results of those tests. Quantified benefits are the annualized sum of both health and non-health benefits. Unquantified benefits include, among others, possible

reduction in costs from lawsuits. We discuss the benefits of phasing out of FDA's general enforcement discretion approach for IVDs offered as LDTs in section II.E.

This phaseout policy will result in compliance costs for laboratories that are ensuring their IVDs offered as LDTs are compliant with statutory and regulatory requirements, as described in section V of the preamble. We discuss the costs of the phaseout policy in section II.F. These costs overlap somewhat with effects associated with this phaseout policy in the form of user fees, including annual registration fees, fees for premarket applications/submissions, and annual fees for periodic reporting concerning PMA-approved devices, which are paid from laboratories to FDA. These fees are paid by laboratories but are revenue for FDA; the approach to estimating fee effects is distinct from the approaches for either benefits or costs, so they will be presented as transfers. We discuss transfers in section II.H.

Table 1 summarizes the annualized benefits, costs, and transfers of the phaseout policy. At a seven percent discount rate, 20-year annualized benefits range from about $0.99 billion to $11.1 billion, with a primary estimate of $3.51 billion per year. At a three percent discount rate, 20-year annualized benefits range from $1.24 billion to $13.62 billion, with a primary estimate of $4.34 billion per year. At a seven percent discount rate, 20-year annualized costs range from about $566 million to $3.56 billion, with a primary estimate of $1.29 billion per year. At a three percent discount rate, annualized costs range from about $603 million to $3.79 billion, with a primary estimate of $1.37 billion per year. At a seven percent discount rate, 20-year annualized transfers range from $20 million to $81 million, with a primary estimate of $41 million per year. At a three percent discount rate, 20-year annualized transfers range from $29 million to $115 million, with a primary estimate of $58 million per year. These estimates do not include anticipated offsets from user fees. At a seven percent discount rate, 20-year annualized costs

to FDA range from $61 million to $243 million, with a primary estimate of $121 million per year. At a three percent discount rate, 20-year annualized costs to FDA range from $65 million to $259 million, with a primary estimate of $129 million per year. Factoring in offsets from user fees at current levels, estimated costs to FDA are reduced to $40 million to $162 million at a seven percent discount rate, with a primary estimate of $81 million, and to $36 million to $144 million at a three percent discount rate, with a primary estimate of $72 million, covering approximately 30 to 40 percent of the estimated costs to FDA.

Table 1. Summary of Benefits, Costs and Transfers (millions of 2022 U.S. dollars)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)	$3,509	$988	$11,096	2022	7%	20 years	Major sources of benefits will be the avoidance of harms to patients from use of problematic IVDs offered as LDTs and the avoidance of spending on such IVDs.
		$4,341	$1,244	$13,619	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized ($m/year)	$1,287	$566	$3,559	2022	7%	20 years	A portion of foreign costs will be passed on to domestic consumers. We estimate that up to $147 million in annualized costs (7%, 20 years) to foreign facilities could be passed on to
		$1,372	$603	$3,789	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
								domestic consumers.
Transfers	Federal Annualized Monetized ($m/year)	$41	$20	$81	2022	7%	20 years	The main portion of transfers will be user fees for premarket submissions.
		$58	$29	$115	2022	3%	20 years	
		From: Device Industry			To: FDA			
	Other Annualized Monetized ($m/year)					7%		
						3%		
		From:			To:			
Effects	State, Local, or Tribal Government: No significant effects Small Business: The phaseout policy will have a significant economic impact on a substantial number of small laboratories that manufacture IVDs offered as LDTs. Wages: N/A Growth: N/A							

C. Comments on the Preliminary Economic Analysis of Impacts and Our Responses

On October 3, 2023, FDA published the proposed rule Medical Devices: Laboratory Developed Tests (88 FR 68006). Accompanying the proposed rule was a comprehensive preliminary regulatory impact analysis (hereinafter referred to as the preliminary analysis or PRIA) on which we requested public comments (Ref. [1]). We received many comments and have organized these comments and our responses by topic in the paragraphs below. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value, importance, or the order in which it was received.

1. Comments (Number of Laboratories)

Comments suggested using data from the CMS Laboratory Registry which provides information on the number of laboratories in the United States and their accreditation status to estimate the number of laboratories affected by the rule.

Response: As mentioned in the PRIA, we acknowledge that we do not know the exact number of laboratories that will be affected by this rule. After reviewing comments, FDA revised the number of affected laboratories from 12,000 to 11,808 using data from the CMS Laboratory Registry. We still use information about laboratories in New York State (NYS) to estimate the percent of CLIA-certified laboratories that both comply with high complexity requirements and make IVDs offered as LDTs, assuming that NYS is representative of the U.S. laboratory community. We explain our revised estimate in greater detail in section II.D.1 and appendix A of this analysis.

2. Comments (Number of IVDs Offered as LDTs)

Some comments claimed FDA overestimated the number of IVDs offered as LDTs on the market while others claimed FDA underestimated this number. One comment stated that there are 160,000 IVDs offered as LDTs in the United States from 12,000 laboratories (or 13 IVDs offered as LDTs per laboratory). Other comments provided estimates of the number of IVDs offered as LDTs ranging from 92 to 310 IVDs offered as LDTs per laboratory.

Response: As mentioned in the preliminary analysis (section II.D.1), we acknowledge that some large reference laboratories may make a large number of new IVDs offered as LDTs per year, whereas smaller laboratories may focus on fewer IVDs overall and may not introduce many or any new IVDs each year. Using the additional estimates on the number of IVDs offered as LDTs received from comments, the weighted average estimate of the affected tests is calculated to be approximately 69 IVDs offered as LDTs per affected entity, which is close to

our original estimate of 67 IVDs offered as LDTs per affected entity[3]. We have not revised our estimate based on these data because the estimate did not change significantly.

However, we adjusted our estimate to reflect the enforcement discretion policies in the final phaseout policy as well as the Agency's intention to initiate the reclassification process for most IVDs that are currently class III (high risk) into class II (moderate risk).[4] FDA will also continue taking a risk-based approach in the initial classification of individual IVDs to determine the appropriate level of regulatory controls and whether a new test may be classified into class II through De Novo classification (and special controls established), rather than being class III and subject to the PMA pathway. Based on its experience, the Agency believes that special controls could be developed, along with general controls, that could provide a reasonable assurance of safety and effectiveness for most future companion diagnostic and infectious disease IVDs. As such they would be regulated as class II devices. As a result of this adjustment, and prior to additional adjustments to address enforcement policies, the estimated numbers of PMAs and PMA supplements submissions are lower while the estimated numbers of 510(k)s and De Novo submissions are higher after potential reclassification (see Table A.5). As the final phaseout policy includes an enforcement discretion policy with regards to QS requirements (except for requirements under 21 CFR part 820, subpart M (Records)) and premarket review requirements for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as

[3] The new estimate of 69 IVDs offered as LDTs per affected entity was derived using comments and the initial PRIA estimate of 67. Specifically, we weighted together a maximum estimate of 310, a high estimate of 192, a middle estimate of 67, a low estimate of 13, and a minimum estimate of 1.

[4] FDA -CDRH Announces Intent to Initiate the Reclassification Process for Most High Risk IVDs. https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-announces-intent-initiate-reclassification-process-most-high-risk-ivds. As discussed in the preamble to the final rule, FDA notes that the reclassification process will include opportunities for public comment and FDA aims to complete the process before stage 4 of the phaseout policy.

described in the preamble, we expect that fewer IVDs offered as LDTs will be affected by stages 3 through 5 of the phaseout policy than we estimated in our preliminary analysis. In addition, FDA has revised the phaseout policy to include several other enforcement discretion policies for certain other types of IVDs (see section V.B of the preamble) and we have revised our estimates accordingly. Our updated estimates are addressed in sections II.F.3 and II.F.4 of this document.

3. Comments (Percent of IVDs That Are Offered as LDTs)

As discussed in section VI.C of the preamble, some comments claimed FDA overestimated the number of IVDs offered as LDTs on the market. Relatedly, comments suggested that the percent of test order volume for IVDs offered as LDTs is lower than 50%. One comment claimed that FDA's estimate of the number of IVDs offered as LDTs was more than "10 times what researchers found in a peer-reviewed study published in the American Journal of Clinical Pathology of actual clinical test orders at University of Utah Health: 3.9%" (see Ref. [3]). Another comment stated that only 6% of tests performed in their laboratory are offered as LDTs.

Other comments suggested that FDA underestimated the number of IVDs offered as LDTs on the market. Among these, a comment noted that their laboratory, itself part of an academic medical center, offers 123 LDTs out of 124 tests, a percentage higher than 99%. Another comment stated that more than 99% of their tests are LDTs, and further clarified that these tests comprised an even higher percent of their test volume.

Response: Based on public comments, the percent of IVDs offered as LDTs and the percent of test order volume comprised by such appear to vary widely across settings. Using test orders from a U.S. academic hospital system, Rychert et al. (2023) estimate that IVDs offered as LDTs are 3.9% of test order volume and 45% of distinct tests (Ref. [2]). Specifically for

estimating the percent of patients who are tested with IVDs offered as LDTs, we thus consider a range from 3.9% to 45%, with a primary estimate of 10%. This reflects the assumption that, while we take 45% as a reasonable estimate of the percent of IVDs that are offered as LDTs, we consider the percent of patients tested with those IVDs offered as LDTs to be closer to the referenced 3.9%, and, using professional judgement, selected 10% as our primary estimate, rather than using 3.9% directly, to reflect uncertainty given that the 3.9% was based on information for one single laboratory. Compared to the estimate of 50% used in the preliminary analysis, the revised estimate of 10%, if holding all else equal, reduces estimated benefits by a factor of five. With respect to the analysis in section II.E.2, this reflects that order volume likely better represents distinct patients.

4. Comments (Attribution of Diagnostic Error to Analytic Phase of Laboratory Tests)

Comments suggested that the percent of diagnostic errors attributable to faulty diagnostic test results is likely lower than 50%, the estimate we used in the preliminary analysis. A comment suggested instead, based on published literature, a range of 1-4%, with a central estimate of 2.5% (Refs. [3], [4], [5], [6], [7], [8], [9], [10]).

Response: Our final analysis uses an updated methodology which no longer directly estimates this parameter. However, our range of estimates of the number of diagnostic errors attributable to faulty tests and resulting in harm is consistent with much rarer attribution of diagnostic errors to tests. This analysis estimates in total about 53,000 annual preventable harms attributable to diagnostic tests (the sums of the primary estimates of avoidable harms across Table 5, Table 11, and Table 14). Singh et al. (2014) estimate that approximately 12 million U.S. adult patients experience diagnostic errors in outpatient care every year (Ref. [11]). Our primary estimate thus represents about half a percent of this total. As our estimate of preventable harms

attributable to diagnostic tests would represent a still lower percentage of all diagnostic errors (including those occurring in settings other than outpatient care), we do not consider this estimate inconsistent with attribution rates suggested in public comment.

5. Comments (Percent of IVDs Offered as LDTs that are Problematic)

Comments stated that the percent of IVDs offered as LDTs that are problematic is likely much lower than 47%, the estimate we used in the preliminary analysis. Comments also suggested that it is inappropriate to extrapolate this parameter from as narrow a sample as cited in the preliminary analysis.

Response: We agree that a broader basis for estimating this parameter is appropriate and have revised the relevant analysis accordingly, as described in detail in section II.E.1.a "Cancer: Mortality Risk." Using statistics from the NYS Department of Health Clinical Laboratory Evaluation Program (CLEP) (Ref. [12]) and FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests, [5] we consider a range of scenarios in which 22%, 38%, and 54% of IVDs offered as LDTs without FDA oversight would be a problematic IVD. This was extrapolated to estimate that 22%, 38%, and 54% of patients tested with IVDs offered as LDTs would be tested with problematic IVDs. Compared to the estimate of 47% used in the preliminary analysis, the revised primary estimate of 38%, if holding all else equal, reduces estimated benefits by approximately one fifth.

6. Comment (IVDs Offered as LDTs Perform Better Than FDA-Authorized[6] Tests)

[5] 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.

[6] For purposes of this analysis, "FDA-authorized" refers to FDA permitting the marketing of a device via the premarket approval, 510(k), De Novo classification, BLA, or HDE pathway and to devices that are exempt from premarket notification. This term does not include devices authorized for emergency use under section 564 of the FD&C Act.

As further detailed in section VI.C.4 of the preamble, some comments pointed out omission of multiple publications claiming comparable or better performance of IVDs offered as LDTs compared to "FDA IVDs." Some comments suggested that patients would lose access to IVDs offered as LDTs that perform well, even some IVDs offered as LDTs that may perform better than FDA-authorized IVDs. Comments also suggested adjusting downwards our estimates of benefits from avoiding preventable misdiagnosis-related harms by subtracting harms from baseline problems of FDA-authorized tests.

Response: We do not agree that IVDs offered as LDTs generally perform comparably to or better than FDA-authorized tests. Thus, we do not agree that this analysis should reflect such a situation. Concerning the scientific merits of the claims in these comments, please refer to FDA's responses in section VI.C.4 of the preamble, "Evidence of the Need for Greater FDA Oversight." In particular, we discuss publications purported to compare the performance of IVDs offered as LDTs and FDA-authorized tests in our response to Comment 34.

With respect to estimating the difference in reliability between problematic IVDs offered as LDTs, specifically, and FDA-authorized competitor tests, we lack systematic data on the exact issues with all problematic IVDs offered as LDTs and their particular uses in the process of diagnosis. As described in section II.E.1.a "Cancer: Mortality Risk," we consider a range of rates at which avoidable diagnostic error might result from usage of problematic IVDs offered as LDTs that would not occur using an FDA-authorized test.

7. Comments (Effectiveness of FDA Review in Assuring Reliability of Diagnostic Tests)

Citing examples of FDA-authorized tests with alleged issues affecting reliability, comments suggested that our analysis of the proposed phaseout policy overestimated the

effectiveness of FDA review in assuring the reliability of diagnostic tests and reducing the use of problematic IVDs offered as LDTs.

Response: Unlike in our preliminary analysis, as explained in section II.E.1.a, we now use statistics from the NYS CLEP to inform our estimates of avoidable problematic IVDs offered as LDTs. We believe this is a relevant extrapolation to expected detection of reliability issues through FDA oversight.

8. Comment (Diagnostic Tests Only a Part of Diagnosis)

One comment expressed concern that FDA does not consider that the risks of IVDs offered as LDTs, including erroneous results, "is mitigated by the fact that they are part of a multi-faceted medical assessment and are rarely used in isolation for clinical decision-making."

Response: Due to uncertainty about the rate at which erroneous test results lead to erroneous treatment decisions, this analysis considers that inaccurate results might be identified during follow-up or other parts of the process of diagnosis before leading to harm from diagnostic error. As described in section II.E.1.a "Cancer: Mortality Risk," we consider a range of rates at which avoidable errors might result from usage of problematic IVDs offered as LDTs that would not occur using an FDA-authorized test. However, although for the purpose of this analysis we consider a wide range for these rates, FDA expects that erroneous test results often result in erroneous treatment decisions. As discussed in the response to Comment 6 in the preamble, FDA does not consider all clinicians to be aware of the limitations of tests. FDA routinely consults with healthcare providers and has encountered many who do not understand the limitations of tests and do not consider that a test result provided by a test may be incorrect. For additional discussion of this comment please see our response to Comment 6 in the preamble.

9. Comments (StatinCheck Problem)

Comments requested an explanation of why we included, in the preliminary analysis, the StatinCheck test for KIF6 genotype as an example of a problematic test.

Response: This test was marketed as a way to predict the risk of heart disease and determine a patient's response to statin drugs, based on the belief that patients with the Trp719Arg polymorphism of the KIF6 protein had an elevated risk of cardiovascular disease (CVD) events and would have a greater reduction in CVD events when on statin therapy than patients without this polymorphism. However, the results from studies of the association between the polymorphism, CVD risk, and statin response were conflicting, and multiple scientific publications reported no association between the polymorphism and elevated CVD risk or statin response (Refs. [13] [14]). Accordingly, the totality of scientific evidence does not support that there is a clinically valid relationship between the polymorphism, elevated CVD risk, and statin response. In 2011, FDA informed the manufacturer that its submission for premarket approval of this test was not approvable stating that the evidence submitted was insufficient to support the test's safety and effectiveness in determining risk of heart disease or in predicting statin response. As described in FDA's 2015 report, additional problems included that the test was incorrectly validated and marketed for unproven uses. Inaccurate assessment of patient risk or likelihood of responding to statin therapy could lead to overtreatment, with an associated risk of adverse events, as well as undertreatment, with the risk of failing to prevent CVD events and death.

10. Comments (Non-Invasive Prenatal Screening Tests Require Follow-Up)

As detailed in section VI.C of the preamble, FDA received comments regarding FDA's use of a New York Times article on NIPS as evidence of a problem (Ref. [15]). Specifically,

comments stated that the article conflated screening with diagnostic testing. They asserted that the article mischaracterized false positive results as test failures and that the "problem" with this category of tests is with "the lack of understanding of its purpose and limitations by the providers and patients who were interviewed by the reporters."

Response: FDA agrees that NIPS tests, which may tell people the risk of their fetus having certain genetic abnormalities, are different from diagnostic tests used to more definitively confirm or rule out a suspected genetic abnormality. FDA agrees with comments that NIPS tests should not be used to confirm or rule out a suspected abnormality. While higher false positive rates are often more acceptable for screening tests than tests used for making a diagnosis, appropriate false positive rates for any particular test needs to be considered in the context of a full benefit-risk evaluation for that particular test. After publication of the New York Times article, FDA issued a safety communication to explain the limitations of NIPS tests and provide information to educate both patients and health care providers to help reduce the inappropriate use of NIPS tests.[7] Increased oversight of NIPS tests, including labeling requirements, can help ensure such tests are appropriately labeled with transparent information regarding performance, clear instructions, and appropriate limitations. Including the example of NIPS in this final analysis reflects our expectation that phasing out the enforcement discretion approach will ensure tests are appropriately safe and effective for their intended use. We also expect truthful, accurate, and clear statements about test use and performance to prevent patient and provider misunderstanding.

11. Comments (Innovation)

[7] Available at: https://www.fda.gov/medical-devices/safety-communications/genetic-non-invasive-prenatal-screening-tests-may-have-false-results-fda-safety-communication

FDA received comments stating that the phaseout policy will have a negative impact on innovation in the testing space, as laboratories working to come into compliance would be either unable or unwilling to engage in innovative test development. Some comments stated that the regulatory constraints associated with the phaseout policy would cause laboratory manufacturers to develop fewer tests, hindering the timely development and deployment of cutting-edge therapies and diagnostic tools and ultimately harming patients. A comment from the Association of Pathology Chairs (APC) stated that it had conducted a survey of its members and found that 92% (36/39) of APC survey respondents reported that there will be less innovation to create and offer new tests to improve patient care due to the FDA's proposed phaseout policy. Comments claimed that the high cost of premarket review may lead to less investment in innovation, fewer new tests developed, and longer timelines for new innovation to reach the market, and that some tests may not have market viability, given the premarket review costs.

Several comments noted that laboratories must be able to modify existing tests quickly to diagnose new conditions and monitor the impact of new therapies. Some comments stated that stifling modifications of currently marketed IVDs offered as LDTs would force pathologists and other healthcare providers to use older, less optimal tests, and noted that many patients do not have the time to wait for diagnostic development and rely on laboratories to be nimble and adapt to changing diagnostic criteria. One comment asserted that predetermined change control plans (PCCPs) would not help alleviate delays in modifications because only manufacturers can submit PCCPs, and thus laboratories seeking to modify an IVD for local conditions would need to undertake premarket review to do so. One other comment expressed concern that the phaseout policy would lead to slowed growth in the number of LDTs manufactured by laboratories because the phaseout policy would "prohibit" labs from sharing their discoveries about such

IVDs with each other. This comment claimed that the sharing of this knowledge in the past had caused quicker development and modification of IVDs offered as LDTs.

Response: As explained in the preamble to the final rule, the phaseout policy is intended to better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs -- while also accounting for other important public health considerations such as patient access and reliance.

Premarket review is not required for all IVDs offered as LDTs. FDA premarket review is required only for certain tests (generally those in class II or class III). FDA estimates that approximately 50 percent of IVDs offered as LDTs will not require premarket review. A manufacturer's modifications to tests that have already been cleared, approved, or granted marketing authorization by FDA only require FDA review in certain circumstances (see 21 CFR 814.39; 21 CFR 807.81(a)(3)). Even when premarket review is required for an IVD offered as an LDT, FDA does not agree that such review necessarily impairs innovation. In fact, sponsors have sought and obtained FDA authorization for innovative IVDs offered as LDTs. FDA also has several programs that may facilitate the development and premarket authorization of innovative tests.

Moreover, better assuring the safety and effectiveness of IVDs offered as LDTs will foster innovation. By applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, FDA's phaseout policy will remove a disincentive for non-laboratory manufacturers to develop novel tests. We anticipate that phasing out the general enforcement discretion approach for LDTs will spur innovation for IVDs for which there is a reasonable assurance of safety and effectiveness.

12. Comments (Impact on Prices)

Several comments stated that ending the general enforcement discretion approach for LDTs would lead to higher prices for clinical tests due to the costs of complying with applicable FDA requirements. Some comments further stated that the cost of complying with applicable requirements would result in the closure of many laboratories or the outsourcing of certain laboratory tests, which in turn will increase the costs of tests due to decreased test availability, decreased market competition, increased handling costs (e.g., costs associated with shipping samples to a centralized laboratory), or supply chain contractions. One comment expressed skepticism regarding FDA's statement that any losses may be offset by the market entry of IVDs from other manufacturers. FDA also received a comment which argued that increased prices for clinical tests will disincentivize people from seeking preventive care until they suffer an emergency, which will increase costs for the overall healthcare system. Collectively, these comments suggested that laboratories will pass increased costs to their customers, which some comments noted could result in higher insurance premiums. However, one comment stated that insurance companies will be more likely to cover tests (because they will have FDA authorization), which may allow for greater access to more affordable testing. One comment noted that it is inaccurate to assume that IVDs offered as LDTs are always cheaper.

Response: FDA recognizes that some laboratories may pass the costs of compliance with applicable requirements, including the specific examples listed in the comments, to their customers by raising prices for IVDs offered as LDTs. We also recognize that if many laboratories reduce operations or exit the market, production may be concentrated in a few large laboratories, which may cause prices for certain IVDs offered as LDTs to increase. However, we note that in the final phaseout policy, which will also affect small laboratories and Academic

Medical Centers (AMCs), there may be less laboratories that scale back operations or exit the market relative to the estimates in our preliminary analysis.

FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under 21 CFR 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as described in the preamble. FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP.[8] FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under 21 CFR part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. These enforcement discretion policies may significantly reduce the costs of compliance under the final phaseout policy, thus reducing the number of laboratories that scale back operations or exit the market. In addition, we anticipate that FDA oversight could help to support coverage and reimbursement determinations for IVDs offered as LDTs, which we anticipate will make certain IVDs offered as LDTs for which there is a reasonable assurance of safety and effectiveness more affordable for patients. As a result, FDA does not agree that patients will necessarily be disincentivized from seeking preventive care resulting in increased costs to the healthcare system as a result of the phaseout policy.

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

In addition, phasing out the general enforcement discretion approach for LDTs will help to reduce other healthcare costs. Greater oversight by FDA will help to address the hidden costs associated with unsafe or ineffective IVDs (including IVDs promoted with false or misleading claims), such as costs incurred from inappropriate treatments, additional or repeat testing, unnecessary consultations with providers, or additional treatment that became necessary due to the progression or worsening of a disease or condition following misdiagnosis. While certain costs may be passed on to individuals and insurers, we expect some of these costs will be offset by the associated benefits.

13. Comments (Increased Labor Cost/Strain)

FDA received comments expressing concern that phasing out the general enforcement discretion approach for LDTs would require laboratories to have increased resources to afford the necessary staffing and other costs related to test development and regulatory submissions and emphasized the thin financial margins with which small laboratories operate. Some comments stated that the impact on small laboratories will result in a loss of expertise and infrastructure. In addition, comments noted that such centralization of IVDs offered as LDTs at large laboratories may negatively impact medical education and training in pathology, resulting in labor shortages. Some comments also suggested that workforce shortages will make it difficult for FDA to recruit and retain adequate numbers of qualified reviewers trained in laboratory diagnostics needed to review premarket submissions, which could potentially lead to delays in FDA's premarket review process and patient access to tests.

Response: FDA appreciates the concerns regarding financial and administrative challenges for smaller laboratories. FDA anticipates that the enforcement discretion policies discussed in section V.B of the preamble will sufficiently address these concerns and help to

avoid undue disruption to the testing market. For example, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under 21 CFR part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3 of the preamble, which means laboratories would generally not need to dedicate staff or resources to handle premarket submissions for their existing IVDs offered as LDTs.

It is possible that some laboratories could need additional staff to handle premarket submissions for new IVDs and we account for this in our analysis. However, we expect that FDA's enforcement discretion policy for currently marketed IVDs offered as LDTs will greatly reduce the volume of submissions from the estimate in our preliminary analysis, thereby avoiding any sudden or drastic increase in labor costs.

14. Comments (Underestimation of Costs)

Several comments stated that costs are substantially underestimated. Some comments elaborated on specific types of costs, especially costs of premarket review. In support of their arguments some comments provided cost estimates for premarket review per entity while others provided cost ranges per test including analytical and clinical validation costs. Another comment focused on how the cost of modifying an SOP could be more burdensome than estimated as it would have to occur for every IVD offered as an LDT. Some comments also conveyed concern that the cost of a possible increase in LDT outsourcing due to FDA's phaseout of enforcement discretion were not considered. Several comments stated that the costs of hiring new labor to comply with the phaseout of enforcement discretion was underestimated.

Response: FDA has revised the phaseout policy to include several enforcement discretion policies for certain types of IVDs as described in section V.B of the preamble. For example, FDA intends to exercise enforcement discretion for premarket review and QS requirements (except for requirements under 21 CFR 820, subpart M (Records)) for IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule and that are not modified, or that are modified as described in the preamble. As such, we do not expect that premarket submissions will be submitted for most currently marketed IVDs offered as LDTs in the immediate future, thus reducing the costs of the phaseout policy including the costs of premarket submission and review. We have revised our estimates consistent with revisions to the phaseout policy as explained in section II.F of this analysis.

15. Comments (Outsourcing Costs and Costs of Switching to FDA-Authorized Tests)

Some comments stated that if FDA phases out the general enforcement discretion approach for LDTs, the commenters may decide to switch from an IVD offered as an LDT to an FDA-authorized test or to outsource their tests to other laboratories. Some comments provided information about the cost differential between an IVD offered as an LDT and an FDA-authorized test or from outsourcing certain tests. Some comments provided estimates on the number or percentage of tests that they would consider outsourcing or switching to an FDA-authorized test.

Response: FDA has revised the phaseout policy to include several enforcement discretion policies for certain types of IVDs as described in section V.B of the preamble. For example, FDA intends to exercise enforcement discretion for premarket review and QS requirements (except for requirements under 21 CFR 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final

rule and that are not modified, or that are modified as described in the preamble. As such, we generally do not expect laboratories with currently marketed IVDs offered as LDTs to switch from an IVD offered as an LDT to an FDA-authorized test or to outsource their tests to other laboratories. We agree, however, that some laboratories may pursue outsourcing their testing needs or switching to use of an FDA-authorized test rather than introducing a new test, that does not fall within an enforcement discretion policy in the phaseout policy. However, as we explain in section II.F.6. of this FRIA, the cost of switching to an FDA-authorized test when available, would cost less than the cost of submitting a premarket submission. A laboratory would likely switch to FDA-authorized tests or outsource their testing needs only if submitting a premarket submission was more costly than either of these alternatives. Either way, the decision would be a private decision made according to their business plan. To the extent that any number of laboratories switch to any number of FDA-authorized tests, their costs would be less than the costs of submitting a premarket submission.

16. Comment (FDA Would Not Have Sufficient Resources To Review IVDs Offered as LDTs)

Some comments expressed concerns that FDA would not have sufficient resources to conduct timely premarket review of IVDs offered as LDTs to meet the public health needs. Some of these comments questioned whether FDA would have adequate capacity to provide timely review of applications/submissions for IVDs offered as LDTs because many EUA requests were not reviewed due to resource limitations during the COVID-19 pandemic. At least one comment cited FDA's review of a particular EUA request for an LDT during the COVID-19 pandemic, in which FDA's review of the request did not conclude until after the subject LDT had been removed from the market, as proof that FDA does not have adequate resources to conduct

premarket review of IVDs offered as LDTs. Another comment referenced a supposed FDA delay in recognizing a particular consensus standard, based on FDA's "prolonged review."

Other comments referenced FDA's MDUFA IV performance report from FY2020 to 2022 (during the COVID-19 pandemic) and predicted that the increased volume of submissions from laboratory manufacturers that would result from the phaseout policy would affect FDA's overall ability to review premarket submission for all IVDs, meet its MDUFA performance goals, and conduct other essential work, including policy and post-market activities. Finally, some comments recommended that FDA modify the phaseout policy to prolong the period of time prior to phasing out the general enforcement discretion approach with respect to premarket review requirements, and/or continue to apply the general enforcement discretion approach with respect to premarket review requirements for certain LDTs, to reduce the FDA resource needs.

Response: FDA disagrees that the Agency will lack sufficient resources to conduct premarket review of IVDs offered as LDTs in a timely manner. First, FDA does not intend to phase out the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs until 3½ years after publication of the phaseout policy, and for moderate- and low-risk IVDs (that require premarket submissions), until 4 years after publication of the phaseout policy. This timeline aligns with the next reauthorization of MDUFA. This alignment will provide an opportunity for FDA and industry to negotiate regarding user fees and performance goals with the knowledge that laboratory manufacturers will be expected to comply with applicable premarket review requirements.

Second, FDA generally intends to exercise enforcement discretion with respect to certain requirements for certain tests as described in the final phaseout policy. These enforcement discretion policies are discussed further in section V.B of the preamble and collectively will

significantly reduce the number of premarket submissions for IVDs offered as LDTs, as compared to our preliminary estimates.

Third, FDA's device authorities require premarket review only for certain IVDs. FDA estimates that approximately 50 percent of IVDs currently under active oversight are low risk and do not require premarket review, and FDA assumes this estimate also applies to IVDs offered as LDTs (see section II.F.2.c of this analysis). However, there are uncertainties surrounding the estimate of total numbers of IVDs offered as LDTs on the market because FDA generally has not enforced the registration and listing requirements for LDTs under section 510 of the FD&C Act (21 U.S.C. 360), 21 CFR part 607, and 21 CFR part 807 (excluding subpart E). By 2 years after publication of this final rule, at stage 2 of the phaseout policy, FDA will obtain registration and listing information from laboratory manufacturers offering IVDs as LDTs. This information will help FDA assess and plan for the resources needed for premarket review of those IVDs before stages 4 and 5 of the phaseout policy.

Fourth, FDA is currently working to enhance its 510(k) Third Party Review Program to handle the review of low- and moderate-risk devices by recognized Third Party review organizations. This will free up Agency staff time to review more complex, innovative, high-risk devices. FDA estimates that half of the IVDs offered as LDTs for which a 510(k) will be submitted will be reviewed under the Third Party review program. FDA also recognizes that if CLIA accreditation organizations seek accreditation under FDA's Third Party review program, there may be certain efficiencies or other advantages, because the two programs are complementary, as described in response to Comment 7 of the preamble. FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP and to generally not enforce requirements for LDTs

manufactured and performed within the Veterans Health Administration (VHA) and the Department of Defense (DoD). See section II.G of this analysis.

Finally, FDA disagrees that decision timelines on EUA requests, in general, are a good indicator to predict FDA's timelines for review of premarket applications/submissions for IVDs offered as LDTs, and further disagrees that FDA's review of any one particular EUA request submitted for an LDT during the COVID-19 pandemic is indicative of how FDA will review premarket applications/submissions for IVDs offered as LDTs generally. As discussed in response to comment 275 in the preamble, FDA's authority to issue EUAs for LDTs is under a different statutory provision (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)) than traditional premarket reviews. Moreover, FDA is not required to review individual EUA requests submitted to FDA or review them on a specific timeline, or to authorize the emergency use of a medical product even if it meets the relevant criteria for an EUA, giving FDA flexibility to determine how to prioritize its efforts in emergencies to protect and promote public health. Second, during the COVID-19 pandemic, FDA received a large influx of submissions that had not been anticipated. In the context of the phaseout policy, FDA has estimated the number and type of premarket submissions we can expect in Stages 4 and 5, and annually thereafter, and can prepare for those submissions. See our responses to comments 37 and 275 in the preamble for additional discussion on this topic.

17. Comment (Small Entities)

As discussed in section VI.G of the preamble, FDA received comments expressing concern that phasing out the general enforcement discretion approach for LDTs will put financial and administrative pressure on small laboratories. These comments state that the phaseout of general enforcement discretion could result in laboratory closures and potential monopolies in

the testing space. Several comments stated that large laboratories will be able to monopolize LDT processing as they have the resources to afford the necessary staffing and other costs related to test development and regulatory submission. One comment discussed small laboratories within a medical system closing, stating that the removal of pathologists due to this kind of laboratory exit would decrease the quality of patient care.

Response: FDA appreciates the concerns regarding financial and administrative challenges for smaller laboratories. Specifically, FDA recognizes that smaller laboratories may face an increase in total cost such that they will exit the market and potentially cause increased testing market concentration. The extent in which smaller laboratories may be disproportionately impacted by the phaseout of the general enforcement discretion approach for LDTs, is dependent on the number of IVD's offered as LDTs per lab. FDA anticipates that the enforcement discretion policies discussed in the preamble of the final rule will moderate these concerns and help to avoid complete disruption to the test market. As noted in Appendix B – Table 8, the average costs per LDT are smallest for stages 1 through 3 of the phaseout policy representing 10% of costs and up to 59% of affected tests, whereas average costs per LDT for stages 4 and 5 represent 90% of costs affecting 3% of tests. The percentage of tests that may experience costs under stages 4 and 5 will increase as new laboratories and tests enter the market during and after stages 4 and 5, as they will fall within the enforcement discretion policy for currently marketed tests. However, they may still fall within the scope of other enforcement discretion policies described in the preamble to the final rule, including those for unmet needs and LDTs approved by NYS CLEP. However, in the event that a new lab does not fall within the scope of other enforcement discretion policies, costs under stages 4 and 5 could present as a potential barrier to entry in the LDT market for new laboratories. In Table B.7, total costs and

transfers for all stages of the phaseout policy are estimated to be on average anywhere between 2.5, 5.8 and 16 percent over receipts for all entities. We do not have the information about labs to determine how the average estimates are distributed among the firms (including new firms) according to their size categories. Also, costs would be higher for a lab that has several IVDs offered as LDTs but sells fewer unit tests whereas costs would be smaller for labs with only one IVD offered as LDTs selling a large number of unit tests. In the same manner, profit margins could be higher for labs with a smaller number of IVDs offered as LDTs but with high volume unit tests sold, compared to labs with a larger number of IVDs offered as LDTs but with low volume units tests sold. Depending on profit margins with respect to revenue, the costs of this rule may be prohibitive for some small labs, making it more likely that some small entities in this size category will exit the market, reduce operations, sell the business, be subject to acquisitions by larger firms or not enter the market. If profit margins were too small for many small firms considering the costs, it is possible that this rule will be too burdensome for some small entities.

While we do not have the data on profit margins to properly estimate the number of labs that would be adversely impacted by this rule, we estimate that small laboratories make fewer IVDs offered as LDTs than large firms. We estimate that small labs make up 92 percent of all labs, and that they also hold a 24 percent share of IVDs offered as LDTs. With the low number of IVDs offered as LDTs per small lab, it is more likely that the percent of costs over receipts per lab would be closer to our low average estimate 2.7 percent.

With the above referenced revisions to the phaseout policy, we do not expect significant disruptions to access to IVDs offered as LDTs, significant increases in test prices, or delays in diagnosis and treatment. However, the high cost of pre-market approval also makes innovation less likely to come from smaller labs.

18. Comment (Firm Exit and Market Concentration)

Some comments have claimed that certain laboratories, such as academic, small, public health, and specialty laboratories, will disproportionately exit the market relative to their counterparts. These comments claim that since these labs already have low revenues, any additional cost could be enough to cause market exit.

Other comments stated that by reducing the availability of IVDs offered as LDTs through market exit, the phaseout policy would lead to delays in testing, including by potentially increasing reliance on reference laboratories which may increase the time individuals obtained test results. Some comments expressed concern that the laboratories surviving general enforcement discretion phaseout would receive an influx of test orders and may not be able to handle the test volume, which may have an overall negative impact on the turnaround time for test results. Two comments have addressed the exit of academic labs as particularly concerning given their role in diagnosing and monitoring rare diseases. Further, many comments stated that a potential increase in firms exiting the market could increase unemployment among laboratory technicians and increase market concentration in the healthcare industry.

A few comments also addressed children's hospital laboratories as particularly likely to be negatively affected by the phaseout policy. These comments stated that because these hospitals rely largely on Medicaid payment, the laboratories in these hospitals may have small revenue levels and may reduce their IVD offerings, exit the market, or send samples to other laboratories for testing if the total cost increase for meeting applicable requirements that result from the phaseout policy is too high.

Response: FDA appreciates the comments on potential firm exit and market concentration as a result of the phaseout policy. Given that FDA intends to exercise enforcement

discretion and generally not enforce premarket review and QS requirements (except for requirements under 21 CFR 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule and that are not modified, or that are modified as described in the preamble, and for LDTs developed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system (as described in section V.B.3 of the preamble), we do not expect significant market concentration and firm exit to result from the phaseout policy. With the above referenced revisions to the phaseout policy, we also do not expect current disruption to access to IVDs offered as LDTs, significant increases in test prices, or delays in diagnosis and treatment.

D. Summary of Changes from the Proposed Rule

Compared to the preliminary economic analysis, this final analysis reflects revisions to the phaseout policy and to our analytical methodology. We include updates and revisions to our discussion of baseline conditions, estimated health and non-health benefits, costs, budgetary impacts, transfers, regulatory alternatives, and impacts to small entities as summarized below.

1. Changes to the Phaseout Policy

The final phaseout policy differs significantly from the proposed policy in that it includes the following additional enforcement discretion policies:

- FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of requirements under 21 CFR part 820, subpart M (Records), for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as described in section V.B.3 of the preamble.

- FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP;
- FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements, with the exception of requirements under 21 CFR part 820, subpart M (Records), for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system;
- FDA intends to exercise enforcement discretion and generally not enforce requirements for LDTs manufactured and performed within the Veterans Health Administration (VHA) or the Department of Defense (DoD); and
- FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of requirements under 21 CFR part 820, subpart M (Records), for non-molecular LDTs for rare red blood cell antigens where such tests are manufactured and run in transfusion services and immunohematology laboratories and where there is no alternative available to meet the patient's need for a compatible blood transfusion.

Where relevant, we adjust estimates in this final analysis in accordance with these changes to the phaseout policy. More details of IVDs within the scope of the phaseout policy are described in section V.A of the preamble.

2. Baseline Conditions

After reviewing comments, FDA revised the number of laboratories affected by the phaseout policy using data from the CMS Laboratory Registry as explained in appendix A.

Using the CMS data, the revised primary estimate of affected laboratories is 1,181, which is close to the estimate of 1,200 in the preliminary analysis.

3. Benefits

We have made several changes to our analysis of health benefits. While there are individual changes that increase as well as decrease estimated benefits, overall total estimated benefits have decreased due to incorporating new information and assumptions. However, while including data and information from public comments as well as additional research has lowered estimated annualized benefits from expected reductions in cancer mortality to about one fiftieth of the preliminary estimate, we now also use this information to quantify benefits that we previously discussed qualitatively or only addressed incompletely. In particular, we now include general, yearly estimates of mortality avoidable in cardiovascular disease and morbidity avoidable in infectious diseases.

In response to comments, and as described in section II.E.1.a of this analysis, we have revised our methods for estimating avoidable harms related to cancers. We have also applied revised methods in newly estimating avoidable harms related to cardiovascular and infectious diseases. Revisions concern both reference information and analytical assumptions.

We now source certain parameters addressed in public comments, such as the rate of usage of IVDs in cancer, cardiovascular diseases, and infectious diseases, from published literature and other data. Additionally, we now estimate the rate of usage of problematic IVDs offered as LDTs based on application review statistics from the NYS Department of Health Clinical Laboratory Evaluation Program (CLEP) (Ref. [12]) and FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests.[9]

[9] Memorandum to File from Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, RE:

We have also refined analytical assumptions. For example, although we did not assume in the preliminary analysis that 100% of uses of problematic IVDs offered as LDTs result in a harm from diagnostic error, we have refined our assumptions to avoid any implication that this is the case.

Due to our high degree of uncertainty about several of the parameters used to estimate health benefits, we now use Monte Carlo simulations to determine a plausible range for benefits pertaining to each disease category by allowing parameters to vary independently of each other. Not using such an approach would implicitly convey a strong and unrealistic assumption that all uncertain parameters share a joint probability distribution and are perfectly dependent (i.e., aligning all best- and worst-case scenarios across parameters).

With respect to non-health benefits, we have removed discussion and estimates made in section II.E.3 of the Preliminary Regulatory Impact Analysis (PRIA) (Ref. [1]) where we had previously requested supporting information in public comment and did not receive any. Additionally, we have edited discussion for clarity, in part to address certain public comments.

Finally, as described in sections II.E.1 and II.E.3, we adjust estimates of benefits to account for existing review by NYS CLEP and the enforcement discretion policy for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule.

4. Costs

We have made several changes to our cost analysis. We use updated data for wages, FDA costs, and MDUFA fees. We made the following revisions as a result of changes to the final phaseout policy: exclude currently marketed IVDs offered as LDTs that were first marketed prior

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.

to the date of issuance of the final rule from premarket review and QS (except for records) compliance costs; exclude LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system from premarket review and QS compliance costs (except for records); and exclude LDTs expected to be reviewed by NYS CLEP from premarket review compliance costs. We also consider that some of the IVDs currently classified in class III, requiring PMAs/PMA supplements, may be reclassified to Class II or Class I (described in Appendix A and section II.F.4).

We have revised our estimates of FDA review costs to adjust the FTE weight of PMA review costs, to include review costs of MDRs, IDEs, and Q-submissions, and to consider premarket submissions that will be reviewed by third party or NYS CLEP (see section II.G). We have also refined some estimates in the analysis based on data received in public comments.

5. Regulatory Alternatives

The section on regulatory alternatives in the final analysis retains only the first two regulatory options from the preliminary analysis. For the final analysis, we include as an additional alternative the phaseout policy as initially proposed. See section II.J.

II. Final 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 since 1976, FDA has exercised enforcement discretion such that it generally has not enforced applicable legal requirements with respect to most LDTs because they mostly:

- were manufactured in small volumes by local laboratories that served their local communities;
- were typically intended for use in diagnosing rare diseases or other uses to meet the needs of a local patient population or were generally similar to well-characterized, standard IVDs;
- tended to employ manual techniques (and did not use automation) and were performed by laboratory personnel with specialized expertise;
- 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, such as general purpose reagents or immunohistochemical stains marketed in compliance with FDA requirements.

This enforcement discretion approach for LDTs developed as a matter of general practice.

However, since 1976, the development and usage of LDTs have evolved considerably. LDTs are now more complex, sometimes including proprietary algorithms. 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. They are often performed 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. Some LDTs are manufactured by corporations that market the IVDs nationwide as they accept specimens from patients across the country and run their tests in very large volumes in a single laboratory.[10] In this regard, most LDTs today are similar to other IVDs that have not been under FDA's general enforcement discretion approach.

Clinical laboratory tests are foundational to healthcare. The Centers for Disease Control and Prevention (CDC) estimates that 70 percent of medical decisions are based on laboratory test results (Ref. [16]). IVDs offered as LDTs are a growing sector of that market (Ref. [17]). Given the role these tests play in modern healthcare, their safety and effectiveness significantly impact public health. 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 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.

B. Need for the Rule

As the growing number of IVDs offered as LDTs entering and currently on the market (some of which may be problematic IVDs) typically are not reviewed by FDA, patients might be at risk when their providers rely on certain IVDs offered as LDTs to guide their care. 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 costing the opportunity for life-saving treatment), and the spread of infectious diseases.

[10] See, e.g., Pew Research Center (Ref. [27]), Grand View Research (Ref. [17]), and Congressional Research Service (Ref. [73]). 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.

While laboratories that offer IVDs are regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA),[11] CLIA addresses laboratory operations and personnel qualifications and not the development of individual tests in a laboratory (see 42 U.S.C. 263a and 42 CFR part 493) (Ref. [18]). In particular, under CLIA, CMS does not:

- regulate laboratory test development;
- evaluate the performance of an IVD before the test is offered to patients and healthcare providers;
- assess clinical validity (i.e., the accuracy with which a test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient);
- regulate certain manufacturing activities, such as design controls and acceptance activities;
- provide human subject protections for patients who participate in IVD clinical research trials; or
- require adverse event reporting.

By contrast, the device provisions of the FD&C Act and FDA's regulations focus on the safety and effectiveness of the IVDs themselves. Given this distinction, CMS has described the FDA and CMS "regulatory schemes" as "different in focus, scope and purpose, but […] intended to be complementary (Ref. [19])."

[11] 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.

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.[12] While FDA had received requests for EUAs for tests from laboratories in prior emergencies, the scope of the COVID-19 pandemic resulted in an unusually high number of EUA requests from laboratories, revealing the approach that many laboratories might 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 or validation problems, or both. The tests involved relatively well-understood techniques and the laboratories represented these tests as appropriately validated.[13] To the extent that this sample represents larger trends in the performance of IVDs offered as LDTs, it indicates 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 (Ref. [20]). 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. [21]).

[12] These requests resulted in review because FDA did not generally exercise enforcement discretion for LDTs intended for emergencies/potential emergencies/material threats declared under section 564 of the FD&C Act.
[13] 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

News and other outlets have also reported on problems with IVDs offered as LDTs, including the New York Times (Ref. [15]), and lawsuits have been filed relating to pharmacogenomic and non-invasive prenatal screening IVDs offered as LDTs.[14]

FDA has received complaints, allegations, and reports regarding IVDs offered as LDTs for oncology, non-invasive prenatal screening, and infectious diseases, among others. Some laboratories have submitted data to FDA in premarket submissions for their IVDs offered as LDTs, and we have observed that many failed to perform the appropriate studies to show that their IVDs work. Some have submitted data from appropriate studies, but the data show that their IVDs do not work. In both cases, laboratories have continued to offer such IVDs for clinical use.

While it is theoretically possible that, over time, patients and providers might learn the differences between competing tests and eventually stop purchasing ineffective tests regardless of regulation, that has not universally happened to date, even though the disparity between IVDs offered as LDTs and IVDs meeting applicable FDA requirements has been ongoing for decades. Further, we know from experience that providers and patients often do not even know what test was performed by a laboratory and, without widespread awareness of the different types of tests and regulatory disparities, we expect that learning of this kind would be rare, if it ever occurred, and would be complicated by the rapidly changing market, with new tests introduced regularly. Moreover, during the time that it would take for any such learning to occur, providers and patients may be using inaccurate or unreliable tests, with all the associated risks to patients. As for patients, ability to internalize the relevant risks may be precluded by not knowing the

[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, *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).

difference between IVDs offered as LDTs and FDA-authorized IVDs or having meaningful informed choice in the purchase decision.

Furthermore, FDA is aware that some entities have adopted business practices that claim a connection to laboratories in order to offer 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. [22] and [23]). For example, FDA notes:

- manufacturers offering unauthorized home specimen collection kits manufactured outside of the laboratory for use with LDTs;
- software developers offering software for high-risk clinical use with LDTs through laboratory partnerships;
- laboratories offering test kits previously alleged to be "research use only" test kits;
- manufacturers of home specimen collection kits with consumer facing platforms providing the ordering and resulting interface while outsourcing testing to unspecified laboratories; and
- contract manufacturers claiming to be consulting firms that design and validate tests for customer laboratories to perform.

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. IVD manufacturers who are not laboratories might 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 (Refs. [24] and [25]). We anticipate that applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, and phasing out the general enforcement discretion approach for LDTs, will better assure the safety and effectiveness of IVDs offered as LDTs, and remove a disincentive for non-laboratory manufacturers to develop novel tests, thereby spurring innovation and access to IVDs for which there is a reasonable assurance of safety and effectiveness. Without the phaseout policy, and without better assurance of the safety and effectiveness of IVDs offered as LDTs, limited investment and healthcare funding may be expended on improving problematic IVDs.

The enforcement discretion approach for LDTs has created distortions in the diagnostics market.[15] These distortions not only complicate understanding the IVDs used in clinical practice, impeding FDA's ability to ensure the safety and effectiveness of IVDs, but might also disincentivize high standards of quality control and accuracy and thus entail social costs.[16]

In order to curtail offering of problematic tests, FDA is phasing out the general enforcement discretion for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs.

In addition, to ensure clarity and understanding by industry and the public, FDA is amending its regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory.

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[15] Market distortions may be associated with events, decisions, or interventions taken by governments, companies, or other agents that influence the market in ways that undermine optimal allocation as modeled under the First Fundamental Theorem of Welfare Economics. Related concepts include market failure, government failure or behavioral bias (Ref. [71]).

[16] Social costs are costs incurred from the viewpoint of society (including external costs), beyond just stakeholders (private costs). When laboratories avoid paying for external costs arising from their actions (such as costs to manufacture 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, along with private costs, affect whether society is operating at a socially efficient rate of output (Ref. [72]).

C. Purpose of the Rule

The purpose of the rule, which amends 21 CFR part 809, is 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 will reflect the fact that the device definition in the FD&C Act does not differentiate between entities manufacturing the device, and will provide further clarity to stakeholders affected by the accompanying changes to FDA's general enforcement discretion approach for LDTs.

In addition, as discussed in section V of the preamble to the rule, FDA is also phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs (i.e., FDA's expectations for compliance will generally be the same). This phaseout policy includes limited enforcement discretion policies for specific categories of IVDs manufactured by a laboratory, including currently marketed IVDs offered as LDTs and LDTs for unmet needs. This phaseout policy is intended to better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance. In addition, by applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, FDA will give stakeholders more stability, clarity, and confidence, and facilitate investment in the development of innovative IVDs.

For additional discussion, see section III.B of the preamble.

D. Baseline Conditions

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

FDA's general enforcement discretion approach for LDTs) against which to measure the costs and benefits of the phaseout policy and the regulatory alternatives discussed in section II.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. [26]).[17] However, as discussed in the preamble and section II.F "Costs," the phaseout policy will affect not only LDTs, but IVDs manufactured and offered as LDTs, 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.[18, 19] Throughout this document, we refer to these IVDs as "IVDs offered as LDTs."

As described in section V of the preamble, FDA is including various enforcement discretion policies with regard to all applicable requirements for 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 (discussed in section III of the preamble):

- use of manual techniques (without automation) performed by laboratory personnel with specialized expertise;
- use of components legally marketed for clinical use; and

[17] This includes laboratories operating under State licensure programs deemed exempt from CLIA.
[18] This discussion concerns only laboratories that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing (including laboratories operating under State licensure programs deemed exempt from CLIA), as 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 preamble to the final rule, tests offered by such laboratories have never fallen within FDA's general enforcement discretion approach.
[19] 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 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 (Ref. [18]).

- design, manufacture, and use within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing.

FDA will also continue the general enforcement discretion approach for Human Leukocyte Antigen (HLA) tests that are designed, manufactured and used in a single CLIA-certified, high-complexity histocompatibility laboratory that meets the requirements to perform high-complexity histocompatibility testing when used:

- in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing,
- for HLA antibody screening and monitoring, or
- for conducting real and "virtual" HLA crossmatch tests.

FDA will also continue the general 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.

FDA also intends to continue the general enforcement discretion approach for LDTs manufactured and performed within DoD or VHA. To meet the needs of their patient populations (i.e., military personnel, veterans, and their families) and fulfill their mandates, DoD and VHA often manufacture unique LDTs, such as tests for diseases or chemicals to which their patients may be exposed while serving abroad but which do not exist at home.

We lack information to quantify the number of tests that fall in the above categories and thus the exclusions are not assessed in this regulatory impact analysis.

FDA also intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of requirements under 21 CFR 820, subpart M (Records), for currently marketed IVDs offered as LDTs that were first marketed prior to the

date of issuance of this rule that are not modified, or that are modified in certain limited ways. FDA generally expects compliance with premarket review and QS requirements when a laboratory changes the indications for use of the IVD, alters the operating principle of the IVD (e.g., changes in critical reaction components), includes significantly different technology (e.g., addition of artificial intelligence / machine learning to the test algorithm, a change from targeted sequencing to whole genome sequencing, a change from immunoassay to mass spectrometry, or a change from manual to automated procedures), or adversely changes the performance or safety specifications of the IVD.

In addition, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of requirements under 21 CFR 820, subpart M (Records), for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. For the purpose of this phaseout policy, FDA considers an LDT to be for an unmet need where there is no available FDA-authorized test that meets the patient's needs. This may be because – (1) there is no FDA-authorized IVD for the disease/condition; (2) there is an FDA-authorized IVD for the disease/condition but it is not indicated for use on the patient, or a unique attribute needs to be added to the IVD to meet the patient's needs; or (3) there is an FDA-authorized IVD but it is not available to the patient. This is discussed further in section V.B.3 of the preamble.

FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP.

We expect that a number of laboratories offering IVDs as LDTs, and those IVDs, do not currently meet applicable requirements—including premarket review, quality system,

registration and listing, and adverse event reporting requirements—given FDA's general enforcement discretion approach for LDTs.

We do not have complete information about IVD performance or patient harm. As discussed in detail in section III.B of the preamble, FDA has increasingly seen problems with IVDs offered as LDTs that have caused or might be causing harm. However, the tests involved likely do not represent all problematic tests that might be affected by the phaseout of the general enforcement discretion approach for LDTs, as laboratories do not typically submit premarket submissions for IVDs offered as LDTs to FDA or report adverse events associated with those tests given the general enforcement discretion approach.

Without registration and listing information, it is difficult to estimate the exact baseline number of manufacturers of IVDs offered as LDTs that will be affected by the phaseout policy. 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 will obtain upon the phaseout of the general enforcement discretion approach, it is difficult to estimate the exact baseline number of patients that can benefit from the phaseout of the general enforcement discretion approach given current information. In order to account for potential uncertainty and variability, we present all expected costs and benefits in ranges of low, central, and high estimates. 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 not generally registered and listed, we do not know the exact number of laboratories or IVDs offered as LDTs that will be affected by the phaseout of the general enforcement discretion approach for LDTs.

Comments suggested we use CMS data to estimate the number of affected labs. Using the CMS data, we estimate that there are 11,808 high complexity CLIA laboratories that have IVDs offered as LDTs that will be affected by the phaseout of the general enforcement discretion approach. We therefore revise our original estimate of 12,000 to 11,808. The steps in developing this estimate are explained in appendix A. Laboratories that meet the requirements to perform high complexity testing are the only laboratories that can perform LDTs under CLIA regulations, because LDTs are considered high complexity tests (Ref. [27]). Additionally, while CLIA regulations contemplate that such laboratories may deploy IVDs offered as LDTs, we do not expect that every such laboratory does so. We are not aware of suitable sources for the exact number of such laboratories that are currently offering IVDs as LDTs.

We rely on information about laboratories and IVDs in NYS to estimate the percent of high complexity labs that make IVDs offered as LDTs (Ref. [28]). NYS requires laboratories offering tests to NYS residents, whether or not the laboratory is located in NYS, to obtain a permit through the NYS CLEP, as well as "explicit test-specific approval" for certain IVDs that are not "designated as FDA-cleared, approved or exempt." (Ref. [29]) To FDA's knowledge, NYS is the only state that requires approval for 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 IVDs 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 indicating that there are approximately 500 laboratories located in NYS with a NYS CLEP permit that are certified under CLIA and that meet or exceed the regulatory requirements under CLIA to perform high complexity testing, and that approximately 50 of such laboratories offers at least one IVD as an LDT approved by NYS CLEP (Ref. [28]). From these data, we calculate that approximately 10% of laboratories located in NYS that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing are manufacturing IVDs offered as LDTs.

For our primary estimate, we assume that NYS is representative of the U.S. laboratory community, 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 11,808 (or 1,181) 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 potential variability across the country, we estimate the proportion of high complexity laboratories making IVDs offered as LDTs to vary from 5% of 11,808 (or 590) laboratories to a high estimate of 20% of 11,808 (or 2,362) affected laboratories by reducing the primary estimate by 50% and doubling the primary estimate, respectively.

Based on these two sources and methods, for purposes of this analysis, we use 590, 1,181 and 2,362 as low, central (primary), and high estimates of the number of laboratories affected by the phaseout of the general enforcement discretion approach for LDTs. We also expect that there will 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 2010 to 2018 in the

United States (approximately 8 percent) (Ref. [30]). Multiplying this by the number of affected entities, we estimate the number of new laboratories per year to range from 47 to 189, with a primary estimate of 94.[20]

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 IVDs across the country. According to NYSDOH's website, there are currently approximately 2,200 IVDs with approval from NYSDOH offered by laboratories located in NYS (Ref. [29]). 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. [28]), as well as the breakdown of risk categories for submissions to NYS, as determined by NYS CLEP risk criteria. From these data, FDA calculated that each laboratory in NYS that manufactures IVDs offers an average of 67 IVDs as LDTs. Extrapolating to the rest of the country, FDA estimates that 39,557, 79,114, or 158,227 IVDs may be currently offered as LDTs and therefore affected by the phaseout of the general enforcement discretion approach, based on the low, central, and high estimates of affected entities discussed above (see Table 2). 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

[20] 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 (502=1,683-1,181) is less than 5% of our primary estimate. We also consider varying our estimates by -5% and +10% to be sufficient for estimating the range of variability between our low and high estimate.

that laboratories within NYS that manufacture IVDs offered as LDTs introduce an average of 6 new IVDs offered as LDTs per year.[21] For purposes of this analysis, we assume that laboratories in NYS are representative of the U.S. laboratory community, and estimate that 3,542, 7,085, or 14,170 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.[22] In addition, we expect 50 percent of currently marketed IVDs offered as LDTs (34 IVDs offered as LDTs per laboratory = 67 * 0.5) will be modified in such a way as to require premarket review over the next twenty years. We thus estimate 2 IVDs offered as LDTs per year per laboratory will be modified in such a way as to require premarket review (2 = 34 / 20 years). The total number of new IVDs offered as LDTs per year is estimated to range from 5,007 to 20,026, with a primary estimate of 10,013. 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. Throughout this analysis, we define the terms "affected labs" and/or "affected entities" as laboratories offering IVDs as LDTs and therefore affected by the phaseout of the general enforcement discretion approach for LDTs. In a similar manner, we also define the terms "affected IVDs" as IVDs offered as LDTs associated with costs as incurred during their relevant policy stages 1 through 5 (discussed in detail in section II.F).

[21] 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.

[22] We use an average of firms' entry and exit rates from 2010 to 2018 in the U.S. (8 percent) (Ref. [30]).

Table 2 shows the estimated number of laboratories and IVDs offered as LDTs affected by the phaseout of the general enforcement discretion approach for LDTs.

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

	Primary Estimate	**Low Estimate**	**High Estimate**
Affected Labs	1,181	590	2,362
New Affected Labs Entering the Market Per Year	94	47	189
Affected Tests Currently on the Market	79,114	39,557	158,227
New Affected Tests Per Year	10,013	5,007	20,026

Notes: Product across table may not be exact due to rounding. The number of new affected IVDs per year include currently marketed IVDs that would be modified and new affected IVDs from both affected labs and new labs entering the market per year. These numbers reflect the baseline numbers for affected laboratories and affected tests and are further adjusted in later sections of this analysis to estimate costs under Stages 4 and 5, where only a subset of these laboratories and tests may incur costs, as described in sections II.F.4 and II.G.

2. Baseline Market Revenue

Data from the 2017 U.S. Census for the entire industry under NAICS code 621511 reported 3,365 firms with $36 billion in annual revenues.[23] From Table 2 above, we estimate 1,181 affected laboratories or firms which represent 35% of the 3,365 firms in the Census data. If we assume the same average annual receipts for all firms, then the corresponding annual receipts for affected laboratories would represent 35% of total annual receipts or $15 billion (in 2022 dollars).[24]

[23] 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 NAICS 621511which includes revenue for both IVDs offered as LDTs and other IVDs (although the Census does not distinguish between IVDs offered as LDTs and other IVDs). Source: https://www.census.gov/data/tables/2017/econ/susb/2017-susb-annual.html

[24] We convert 2017 dollars to 2022 dollars using CPI of 1.19 for 2017-2022. The product of $36 billion x 0.35 x 1.19 is about $15 billion.

In Table 3, we estimate annual industry revenue in 2023 between $19 and $21 billion based on a projection from 2017 Census data of the $15 billion using compounded annual growth rates (CAGRs) of 4.2% and 6% (Refs. [17] [31]).[25]

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

Year	**Primary** (Average between low and high projection)	**Low** Projection ($1,000) (4.2% CAGR)	**High** Projection ($1,000) (6% CAGR)
2023	$20,093,935	$19,062,398	$21,125,471
2030	$28,594,674	$25,424,450	$31,764,898

3. 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, 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 after this rule become effective (Ref. [32]).[26] The estimated annual reviews for premarket submissions/applications are adjusted to account for the enforcement discretion polices discussed

[25] The calculation for future value in 6 years using a CAGR of 4.2% is:
Future Value (FV) = Present Value (PV) x (1+4.2%)^6 = $15 billion x (104.2%)^6 = $19 billion.

[26] For the purposes of this document, we used PMAs, 510(k)s, and De Novos as the primary submission types anticipated for IVDs offered as LDTs. We assume that some IVDs offered as LDTs may also be biological products subject to licensure under section 351 of the Public Health Service Act and instead require submission of a Biologics License Application (BLA). Most licensed IVDs are tests intended for use as blood donor screening tests or HCT/P donor screening tests subject to 21 CFR 610.40 and 1271.80(c), respectively, or tests for determination of blood group and Rh factors subject to 21 CFR 640.5. As explained in the preamble, FDA's general enforcement discretion approach for LDTs has never applied to such tests. Therefore, we anticipate that there will be a limited number of IVDs offered as LDTs that are subject to licensure. While it is possible that some IVDs offered as LDTs may be submitted for review in Humanitarian Device Exemption (HDE) applications, the number of HDEs for IVDs has historically been negligible and many LDTs eligible for review under an HDE application may also fall within the enforcement discretion policy for certain LDTs for unmet needs. The volume of such submissions, if any, is expected to be much lower than the volume of PMAs, 510(k)s, and De Novos and, as discussed in the preamble to the rule, laboratories that intend to submit a BLA or HDE application for an IVD offered as an LDT should do so within the same timeframe for submission of PMAs under the phaseout policy. For the purposes of this document, we assume BLAs to be equivalent to PMAs in costs and benefits, and we assume HDEs to have a negligible impact on the calculations in this document. Therefore, the portion of IVDs offered as LDTs that are expected to submit BLAs and HDEs are included in the PMA numbers.

above, potential reclassifications of class III IVDs to class II, and the 510(k) Third Party Review Program.

Table 4. FDA Review Workload by Submission Type

Submission/Application Type	5-Year Average (FY 2017 to 2021)	Expected Annual Reviews for New IVDs Offered as LDTs		
		Primary	Low	High
Original PMAs, PDPs, Panel-Track PMA Supplements	73	103*	52*	206*
510(k) Premarket Notifications	3,877	1,090	545	2,179
De Novo Classification Requests	66	267	134	534

Note: FDA annual reviews of Q-submissions, MDRs and IDE applications are not included in Table 4 but are estimated in section II.G Budgetary Impacts and described in Table 38.
* The estimated reviews include original PMAs and panel-track PMA supplements. See Table 29 and Table 31 for estimated numbers of original PMAs and panel-track PMA supplements, respectively. Totals may not add due to rounding.

4. Baseline Risk of Problematic IVDs

We measure benefits of phasing out the general enforcement discretion approach for LDTs against a baseline scenario in which FDA continues the general enforcement discretion approach with respect to all applicable requirements for all IVDs offered as LDTs. Due to the current general enforcement discretion approach for LDTs, we lack systematic data on the exact incidence of harms specifically resulting from usage of problematic IVDs offered as LDTs that can be avoided by phasing out the general enforcement discretion approach for LDTs.

To estimate the baseline incidence of harms that can be avoided by phasing out the general enforcement discretion approach for LDTs, we focus mainly on three broad disease categories identified by Newman-Toker et al. (2021) as accounting for about 75% of serious misdiagnosis-related harms in the U.S.: cancers, cardiovascular disease, and infections (Ref. [33]). As described in the following section, we multiply the numbers of U.S. patients in each disease category—estimated from sources described below—by rates from literature of the

proportions of patients in each category that are tested using IVDs. Based on Rychert et al. (2023) (Ref. [2]), as described in section II.E.1, we estimate that 3.9% to 45% of patients tested with IVDs are tested with IVDs offered as LDTs. This yields our baseline estimates of the numbers of patients tested using IVDs offered as LDTs. To estimate usage specifically of problematic IVDs that can be curtailed by phasing out the general enforcement discretion approach for LDTs, we refer to statistics from NYS CLEP on application review outcomes and FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests. Since we do not expect that LDTs approved by NYS CLEP would undergo FDA premarket review, when estimating numbers of U.S. patients in each disease category, we exclude from this analysis the number that we attribute, proportionally by population, to New York state. We note however for LDTs approved by NYS CLEP, FDA intends to exercise enforcement discretion with respect to premarket review requirements but not other applicable requirements under the FD&C Act and FDA regulations.

Lacking systematic data on the exact issues with applications for LDTs initially rejected by NYS CLEP and those LDTs' roles in the process of diagnosis, we consider a range of rates at which avoidable errors might result from usage of problematic IVDs offered as LDTs.

Finally, in section II.E.3 "Summary of Benefits," we adjust estimated total benefits to account for the enforcement discretion policy for IVDs offered as LDTs that are already currently on the market. As a result of exercising enforcement discretion with respect to premarket review and QS requirements, with the exception of requirements under 21 CFR 820 subpart M (Records), for currently-marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule, IVDs offered as LDTs will generally undergo premarket review only in certain circumstances. However, FDA expects these IVDs to be in

compliance with other applicable requirements under the FD&C Act and FDA regulations, including post market requirements, as discussed in the phaseout policy. In order to account for this, we adjust estimated total benefits in each year—beginning with enforcement of QS and premarket review requirements—based on the proportions of IVDs falling within an enforcement discretion policy versus IVDs not falling within an enforcement discretion policy. We note, however, as described in section V.B.3 of the preamble, FDA intends to take targeted steps to address currently marketed IVDs offered as LDTs that are problematic. In particular, we intend to use available tools to identify and act against currently marketed IVDs offered as LDTs that specifically raise concerns, such as IVDs that are potentially inaccurate or poorly validated.

E. Benefits

Expected benefits of phasing out the general enforcement discretion approach for LDTs consist mainly of avoided harms to patients, including unnecessary costs, monetary and otherwise, that would result from usage of problematic IVDs offered as LDTs. Harms can vary in severity according to the particular problematic aspects of an IVD and their consequences for patient care.

We expect the phaseout to produce both health and pecuniary benefits via averting diagnostic error and its consequences, such as incorrect or unnecessary treatment, treatment delays, and disease progression or transmission. Pecuniary benefits also include reduced spending on problematic IVDs offered as LDTs, including non-invasive prenatal screening (NIPS) tests, as well as reduced spending on litigation over alleged harms caused by problematic IVDs.

1. Reduction in Harms from Diagnostic Errors

We expect public health benefits from phasing out the general enforcement discretion approach for LDTs due to improved safety and effectiveness of IVDs offered as LDTs. To

estimate the baseline incidence of harms that can be avoided by the phaseout, we focus mainly on three broad disease categories identified by Newman-Toker et al. (2021) as accounting for about 75% of serious misdiagnosis-related harms in the U.S.: cancers, cardiovascular disease, and infections (Ref. [33]).

a. Cancer: Mortality Risk

We quantify health benefits in the form of reduced baseline mortality risk based on expected reduction of cancer related 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 phaseout policy will lead to other benefits as well, such as reduced risk of undergoing unnecessary, potentially harmful treatments based on false positive diagnoses.

We also present these estimates with the caveat that the incidence of misdiagnosis-related mortality 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. [34]).[27] 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

[27] 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 other assumptions estimated 549 000 serious harms. Results were compatible with setting-specific serious harm estimates from inpatient, emergency department and ambulatory care (Ref. [34]).

diagnosis had been correct, but this would not necessarily be counted as a death due to misdiagnosis.[28] 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. [33]).

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

Expected Reduction in Cancer Misdiagnosis

To estimate the reduction in cancer mortality risk from the phaseout policy, we start from an estimate of annual deaths attributable to diagnostic error and apply four probabilities: the probability of a patient having been tested with an IVD; the probability that the IVD had been offered as an LDT; the probability that the IVD offered as an LDT was problematic; and, finally, the probability that the problematic IVD offered as an LDT resulted in preventable diagnostic error. 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).

Newman-Toker et al. 2019 (Ref. [35]) state that about 5-10% of the 2.7 million deaths annually in the United States are attributable to diagnostic error—or between 0.135 million and 0.27 million fatalities across all misdiagnosed conditions. Based on the annual US incidence of serious misdiagnosis-related harms across vascular events, infections, and cancers per Newman-Toker et al. 2023 (Ref. [34]), we estimate that about 11% (= 1.5M / 13.7M) of misdiagnosis-

[28] In general, the phaseout policy 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. [74]).

related fatalities are associated with cancer. [29] This results in a range of 0.015 million, 0.022 million and 0.03 million misdiagnosis-related deaths from cancer.

Excluding the state of New York proportionally by population,[30] we assume that about 20,900 U.S. misdiagnosis-related cancer deaths occur outside of NY and could thus potentially involve tests not approved by NYS CLEP. It is likely that some patients outside of the state of New York are also tested with LDTs approved by NYS CLEP and hence would not necessarily benefit from the phaseout of enforcement discretion for premarket review requirements but will still benefit from the phaseout of enforcement discretion for other requirements, as would patients inside the state of New York. According to Rohr et al. (2016), 91% of U.S. oncology patients undergo IVD testing (Ref. [36]). Using test orders from a U.S. academic hospital system, Rychert et al. (2023) estimate that IVDs offered as LDTs are 3.9% of test order volume and 45% of distinct assays (Ref. [2]). In estimating the percent of patients tested with IVDs who are tested with IVDs offered as LDTs, we thus consider a range from 3.9% to 45%, with a primary estimate of 10%. Using the primary rate, we estimate that about 13,700 U.S. (non-NY) cancer patients would rely on IVDs offered as LDTs (= 150,554 x 0.91 x 0.10).

To estimate the number of these patients tested with IVDs offered as LDTs that would not be authorized by FDA following a premarket submission to the Agency (i.e., following the phaseout of the general enforcement discussion approach), we consult FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests and statistics from

[29] 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.

[30] According to the Census Bureau as of July 1, 2022, the population of NY was 19,677,151, and the population of the U.S. was 333,287,557. We thus assume that about 5.9% (= 19,677,151 / 333,287,557) of new U.S. cancers are in NY. For the population estimates used, refer to: https://www.census.gov/quickfacts/fact/table/US/PST045222.

NYS CLEP on application outcomes and assume that similar rates of initial denial would apply under FDA oversight.

A public comment from NYSDOH informed us that, since September 30, 2021, among applications subject to technical review:

- 46% were approved based on the original application;
- another 33% were approved in a second round of review after the applicant provided additional information; and
- 20% could not be approved after the second round of review (though they might have been approved later) (Ref. [12]).

Regarding applications not initially approved, NYSDOH stated in its comment:

> "Tests that are not approved based on the original application have a range of issues. Analytical validity issues include design flaws, inadequate validation data, and process problems that call into the question the reliability of the results. For example, the test may not be capable of detecting the target analytes. One application claimed to detect cytomegalovirus (CMV) in a transplant recipient population, but a primer/probe design flaw resulted in the detection of only two CMV subtypes. This error would have endangered patient safety and was only identified during NYS CLEP review. The laboratory redesigned the assay with input from NYS CLEP subject matter experts so that all four subtypes could be detected." (Ref. [12])

We thus consider a range of scenarios reflecting different possible rates of problematic IVDs offered as LDTs. As a low estimate, we consider that 22% of EUA requests in FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests had

significant design issues and indications for use issues.[31] As a high estimate, we use the 54% of submissions that are not initially approved by New York State. We consider initial approval rates because information contained in New York State's public comment suggests that "additional information" included in response to original review may include design changes, and thus tests not initially approved might, without review, have gone on to yield unreliable results. For our primary estimate, we average the above two, resulting in 38%.

In the central scenario with an expected initial rejection rate of 38%, about 720 misdiagnosis-related cancer deaths involve patients tested using IVDs offered as LDTs that will not be authorized by FDA following a premarket submission—at least without changes. We assume that some of the time when these IVDs are used, they yield inaccurate results that would not occur using an IVD that could be authorized by FDA. Of these instances of inaccurate results, some might be caught during follow-up or other parts of the process of diagnosis before leading to harm from diagnostic error.

Lacking systematic data on the exact issues with applications for IVDs offered as LDTs initially rejected by NYS CLEP and these LDTs' roles in the process of diagnosis, we consider a range of rates at which avoidable error might result from usage of problematic IVDs offered as LDTs: from a low of 25% to a high of 75%, with a central estimate of 50%. However, some of these errors might not have consequences for patient care if a patient would in any case be unable or unwilling to obtain treatment. 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

[31] 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.

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. [37]). Assuming that Iowa cancer patients are representative of the rest of the U.S., we thus estimate that diagnostic error has treatment implications for 88% to 92% of patients, with a central estimate of 90%. Thus, using our central estimates, we expect the phaseout policy to avoid about 325 harms from diagnostic error among cancer patients.

Table 5. Avoidable Harms Related to Diagnostic Error Among Cancer Patients

	Primary	Low	High
a) Deaths from Misdiagnosis (Non-NYS)	20,863	13,908	27,817
b) Percent Tested with IVDs	91%	91%	91%
c) Probability of IVD Being Offered as an LDT	10.0%	3.9%	45.0%
d) Patients Tested with IVDs Offered as LDTs (= a * b *c)	1,898	494	11,391
e) Percent of IVDs offered as LDTs Not Authorized by FDA Following a Premarket Submission	38%	22%	54%
f) Tests Using Problematic IVDs Offered as LDTs (= d * e)	721	109	6,151
g) Percent Leading to Diagnostic Error	50%	25%	75%
h) Treatment-to-Diagnosis Ratio	0.9	0.88	0.92
i) Harms Avoidable by the Phaseout Policy (= f * g * h)	325	24	4,244

Value of Reduced Mortality Risk

As a first step in valuing reduced mortality risk from the phaseout policy, we estimate the gain in life expectancy associated with a correct diagnosis for someone who has cancer.

First, we consult 2023 data on estimated new cancer cases along with the five-year relative survival rate covering 2012-2018 (Ref. [38]). The five-year relative survival rate (RSR) in column B of Table 6, represents the percentage of individuals surviving their cancer diagnosis 5 years after diagnosis compared to individuals who are cancer free.[32] We then use the RSR to

[32] 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

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%.

Table 6. 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.

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.

Thus, on average, a person with cancer who is diagnosed has 68.6% of the chance of living another five years than a person has who is cancer free. According to the National Cancer Institute, the median age of a cancer diagnosis is 66 years (Ref. [39]). Per CDC life tables, the 5-year survival rate for all age-66 individuals is approximately 91.13%.[33] 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. [40]) and 11.94 months, or 0.995 years, in cases of lung cancer (Ref. [41]). We average these two survival times, weighting by the numbers of new cases of breast and lung cancer, respectively, from Table 6 above, and thus obtain a survival time for untreated cancer patients of about 1.71 years. While we acknowledge that uncertainty is introduced by assuming that lung and breast cancers are representative of cancer in general, we received no comment indicating that this assumption is unsuitable.

[33] 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

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 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 7 shows these life years discounted to the time of the diagnostic test at rates of three and seven percent.

Table 7. 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

We note that 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.

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 reductions in mortality risk, measured by the willingness to pay for an increase in life expectancy by one year. We use VSLYs derived from the value of a statistical life (VSL) under assumptions of three and seven percent discounting, paired with estimates of the statistical life years gained per case. [34,35] VSLYs are those projected for 2024 but using 2022 base year dollars for consistency with the rest of this analysis. Table 8 below represents our

[34] 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. [42]).
[35] We note that the HHS estimates of VSLY depend on the choice of discount rate.

estimates of the value (at the time of the diagnostic test), of the additional expected life years from an accurate diagnosis.

Table 8. Estimated Value Per Case of Accurate Diagnosis (2022$)

	(a) VSLY (3% discounting)	(b) Value Per Case (VSLY 3%) (= a * 3.018)	(c) VSLY (7% discounting)	(d) Value Per Case (VSLY 7%) (= c * 2.708)
Primary	$546,735	$1,650,181	$915,435	$2,479,329
Low	$255,143	$770,084	$427,203	$1,157,020
High	$832,253	$2,511,942	$1,393,495	$3,774,090

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

To estimate total benefit in Table 9 below, we multiply the estimated reduction in harms by the benefit per avoided harm and by the portion of relevant risk not already internalized in decision-making by medical providers and patients. Because providers who frequently order tests might note quality trends across different labs, we assume that only 95% of the risk of problematic IVDs offered as LDTs is not already internalized at baseline, with a range from 90-100%. Total internalization is unlikely, 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.

Table 9. Widest Range of Recurring (Annual) Benefit from Reduced Mortality from Cancer-Related Diagnostic Error

	Primary	Low	High
a) Harms Avoidable by the Phaseout Policy	325	24	4,244
b) Value Per Harm (VSLY using 3% discounting)	$1,650,181	$770,084	$2,511,942
c) Value Per Harm (VSLY using 7% discounting	$2,479,329	$1,157,020	$3,774,090
d) Percent Not Internalized at Baseline	95%	90%	100%
e) Total Benefit (VSLY using 3% discounting)	$508,931,983	$16,558,006	$10,661,349,657
f) Total Benefit (VSLY using 7% discounting	$764,649,367	$24,877,722	$16,018,239,255

However, due to our high degree of uncertainty about several of the parameters used to estimate the reduction in mortality risk from misdiagnosis related to cancer, we use a Monte Carlo simulation to determine a plausible range for total benefits by allowing each parameter (the rows in Table 5, the values per case in Table 8, and the internalization percentage in Table 9) to vary independently of the others. Whereas Table 9 implicitly assumes that all uncertain parameters share a joint probability distribution and are perfectly dependent (i.e., aligning all best- and worst-case scenarios across parameters), Table 10 below assumes certain parameters to be independent random variables as follows:

- the yearly number of premature deaths from misdiagnosis related to cancer follows a PERT distribution with a minimum, mean, and maximum taken from row (a) of Table 5;
- the probability that an IVD is offered as an LDT follows a PERT distribution with a minimum, mode, and maximum taken from row (c) of Table 5;
- the percent of such tests that would not be authorized by FDA follows a uniform distribution defined by the low and high estimates of row (e) of Table 5;
- the percent of such tests leading to a preventable misdiagnosis follows a uniform distribution defined by the low and high estimates of row (g) of Table 5;
- the treatment-to-diagnosis ratio follows a uniform distribution defined by the low and high of row (h) of Table 5;
- the values per harm using VSLYs that assume three and seven percent discounting follow triangular distributions with minimums, means, and maximums taken from rows (b) and (c), respectively, of Table 9; and

- the percent of risk of problematic IVDs not already internalized at baseline follows a uniform distribution defined by the low and high estimates from row (d) of Table 9.

Per HHS guidance (Ref. [42]), the low, primary, and high benefit estimates in Table 10 represent the 5th, 50th, and 95th percentiles from running the above simulation 100,000 times.

Table 10. Simulated Plausible Range of Recurring (Annual) Benefit from Reduced Mortality from Cancer-Related Diagnostic Error

	Primary	Low	High
e) Total Benefit (VSLY using 3% discounting)	$616,052,630	$191,389,437	$1,800,143,089
f) Total Benefit (VSLY using 7% discounting	$926,834,309	$286,994,300	$2,704,265,559

Given the uncertainty in this analysis and the implausibility of all best- and worst-case scenarios perfectly aligning across the uncertain parameters, we use the results from Table 10 to inform our total benefits estimates in II.E.4 "Summary of Benefits" and in Table 1, the main summary of benefits, costs, and transfers. As we explain in II.E.4 "Summary of Benefits" below, estimates in Table 1 are further adjusted to account for the enforcement discretion policy and the timing of the phase-in.

b. Cardiovascular Disease

Cardiovascular disease is prevalent in the U.S. According to the American Heart Association, in 2020, 48.6% of U.S. adults aged 20 and older had some form of cardiovascular disease, including coronary heart disease, heart failure, stroke, and hypertension (Ref. [43]). Additionally, the CDC notes that "heart disease is the leading cause of death for men, women, and people of most racial and ethnic groups in the United States" (Ref. [44]).

Table 11 below shows our estimated range for the number of harms from diagnostic error among patients with cardiovascular disease that we expect phasing out the general enforcement discretion approach for LDTs to avoid.

Using an estimate by Raisi-Estabragh et al. (2022) of about 20.6 million cardiovascular emergency department encounters in adults in the U.S. between 2016-2018 (Ref. [45]), we estimate about 6.9 million (= 20.6 million / 3) annual cardiovascular emergency department visits. It is likely that not all of these healthcare encounters involve initial diagnoses. However, IVDs are still used in visits concerning known conditions for monitoring of disease, prognosis, predicting treatment response, assessing the risk of developing a disease or disorder, and guiding patient management (Ref. [36]).

Excluding the state of New York proportionally by population,[36] we assume that about 6.5 million such cases are outside of NY and could thus potentially be managed using tests not approved by NYS CLEP. It is likely that some patients outside of the state of New York are also tested with LDTs approved by NYS CLEP and hence will not necessarily benefit from FDA's phaseout of enforcement discretion for premarket review requirements, but will still benefit from the phaseout of enforcement discretion for other requirements. According to Rohr et al. (2016), 62% of U.S. cardiology patients undergo IVD testing (Ref. [36]). Using test orders from a U.S. academic hospital system, Rychert et al. (2023) estimate that IVDs offered as LDTs are 3.9% of test order volume and 45% of distinct assays (Ref. [2]). In estimating the percent of patients tested with IVDs who are tested with IVDs offered as LDTs, we thus consider a range from 3.9% to 45%, with a primary estimate of 10%. Using the primary estimate, we estimate that about 0.4

[36] According to the Census Bureau as of July 1, 2022, the population of NY was 19,677,151, and the population of the U.S. was 333,287,557. We thus assume that about 5.9% (= 19,677,151 / 333,287,557) of CVD-related emergency department encounters are in NY. For the population estimates used, refer to: https://www.census.gov/quickfacts/fact/table/US/PST045222.

million U.S. (non-NY) patients with cardiovascular disease would rely on IVDs offered as LDTs (= 6,461,000 x 0.62 x 0.10).

As described in the previous section on harms related to diagnostic error among cancer patients, we consider a range of estimates of the number of these patients tested using IVDs offered as LDTs that will not be initially authorized by FDA following a premarket submission. As explained above, based on statistics from NYS CLEP on approved and denied applications, we consider initial rejection rates of 22%, 38%, and 54%.

In the central scenario with an expected rejection rate of 38% percent, about 152,000 patients with cardiovascular disease are managed using IVDs offered as LDTs that will not be authorized by FDA following a premarket submission—at least without changes. We assume that some of the time when these tests are used, they yield inaccurate results that would not occur using a test that could be authorized by FDA. Of these instances of inaccurate results, some might be caught during follow-up or other parts of the process of diagnosis before leading to harm from diagnostic error.

Lacking systematic data on the quality of applications for IVDs offered as LDTs rejected by NYS CLEP and these tests' roles in the process of diagnosis, we consider a range of rates at which avoidable errors might result from usage of problematic IVDs offered as LDTs: from a low of 25% to a high of 75%, with a central estimate of 50%. However, some of these errors might not have consequences for patient care if a patient would in any case be unable or unwilling to obtain treatment. Cardiovascular disease includes several different conditions, each of which might go untreated for various reasons. The American Heart Association reports treatment rates of high cholesterol (44.9%) and hypertension (52%), as well as the rate of diabetes patients with established atherosclerotic cardiovascular disease who are treated with a

statin (58.6%) (Ref. [43]). Based on these, we estimate that diagnostic error has treatment implications for 44.9% to 58.6% of patients, with a central estimate of 52%. Thus, using our central estimates, we expect the phaseout policy to avoid about 39,600 harms among patients with cardiovascular disease.

Table 11. Avoidable Harms Related to Diagnostic Error Among Cardiovascular Disease Patients

	Primary	Low	High
a) Annual US Cardiovascular Emergency Department Encounters (Non-NYS)	6,461,262	6,461,262	6,461,262
b) Percent Tested with IVDs	62%	62%	62%
c) Probability of IVD Being Offered as an LDT	10.0%	3.9%	45.0%
d) Patients Tested with IVDs Offered as LDTs (= a * b *c)	400,598	156,233	1,802,692
e) Percent of IVDs Offered as LDTs Not Authorized by FDA Following a Premarket Submission	38%	22%	54%
f) Tests Using Problematic IVDs Offered as LDTs (= d * e)	152,227	34,371	973,454
g) Percent Leading to Diagnostic Error	50%	25%	75%
h) Treatment-to-Diagnosis Ratio	0.52	0.449	0.586
i) Harms Avoidable by the Phaseout Policy (= f * g * h)	39,579	3,858	427,833

Harms from diagnostic error are diverse and can vary widely in severity, from avoidable inconvenience and expense to unnecessary treatments, disability, and premature mortality. As one example, 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, research showed no association between the polymorphism and statin response (Refs. [13] [14]).

Additionally, in April 2011, FDA denied premarket approval of this test, citing lack of sufficient evidence of the safety and effectiveness of the test based in particular on clinical validity concerns.

Approximately 35% of patients in studies on CVD have the Trp719Arg polymorphism (Refs. [13] [14]). 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 health likely occurred, though medical expenditures were likely reduced. According to Conly et al. (2011), the use of high-potency statins results in an increase of 0.13 QALYs relative to the use of low-potency statins (Ref. [46]). Since this consists almost entirely of mortality effects, we value the health gains from high-potency statins in terms of life years. Conly et al. report life expectancy averages of 21.0 years for patients taking low-potency statins and 21.4 years for patients taking high-potency statins. Discounting at three and seven percent, this represents a gain of about 0.22 and 0.10 discounted life years, respectively, at the time of initiation of statin use. However, the use of high-potency statins in Canada costs CAD $1,200 more than low-potency statins (Ref. [46]). Converting to USD at the current rate of CAD $1.36 to USD $1.00, this is about $882. Based on a report prepared for the Department of Health and Human Services comparing international prescription drug prices, prices across all prescription drugs in Canada are about 44% of U.S. prices (Ref. [47]). We thus divide again by 0.44, resulting in a cost difference between high and low potency statins of about $2,005. Using a Value of a Statistical Life Year (VSLY) of $546,735 (the central VSLY that assumes three percent discounting), the value of lost health from using low-potency statins instead of high-potency statins is $121,086 (= $546,735 x 0.2215). The net lost benefit for each person using

low-potency statins is $119,080 (= $121,086 - $2,005), and the estimated total welfare losses are thus about $6.7 billion (= $119,080 x 56,000). Using a VSLY of $915,435 (the central VSLY that assumes seven percent discounting), the value of lost health from using low-potency statins instead of high-potency statins is $94,626 (= $915,435 x 0.1034). VSLYs are those projected for 2024 but using 2022 base year dollar values for consistency with the rest of this analysis. The net lost benefit for each person using low-potency statins is $92,621 (= $94,626 - $2,005), and the estimated total welfare losses over the period 2008-2011 are thus about $5.2 billion (= $92,621 x 56,000).

Thus, as a proxy for the value of an average harm from diagnostic error to a patient with a cardiovascular disease, we use $119,080 as our primary estimate given three percent discounting and $92,621 as our primary estimate given seven percent discounting. Further below, we also include estimates based on the low and high VSLY estimates.[37]

To estimate total benefit in Table 12 below, we multiply the estimated reduction in harms by the benefit per avoided harm and by the portion of relevant risk not already internalized in decision-making by medical providers and patients. Because providers who frequently order tests might note quality trends across different labs, we assume that only 95% of the risk of problematic IVDs offered as LDTs is not already internalized at baseline, with a range from 90-100%. Total internalization is unlikely, 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.

Table 12. Widest Range of Recurring (Annual) Benefit from Avoiding Harms from Diagnostic Error Related to Cardiovascular Disease

[37] Available at: https://aspe.hhs.gov/sites/default/files/documents/7f96080e2812365443347c1cca347188/standard-ria-values-2024.xlsx

	Primary	Low	High
a) Harms Avoidable by the Phaseout Policy	39,579	3,858	427,833
b) Value Per Harm (VQALY using 3% discounting)	$119,080	$54,501	$182,314
c) Value Per Harm (VQALY using 7% discounting	$92,621	$42,154	$142,037
d) Percent Not Internalized at Baseline	95%	90%	100%
e) Total Benefit (VQALY using 3% discounting)	$4,477,436,064	$189,248,233	$77,999,873,099
f) Total Benefit (VQALY using 7% discounting	$3,482,562,142	$146,372,612	$60,768,070,609

Due to our high degree of uncertainty about several of the parameters used to estimate the reduction in morbidity risk from diagnostic error related to cardiovascular disease, we use a Monte Carlo simulation to determine a plausible range for total benefits by allowing each parameter (the rows in Table 11 and the values per case and internalization percentage in Table 12) to vary independently of the others. Whereas Table 12 implicitly assumes that all uncertain parameters share a joint probability distribution and are perfectly dependent (i.e., aligning all best- and worst-case scenarios across parameters), Table 13 below assumes certain parameters to be independent random variables as follows:

- the percent of patients tested with IVDs who are tested with IVDs offered as LDTs follows a PERT distribution with a minimum, mode, and maximum taken from row (c) of Table 11;
- the percent of such tests that would not be authorized by FDA follows a uniform distribution defined by the low and high estimates of row (e) of Table 11;
- the percent of such tests leading to a preventable misdiagnosis follows a uniform distribution defined by the low and high estimates of row (g) of Table 11;
- the treatment-to-diagnosis ratio follows a PERT distribution with a minimum, mode, and maximum taken from row (h) of Table 11;

- the values per harm using VSLYs that assume three and seven percent discounting follow triangular distributions with minimums, means, and maximums taken from the low, primary, and high estimates in rows (b) and (c), respectively, of Table 12; and
- the percent of risk of problematic IVDs not already internalized at baseline follows a uniform distribution defined by the low and high estimates from row (d) of Table 12.

Per HHS guidance (Ref. [42]), the low, primary, and high benefit estimates in Table 13 represent the 5th, 50th, and 95th percentiles from running the above simulation 100,000 times.

Table 13. Simulated Plausible Range of Recurring (Annual) Benefit from Avoiding Harms from Diagnostic Error Related to Cardiovascular Disease

	Primary	Low	High
e) Total Benefit (VQALY using 3% discounting)	$5,430,362,350	$1,716,966,298	$15,579,610,547
f) Total Benefit (VQALY using 7% discounting	$4,233,288,851	$1,327,584,767	$12,131,010,945

Given the uncertainty in this analysis and the implausibility of all best- and worst-case scenarios perfectly aligning across the uncertain parameters, we use the results from Table 13 to inform our total benefits estimates in II.E.4 "Summary of Benefits" and in Table 1, the main summary of benefits, costs, and transfers. As we explain in II.E.4 "Summary of Benefits" below, estimates in Table 1 are further adjusted to account for the enforcement discretion policy and the timing of the phase-in.

c. Morbidity Due to Infections

Table 14 below shows our estimated range for the number of harms from diagnostic errors related to infections that we expect the phaseout policy to avoid. There are many kinds of infectious diseases. Because we cannot comprehensively analyze expected consequences of the phaseout policy with respect to all possible infectious diseases, we base our estimate of the

number of relevant cases on the CDC's statistics on selected national notifiable infectious diseases (Ref. [48]). For the year 2019, CDC reports 2,738,992 cases of those selected infectious diseases, over 93% of which are sexually transmitted infections. We believe this to be about half or more of all serious infectious diseases in the U.S., but we use this figure for lack of a comprehensive accounting of all other possible infectious diseases. Excluding the state of New York proportionally by population,[38] we assume that about 2,577,300 such cases occur outside of NY and could thus potentially involve tests not approved by NYS CLEP. It is likely that some patients outside of the state of New York are also tested with LDTs approved by NYS CLEP and hence would not necessarily benefit from the phaseout of enforcement discretion for premarket review requirements, but will still benefit from the phaseout of enforcement discretion for other requirements. According to Rohr et al. (2016), 64% of U.S. oncology and cardiology clinical decisions involve IVD testing (Ref. [36]), and due to lack of more directly relevant data, the oncology and cardiology estimate is extrapolated to the infectious disease context. Using test orders from a U.S. academic hospital system, Rychert et al. (2023) estimate that IVDs offered as LDTs are 3.9% of test order volume and 45% of distinct assays (Ref. [2]). In estimating the percent of patients tested with IVDs who are tested with IVDs offered as LDTs, we thus consider a range from 3.9% to 45%, with a primary estimate of 10%. Using the primary rate, we estimate that about 164,900 U.S. (non-NY) patients with infectious disease would rely on IVDs offered as LDTs (= 2,577,283 x 0.64 x 0.10).

As described in the earlier section on harms from diagnostic error related to cancers, we consider a range of estimates of the number of these patients tested using IVDs offered as LDTs

[38] According to the Census Bureau as of July 1, 2022, the population of NY was 19,677,151, and the population of the U.S. was 333,287,557. We thus assume that about 5.9% (= 19,677,151 / 333,287,557) of infection-related emergency department encounters are in NY. For the population estimates used, refer to: https://www.census.gov/quickfacts/fact/table/US/PST045222.

that will not be initially authorized by FDA following a premarket submission. As explained above in the section on cancers, based on statistics from NYS CLEP on approved and denied applications, we consider rejection rates of 22%, 38%, and 54% percent.

In the central scenario with an expected rejection rate of 38% percent, about 62,700 patients with infections are tested using IVDs offered as LDTs that will not be authorized by FDA following a premarket submission—at least without changes. We assume that some of the time when these tests are used, they yield inaccurate results that would not occur using a test that could be authorized by FDA. Of these instances of inaccurate results, some might be caught during follow-up or other parts of the process of diagnosis before leading to harm.

Lacking systematic data on the exact issues with applications for IVDs offered as LDTs initially rejected by NYS CLEP and these tests' roles in the process of diagnosis, we consider a range of rates at which avoidable error might result from usage of problematic IVDs offered as LDTs: from a low of 25% to a high of 75%, with a central estimate of 50%. However, some of these errors might not have consequences for patient care if a patient would in any case be unable or unwilling to obtain treatment. There are many kinds of infections, each of which might go untreated for various reasons. Based on treatment rates from Li et al. (2023) for chlamydia and gonorrhea among symptomatic and asymptomatic men and women in the US (Ref. [49]), and assuming equal numbers of men and women patients, overall treatment rates are about 36.42% for gonorrhea and 42.18% for chlamydia. Averaging between these two rates while weighting by their respective shares of notifiable disease cases (about three cases of chlamydia to one case of gonorrhea), we estimate that diagnostic error has treatment implications for 40.7% of infectious disease patients, with a range from 30-50%. Thus, using our central estimates, we expect the phaseout policy to avoid about 12,800 harms among patients with infections.

Table 14. Avoidable Harms from Diagnostic Error Related to Infections

	Primary	Low	High
a) Yearly U.S. Infections (Non-NYS)	2,577,283	2,577,283	2,577,283
b) Percent Tested with IVDs	64%	64%	64%
c) Probability of IVD Being Offered as an LDT	10.0%	3.9%	45.0%
d) Patients Tested with IVDs Offered as LDTs (= a * b *c)	164,946	64,329	742,258
e) Percent of IVDs Offered as LDTs Not Authorized by FDA Following a Premarket Submission	38%	22%	54%
f) Tests Using Problematic IVDs Offered as LDTs (= d * e)	62,680	14,152	400,819
g) Percent Leading to Diagnostic Error	50%	25%	75%
h) Treatment-to-Diagnosis Ratio	0.41	0.30	0.50
i) Harms Avoidable by the Phaseout Policy (= f * g * h)	12,761	1,061	150,307

Harms from diagnostic error are diverse and can vary widely in severity, from avoidable inconvenience and expense to unnecessary treatments, disability, and premature mortality. As over 93% of CDC national notifiable infectious disease cases are sexually transmitted diseases, we use average QALY loss from chlamydia and gonorrhea as a proxy for the value of an average harm from diagnostic error to a patient with an infectious disease. Based on discounted lifetime QALY loss estimates from Li et al. (2023) for chlamydia and gonorrhea among men and women in the US (Ref. [49]), and assuming equal numbers of men and women patients, average QALY losses are about 0.008 from gonorrhea and 0.024 from chlamydia. However, part of this health loss occurs during the acute infection, prior to diagnosis. Considering only the portions of health loss attributable to sequelae based on Figure 6 (Ref. [49]), these losses are about 0.007 from gonorrhea and 0.022 from chlamydia.[39] Averaging between these two diseases while weighting

[39] Li et al.'s Table 1 and Figure 3 imply that QALY gains due to treatment have the following central estimates: 0.008 for women with gonorrhea, 0.002 for men with gonorrhea, 0.061 for women with chlamydia, and 0.006 for men with chlamydia. With the incidence rates and populations from Li et al.'s Tables S-5 and S-6, the weighted average for gonorrhea is 0.005 and for chlamydia is 0.039. These estimates could represent upper bounds on QALY gains to be included in this document's Table 15, reflecting an assumption that misdiagnosis (and thus delayed treatment) produces as much harm as complete lack of treatment. Focusing only on expected values of

by their respective shares of notifiable disease cases (about three cases of chlamydia to one case of gonorrhea), we estimate that the average case entails a discounted lifetime QALY loss of about 0.0185. Health loss estimates by Li et al. consider lifetime sequelae and complications from lack of treatment such as pelvic inflammatory disease, but both gonorrhea and chlamydia are curable within a few days with antibiotics.[40] According to Malek et al. (2013), "delay in seeking care for STDs can [...] increase the likelihood of consequences such as infertility and chronic pelvic pain" (Ref. [50]).

Using a VQALY of $649,215 (the central VQALY that assumes three percent discounting), we thus assume that the value of lost health from an average infectious disease case without timely identification and treatment is about $12,000 (= $649,215 x 0.0185). Using a VQALY of $1,070,162 (the central VQALY that assumes seven percent discounting), the value of lost health is about $19,800. VQALYs are those projected for 2024 but using 2022 base year dollar values for consistency with the rest of this analysis.

Diagnostic error for infectious disease tests may lead to uncontrolled spread of communicable infectious diseases from contact with patients relying on false results from problematic IVDs. Our estimates do not account for harms from these downstream infections.

To estimate total benefit in Table 15 below, we multiply the estimated reduction in harms from diagnostic error by the benefit per avoided harm and by the portion of relevant risk not already internalized in decision-making by medical providers and patients. Because providers

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asymptomatic cases—which might be especially relevant to assessing the consequences of testing-related misdiagnosis—lack of treatment is associated with 0.002 lost QALY (gonorrhea central estimate) or 0.026 lost QALY (chlamydia central estimate). The omission of QALY loss associated with symptomatic cases may give such estimates a tendency toward understatement, but as before, the harm due to misdiagnosis-related delayed treatment is quantified as being equal to the harm of complete lack of treatment, thus generating a simultaneous tendency toward overstatement.

[40] See CDC on "Gonorrhea Treatment and Care" (https://www.cdc.gov/std/gonorrhea/treatment.htm), "Chlamydia Treatment and Care" (https://www.cdc.gov/std/chlamydia/treatment.htm), and "Sexually Transmitted Infections Treatment Guidelines, 2021" (https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf).

who frequently order tests might note quality trends across different labs, we assume that only 95% of the risk of problematic IVDs offered as LDTs is not already internalized at baseline, with a range from 90-100%. Total internalization is unlikely, 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.

Table 15. Widest Range of Recurring (Annual) Benefit from Avoiding Harms from Diagnostic Error Related to Infections

	Primary	Low	High
a) Harms Avoidable by the Phaseout Policy	12,761	1,061	150,307
b) Value Per Harm (VQALY using 3% discounting)	$11,995	$5,598	$18,259
c) Value Per Harm (VQALY using 7% discounting	$19,772	$9,227	$30,098
d) Percent Not Internalized at Baseline	95%	90%	100%
e) Total Benefit (VQALY using 3% discounting)	$145,414,428	$5,347,319	$2,744,440,950
f) Total Benefit (VQALY using 7% discounting	$239,700,470	$8,814,497	$4,523,923,748

Due to our high degree of uncertainty about several of the parameters used to estimate the reduction in morbidity risk from diagnostic error related to infectious diseases, we use a Monte Carlo simulation to determine a plausible range for total benefits by allowing each parameter (the rows in Table 14 and the values per case and internalization percentage in Table 15) to vary independently of the others. Whereas Table 15 implicitly assumes that all uncertain parameters share a joint probability distribution and are perfectly dependent (i.e., aligning all best- and worst-case scenarios across parameters), Table 16 below assumes certain parameters to be independent random variables as follows:

- the percent of patients tested with IVDs who are tested with IVDs offered as LDTs follows a PERT distribution with a minimum, mode, and maximum taken from row (c) of Table 14;
- the percent of such tests that would not be authorized by FDA follows a uniform distribution defined by the low and high estimates of row (e) of Table 14;
- the percent of such tests leading to a preventable misdiagnosis follows a uniform distribution defined by the low and high estimates of row (g) of Table 14;
- the treatment-to-diagnosis ratio follows a PERT distribution with a minimum, mode, and maximum taken from row (h) of Table 14;
- the values per harm using VQALYs that assume three and seven percent discounting follow triangular distributions with minimums, means, and maximums taken from the low, primary, and high estimates in rows (b) and (c), respectively, of Table 15; and
- the percent of risk of problematic IVDs not already internalized at baseline follows a uniform distribution defined by the low and high estimates from row (d) of Table 15.

Per HHS guidance (Ref. [42]), the low, primary, and high benefit estimates in Table 16 represent the 5th, 50th, and 95th percentiles from running the above simulation 100,000 times.

Table 16. Simulated Plausible Range of Recurring (Annual) Benefit from Avoiding Harms from Diagnostic Error Related to Infections

	Primary	Low	High
e) Total Benefit (VQALY using 3% discounting)	$189,393,046	$54,670,583	$577,904,403
f) Total Benefit (VQALY using 7% discounting	$311,957,235	$90,634,571	$953,299,062

Given the uncertainty in this analysis and the implausibility of all best- and worst-case scenarios perfectly aligning across the uncertain parameters, we use the results from Table 16 to inform our total benefits estimates in II.E.4 “Summary of Benefits” and in Table 1, the main

summary of benefits, costs, and transfers. As we explain in II.E.4 "Summary of Benefits" below, estimates in Table 1 are further adjusted to account for the enforcement discretion policy and the timing of the phase-in.

2. Non-Health Benefits

a. Spending on Inappropriate Use of Non-invasive Prenatal Screening (NIPS)

Non-invasive prenatal screening (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. Negative results can help pregnant individuals avoid the risks to fetal health of undergoing more invasive tests. However, as screening tests, positive results only indicate risk of a condition and require follow-up with diagnostic tests to confirm or rule out the suspected condition—in turn requiring discussion between patients and healthcare providers. NIPS test results should not be used by themselves to make critical healthcare decisions and should be discussed with a healthcare provider.

Given the increased use and marketing of these tests and recent media reports, FDA has warned the public of the risk of false results, inappropriate use, and inappropriate interpretation of NIPS test results, which might be addressed by phasing out the general enforcement discretion approach for LDTs. FDA is particularly concerned about reports of patients and health care providers that have made critical health care decisions based on results from these screening tests alone and without additional confirmatory testing, possibly related to misleading marketing.

Screening tests for extremely rare conditions caused by genetic microdeletions have generated significant revenue: "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" (Ref [15]). However, the five most common microdeletion tests

screen for conditions that affect only one in 5,000-20,000 births.[41] According to the NY Times, patients or their providers might lack the requisite understanding of NIPS to make informed purchase decisions: "doctors already order many tests during short prenatal care visits, meaning some probably thought little of tacking on a few more."[42] Additionally, the NY Times reveals evidence that patients or their providers might not understand that positive results from NIPS for rare conditions can be wrong up to 81 to 93 percent of the time (Ref. [15]). Misunderstanding by patients or their providers might result in avoidable distress and premature medical decisions or false reassurance. We consider that increased regulatory oversight might reduce spending on NIPS IVDs offered as LDTs to screen for a particular condition that have potentially unreliable, inaccurate, or misinterpreted results and require confirmatory diagnostic testing. Increased oversight of NIPS tests, including regarding labeling requirements, can help ensure such tests are appropriately labeled with transparent information regarding performance, clear instructions, and appropriate limitations.

A potentially unreliable, inaccurate, or misinterpreted test result imposes, at minimum, the monetary cost of the test to the patient or health care system payor and the burden of any resulting health consequences. We do not attempt to quantify any expected reduction in spending on these tests, but we note that the number of screening tests for microdeletions sold in 2020 was above 400,000, and patients or payors paid approximately an additional $654 for each expanded test.[43]

b. Reduction in Expenses from Lawsuits.

[41] Ibid.
[42] Ibid.
[43] Ibid.

Compliance with applicable legal requirements for IVDs offered as LDTs might also reduce the incidence of litigation related to problematic IVDs apart from that which stems directly from diagnostic error. We cannot quantify the welfare losses due to tort expenses that might be avoided by phasing out the general enforcement discretion approach for LDTs and do not include the avoidance of any such expenses in our estimate of benefits. However, we provide one case study concerning a COVID-19 test offered without emergency use authorization from FDA as an illustrative example.

On March 1st, 2022, Blue Cross and Blue Shield of Minnesota (Blue Cross or BCBSM) filed a lawsuit 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 (Ref. [51]). Blue Cross alleged violations of Minnesota consumer protection law, fraud, and ERISA violations. Among other issues, confusion between quality control processes specified by the test system manufacturer and the lab led GS Labs to issue a correspondence to patients about PCR tests that "inadvertently deviated from applicable laboratory standards for testing facilities" (Ref [52]). The case is currently ongoing (Refs. [51] and [53]).

In a 2022 report from the U.S. Chamber of Commerce Institute for Legal Reform (ILR), high costs in the tort system led 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%) (Ref. [54]). We assume that those total litigation and risk transfer costs are recaptured as savings when problems are prevented by compliance with applicable

requirements instead of corrected via litigation. In a $10 million dollar case, for example, litigation and risk transfer costs would be 47 percent of $10 million dollars or $4.7 million.

3. Summary of Benefits

Quantified health benefits include the avoidance of harms from diagnostic errors related to mortality (cancer and cardiovascular disease) and infections-related morbidity. Unquantified benefits include, among others, costs savings from avoiding payment for problematic IVDs, namely NIPS tests, and possible reduction in costs from lawsuits and reduction in costs to healthcare systems. We also note that we do not count individuals who may have contracted communicable infectious diseases from contact with patients relying on false results from problematic IVDs. We are not able to quantify the extent to which the phaseout policy might prevent the spread of communicable infectious diseases. Additionally, the phaseout policy might remove a disincentive for non-laboratory manufacturers, who do not have the benefit of enforcement discretion, to develop novel tests. These manufacturers may otherwise be discouraged from investing in novel tests due to the prospect of laboratory competitors offering IVDs as LDTs that claim to fulfill, equally effectively, the same needs without having to invest in meeting FDA requirements. This benefit would be distinct from avoiding patient harms by improving reliability in existing testing applications, since novel tests might offer new capabilities. We present total benefits and subtotal health and non-health benefits in Table 17.

Table 17. Total Undiscounted Benefits (Millions 2022$)

Health Benefits (VSLY 3%)		**Recurring Annual Benefits**		
Type	**Level**	Primary	Low	High
Cancer	Generalized	$616	$191	$1,800
Cardiovascular	Generalized	$5,430	$1,717	$15,580
Infections	Generalized	$176	$55	$502
Health Benefits (VSLY 7%)		**Recurring Annual Benefits**		
Type	**Level**	Primary	Low	High
Cancer	Generalized	$927	$287	$2,704

Cardiovascular	Generalized	$4,233	$1,328	$12,131
Infections	Generalized	$291	$91	$830
Total Sum of Benefits (VSLY 3%)		$6,223	$1,963	$17,881
Total Sum of Benefits (VSLY 7%)		$5,451	$1,705	$15,666

We expect benefits to begin to accrue two years after publication of the final phaseout policy, 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 final phaseout policy (year 3 to year 5). We also expect recurring benefits to begin to accrue at an incremental rate of 0%, 50%, 75%, and 100% for the first four years (Table 18).

Table 18. Undiscounted Potential Benefits Over Time (Primary Estimate in Millions 2022$, 20 years, 3% and 7%)

Stage	**Rate**		**Year**	**If VSLY based on 3% discounting**			**If VSLY based on 7% discounting**		
	One-time	**Recurring**		**One-time**	**Recurring**	**Total**	**One-time**	**Recurring**	**Total**
			1	$0	$0	$0	$0	$0	$0
1	0	0	2	$0	$0	$0	$0	$0	$0
2	1/3	1/2	3	$0	$3,111	$3,111	$0	$2,725	$2,725
3 & 4	1/3	3/4	4	$0	$3,151	$3,151	$0	$2,760	$2,760
4 & 5	1/3	1	5	$0	$4,420	$4,420	$0	$3,871	$3,871
	0	1	6	$0	$4,613	$4,613	$0	$4,041	$4,041
	:	:	:						
	0	1	20	$0	$5,899	$5,899	$0	$5,167	$5,167
Sum				$0	$91,718	$91,718	$0	$80,339	$80,339

However, as a result of exercising enforcement discretion with respect to premarket review and QS requirements, with the exception of requirements under 21 CFR 820, subpart M (Records), for currently-marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule, IVDs offered as LDTs will generally undergo review and comply with most QS requirements only in certain circumstances. However, FDA expects such IVDs offered as LDTs to be in compliance with other applicable requirements under the FD&C

Act and FDA regulations, including post market requirements, as discussed in the phaseout policy. We note that as described in section V.B.3 of the preamble, FDA intends to take targeted steps to address currently marketed IVDs offered as LDTs that are problematic. In particular, we intend to use available tools to identify and act against currently marketed IVDs offered as LDTs that specifically raise concerns, such as IVDs that are potentially inaccurate or poorly validated.

In order to account for this, we adjust estimated total benefits in each year—beginning with enforcement of QS and premarket review requirements—based on the proportions of IVDs falling within an enforcement discretion policy versus those that are not. IVDs falling within an enforcement discretion policy will not generally be expected to comply with premarket review and QS requirements (but will be expected to comply with all other applicable requirements as discussed in the phaseout policy). We thus assume that among patients using these IVDs, only half of the estimated potential benefits will be realized. The low and high benefits estimates reflect alternative assumptions that only 25% and 75% of benefits, respectively, will be realized among patients using IVDs falling within an enforcement discretion policy. In each year beginning with enforcement of QS and premarket review requirements in stage 3 and 4, we apply the following adjustment factor to estimated benefits:

$$adjustment = prop.of\ IVDs\ NOT\ falling\ within\ ED\ policy + 0.5 * prop.of\ IVDs\ falling\ within\ an\ ED\ policy$$

In Table 19, the resulting adjusted annualized benefit estimates using three and seven percent discounting are approximately $4.3 billion and $3.5 billion, respectively.

Table 19. Expected Benefits Over Time Accounting for Exercising Enforcement Discretion (Primary Estimate in Millions 2022$, 20 years)

Stage	Year	Proportions of IVDs by enforcement	c) Effect of ED	d) Adj. factor (= b + c*a)	Benefits (3% VSLY)	Benefits (7% VSLY)

		policy (premarket review and most QS requirements)		on benefits					
		a) With ED	b) Without ED			e) Without ED	With ED (=d*e)	f) Without ED	With ED (=d*f)
	1	0.918	0.082	0.5	0.541	$-	$-	$-	$-
1	2	0.818	0.182	0.5	0.591	$-	$-	$-	$-
2	3	0.729	0.271	0.5	0.636	$3,111	$3,111	$2,725	$2,725
3 & 4	4	0.650	0.350	0.5	0.675	$4,667	$3,151	$4,088	$2,760
4 & 5	5	0.580	0.420	0.5	0.710	$6,223	$4,420	$5,451	$3,871
	6	0.517	0.483	0.5	0.741	$6,223	$4,613	$5,451	$4,041
	7	0.462	0.538	0.5	0.769	$6,223	$4,786	$5,451	$4,192
	8	0.413	0.587	0.5	0.794	$6,223	$4,939	$5,451	$4,326
	9	0.369	0.631	0.5	0.816	$6,223	$5,075	$5,451	$4,446
	10	0.330	0.670	0.5	0.835	$6,223	$5,197	$5,451	$4,552
	11	0.295	0.705	0.5	0.853	$6,223	$5,305	$5,451	$4,647
	12	0.264	0.736	0.5	0.868	$6,223	$5,403	$5,451	$4,732
	13	0.236	0.764	0.5	0.882	$6,223	$5,490	$5,451	$4,808
	14	0.211	0.789	0.5	0.895	$6,223	$5,568	$5,451	$4,877
	15	0.188	0.812	0.5	0.906	$6,223	$5,638	$5,451	$4,938
	16	0.168	0.832	0.5	0.916	$6,223	$5,701	$5,451	$4,994
	17	0.149	0.851	0.5	0.925	$6,223	$5,758	$5,451	$5,044
	18	0.133	0.867	0.5	0.934	$6,223	$5,810	$5,451	$5,089
	19	0.118	0.882	0.5	0.941	$6,223	$5,856	$5,451	$5,130
	20	0.104	0.896	0.5	0.948	$6,223	$5,899	$5,451	$5,167
Sum						$107,344	$91,718	$94,026	$80,339
Present Value (Discount Rate matches VSLY)							$64,584		$37,177
Annualized Value (Discount Rate matches VSLY)							$4,341		$3,509

F. Costs

FDA is phasing out the general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs and be expected to meet applicable requirements. This phaseout is intended to help assure

the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance.

FDA intends that the phaseout of enforcement discretion will occur over a four-year period in five key stages as described in section V.C of the preamble. For a few categories of IVDs manufactured by laboratories, FDA is adopting enforcement discretion policies with respect to some or all applicable requirements as described in sections V.B and C of the preamble.

When calculating the costs associated with each stage of the phaseout policy described in the preamble, we use wage information from the Bureau of Labor Statistics Occupational Employment and Wage Statistics.[44] Specifically, we use wage information for a specific industry: medical and diagnostic laboratories.[45]

The remainder of this section discusses the estimated cost of the phaseout policy by stage of the phaseout policy.[46] Section II.F.6 discusses additional cost considerations that we do not quantify.

1. Costs Under Stage 1

Beginning 1 year after the publication date of this final rule, FDA will expect laboratories[47] to comply with MDR requirements (requirements for adverse event reporting)

[44] https://www.bls.gov/oes/current/naics4_621500.htm
[45] NAICS code: 621500
[46] We use several sources to estimate costs associated with the phaseout policy. We use input from ICR packages for correction and removal reporting under Stage 1, but we rely on other sources such as previous RIAs or ERG reports to estimate costs for the other requirements. A major distinction between regulatory impact analysis (RIA) and Information Collection Request (ICR) is that the RIA bases estimates on external factors as yet unknown to FDA while ICR captures real-time data of the elements prescribed in regulations. In addition, the RIA considers affected entities according to specific requirements of regulations while the ICR includes a broader range for the number of respondents. Our estimates, therefore, may be different from the ICR package estimates because the RIA estimates costs of the rule in a different way compared as the costs of burden in the ICR package.
[47] 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 phaseout policy.

under 21 U.S.C. 360i(a)-(c) and 21 CFR part 803, correction and removal reporting requirements under 21 U.S.C. 360i(g) and 21 CFR part 806, and QS requirements under § 820.198 (complaint files). During the first year following issuance of the final rule, laboratories will face costs associated with compliance with Stage 1, as well as costs associated with reading and understanding the rule in its entirety.

a. Reading and Understanding the Rule

We expect that laboratories affected by the phaseout policy 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,[48] we assume that the reading speed of reviewers ranges from 200 to 250 words per minute. The final rule has approximately 150,000 words. The overall burden in hours (per reader) to read the rule ranges from 10.00 hours (= (150,000 words / 250 words per minute) / 60 mins per hour) to 12.50 hours (= (150,000 words / 200 words per minute) / 60 mins per hour). The mean hourly wages for managers and lawyers in this industry are $57.60 and $80.30, respectively.[49] Fully loaded wage rates are $115.20 an hour for managers and $160.60 an hour for lawyers (average: $137.90).[50] We assume that one to three employees will read the rule. The estimated learning costs per entity would range from $1,379.00 (=10.00 hours x $137.90 per hour x 1 employee) to $5,171.25 (=12.50 hours x $137.90 per hour x 3 employees), with a primary cost of $3,064.44 (=11.11 hours x $137.90 per hour x 2 employees). Multiplying this estimate by the total numbers of affected laboratories per year yields a total one-time cost for

[48] https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis
[49] 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
[50] Fully-loaded wages account for employee benefits and overhead on top of the hourly wage, calculated by doubling the published wage rate.

reading the rule between $0.81 million and $12.21 million, with a primary estimate of $3.62 million. The estimated total recurring cost ranges from $0.07 million to $0.98 million, with a primary estimate of $0.29 million (see Table 20).

Table 20. Costs of Reading and Understanding the Rule

	Primary	Low	High
Average reading speed (words/minute)	225	250	200
Length of preamble & codified (words)	150,000	150,000	150,000
Hours	11.11	10.00	12.50
Number of employees to read rule	2	1	3
Labor cost of hourly employee	$137.90	$137.90	$137.90
Per-laboratory cost	$3,064.44	$1,379.00	$5,171.25
Number of affected laboratories	1,181	590	2,362
Number of new laboratories per year	94	47	189
Total One-time Costs (millions)	**$3.62**	**$0.81**	**$12.21**
Total Recurring Costs (millions)	**$0.29**	**$0.07**	**$0.98**

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

b. Medical Device Reporting

Under Stage 1, FDA expects 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. [55]). We expect that laboratories will 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 establish standard operating procedures (SOPs) in response to the MDR requirements. We estimate it will take 1 – 3 management employees with an hourly wage of $61.36 ($122.72 fully-loaded) 8 – 12 hours each to establish a laboratory's SOP and

train the appropriate people on the new procedures. Multiplying these estimates, we estimate the one-time costs of modifying SOPs to be between $0.58 million and $10.43 million, with a primary estimate of $2.90 million. We estimate the recurring costs to range from $0.05 million to $0.83 million, with a primary estimate of $0.23 million. See Table 21.

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 $79.72 ($159.44 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 $4.52 million and $21.09 million, with a primary estimate of $9.79 million. We estimate the recurring costs to be between $0.36 million to $1.69 million, with a primary estimate of $0.78 million.

We expect 0.6% of covered laboratories to establish Health Level Seven (HL7) Individual Case Study Report (ICSR) capability (Ref. [55]).[51] We expect this task to take a single computer and information system manager 48 to 52 hours, working at an hourly wage of $79.72 ($159.44 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 $0.12 million, with a primary estimate of $0.06 million. We estimate the recurring costs to be between $0.002 million to $0.01 million, with a primary estimate of $0.005 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,

[51] We divide the number of entities that would use the HL7ICSR (125 entities) by 20,100 medical device manufacturers and importers covered by the MDR regulation.

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 a recurring cost associated with filing and submitting MDRs. We estimate it will take computer and information system managers 430 hours,[52] working with an hourly wage of $79.72 ($159.44 fully loaded). Multiplying by the number of affected entities, we estimate this recurring cost to range from $40.47 million to $161.88 million, with a primary estimate of $80.94 million.

Overall, we expect the total one-time costs for complying with MDR requirements in Stage 1 of the phaseout policy to range from $5.36 million to $32.57 million, with a primary estimate of $13.21 million. The estimated total recurring costs range from $40.91 million to $164.55 million, with a primary estimate of $82.03 million. See Table 21.

Table 21. Costs of Medical Device Reporting

		Primary	Low	High
One-time/Annual				
Establish SOPs	Hours	10	8	12
	Wage	$122.72	$122.72	$122.72
	Employees	2	1	3

[52] We use annual reporting and record keeping burdens from a prior analysis of medical device reporting. In particular, we use the total number of hours associated with creating a medical device report, multiplied by the average number of reports per respondent (Ref. [55]). We assume that each affected laboratory will list an average number of 67 product listings, an average number of 2 modified product listings, and an average number of 6 new product listings per year, based on our estimates discussed in section II.D.1. We also assume 1.4 MDRs per listing.

	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$2.90*	*$0.58*	*$10.43*
	Recurring Subtotal (millions)	*$0.23*	*$0.05*	*$0.83*
Install and Validate e-Submitter Software	Hours	52	48	56
	Wage	$159.44	$159.44	$159.44
	Employees	1	1	1
	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$9.79*	*$4.52*	*$21.09*
	Recurring Subtotal (millions)	*$0.78*	*$0.36*	*$1.69*
Establish HL7ICSR capability	Hours	50	48	52
	Wage	$159.44	$159.44	$159.44
	Employees	1	1	1
	Entities affected	7	4	14
	New entities per year	1	0	1
	One-time Subtotal (millions)	*$0.06*	*$0.03*	*$0.12*
	Recurring Subtotal (millions)	*$0.005*	*$0.002*	*$0.01*
Acquiring e-Certificate	Search cost	$20.00	$20.00	$20.00
	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	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	1,181	590	2,362
	Recurring Subtotal (millions)	*$0.01*	*$0.01*	*$0.02*
Filing and submitting MDRs	Hours	430	430	430
	Wage	$159.44	$159.44	$159.44
	Entities affected	1,181	590	2,362
	Recurring Subtotal (millions)	*$80.94*	*$40.47*	*$161.88*
Total One-time Costs (millions)		**$13.21**	**$5.36**	**$32.57**
Total Recurring Costs (millions)		**$82.03**	**$40.91**	**$164.55**

Notes: Total one-time and recurring costs include both costs to industry and FDA. See section II.G for FDA review costs of MDRs.

c. Correction and Removal Reporting

Under Stage 1, FDA expects laboratories to comply with correction and removal reporting requirements 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 2023 FDA notice: *Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals* (Ref. [56]).[53] 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 (Ref. [56]).[54] 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 $0.01 million to $0.06 million, with a primary estimate of $0.03 million. Multiplying by the number of new entities per year, we expect a recurring cost of purchasing a digital verification certificate to range from $1,181 to $4,723, with a primary estimate of $2,362.

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 $57.60 ($115.20 fully-loaded) 10 hours to create a single correction and removal report. The 2023 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. In

[53] The ICR package of corrections and removals (OMB control number 0910-0359) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202309-0910-003

[54] We expect that the other 50% of laboratories not using the electronic submission gateway (ESG) would either already have a digital certificate from previous submission or will submit reports of corrections and removals to FDA via mail or email. Specifically, up to 45% will submit using a digital certificate that they already purchased or via email and about 5% of laboratories will submit their reports via mail or email. The burden will be lower for those already purchased the ESG and the burden may be higher for those submitting via mail or email. Due to lack of data, we are unable to quantify the costs for those not using the ESG that we may underestimate the costs of correction and removal reporting affected by this phaseout policy.

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.[55] 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 $0.07 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 phaseout policy to range between $0.01 million to $0.06 million, with a primary estimate of $0.03 million. The estimated total recurring costs range from $0.08 million to $0.30 million, with a primary estimate of $0.15 million. See Table 22.

Table 22. 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	590	295	1,181
	New entities per year	47	24	94
	One-time Subtotal (millions)	*$0.03*	*$0.01*	*$0.06*
	Recurring Subtotal	*$2,362*	*$1,181*	*$4,723*
Recurring Annual				
Reporting	Hours per report	10	10	10
	Number of reports per entity	0.11	0.11	0.11
	Wage	$115.20	$115.20	$115.20
	Entities affected	1,181	590	2,362
	Recurring Subtotal (millions)	*$0.15*	*$0.07*	*$0.30*
Total One-time Costs (millions)		**$0.03**	**$0.01**	**$0.06**
Total Recurring Costs (millions)		**$0.15**	**$0.08**	**$0.30**

[55] 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

d. Complaint Files

Under Stage 1, FDA will expect laboratories to comply with quality system (QS) requirements under 21 CFR part 820.198 (complaint files).[56] In estimating the costs of complaint files, we use number of annual labor hours and proportion of types of labor (from vice president to clerical staff) needed to comply with complaint file requirements (Ref. [57]).[57] We also use wage rates to estimate costs for affected entities (see Table 27). We multiply the labor hours by appropriate wage rates and number of affected entities to estimate costs of complaint files. The estimated total one-time costs for complaint files range from $0.60 million to $6.04 million, with a primary estimate of $2.11 million. The estimated total recurring costs range from $0.01 million to $0.05 million, with a primary estimate of $0.02 million.

Table 23. Costs of Complaint Files

		Primary	Low	High
One-time				
820.198 Complaint files	Hours	14	8	20
Entities affected		1,181	590	2,362
Recurring Annual				
820.198 Complaint files	Hours	2	1	2
New entities per year		94	47	189
Total One-time Costs (millions)		**$2.11**	**$0.60**	**$6.04**
Total Recurring Costs (millions)		**$0.02**	**$0.01**	**$0.05**

2. Costs Under Stage 2

Under Stage 2, FDA will expect that laboratories comply with requirements not covered during other stages of the phaseout policy beginning 2 years after the publication of the phaseout policy. These requirements include registration and listing requirements (21 U.S.C. 360 and 21

[56] The ICR package of QS regulation (OMB control number 0910-0073) is available at: https://www.reginfo.gov/public/do/PRAViewDocument?ref_nbr=202309-0910-003

[57] We assume half of the labor hours would be for complaint files and the other half of the labor hours would be for other activities under subpart M.

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).[58]

a. Registration and Listing

Under Stage 2, FDA expects 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. [58]).[59] We anticipate one-time costs associated with registration and listing requirements and recurring costs associated with re-registration.

We expect the registration and listing will take a general/operations manager 3 hours, working at a wage of $57.60 ($115.20 fully loaded), to complete registration for a single establishment and to list that establishment's IVDs offered as LDTs.[60] We also expect that annual re-registration and listing updates will 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 $0.20 million and $0.82 million, with a

[58] 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 would only be triggered under certain circumstances. Therefore, the costs are likely to be minimal compared to the costs for compliance with the requirements listed below. In addition, if requirements listed below are appropriately satisfied, these other requirements generally should not become applicable.

[59] The ICR package of registration and listing (OMB control number 0910-0625) is available at: https://www.reginfo.gov/public/do/PRAViewDocument?ref_nbr=202206-0910-003

[60] 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.

primary estimate of $0.41 million. The estimated total recurring costs range from $0.08 million to $0.34 million, with a primary estimate of $0.17 million. See Table 24.

Table 24. 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	$115.20	$115.20	$115.20
	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$0.41*	*$0.20*	*$0.82*
	Recurring Subtotal (millions)	*$0.03*	*$0.02*	*$0.07*
Recurring Annual				
Re-registration	Hours	1	1	1
	Wage	$115.20	$115.20	$115.20
	Entities affected	1,181	590	2,362
	Recurring Subtotal (millions)	*$0.14*	*$0.07*	*$0.28*
Total One-time Costs (millions)		**$0.41**	**$0.20**	**$0.82**
Total Recurring Costs (millions)		**$0.17**	**$0.08**	**$0.34**

b. Labeling

Under Stage 2, FDA expects 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 $57.60 ($115.20 fully-loaded), [61] 8 to 54 hours (with a primary estimate of 31 hours) for regulatory affairs personnel and production personnel per laboratory to redesign existing labeling for IVDs offered as LDTs to comply with labeling requirements (Ref. [59]).[62] Manufacturers would spend

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

[62] The ICR package of medical device labeling requirements (OMB control number 0910-0485) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202308-0910-004

these hours to revise the labeling, including among other things, to perform internal review of the new content, to prepare and proofread new artwork, to replace labeling in the production system, and to submit the file to the agency. Multiplying by the number of expected entities, we expect the one-time cost of revising existing labeling to range between $0.54 million and $14.69 million, with a primary estimate of $4.22 million.[63] Multiplying the estimates by the number of new entities per year, we expect the recurring cost to range between $0.04 million to $1.18 million, with a primary estimate of $0.34 million. See Table 25.

Table 25. Costs of Labeling

		Primary	Low	High
Revise existing labeling	Hours	31	8	54
	Wage	$115.20	$115.20	$115.20
	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$4.22*	*$0.54*	*$14.69*
	Recurring Subtotal (millions)	*$0.34*	*$0.04*	*$1.18*
Total One-time Costs (millions)		**$4.22**	**$0.54**	**$14.69**
Total Recurring Costs (millions)		**$0.34**	**$0.04**	**$1.18**

c. Investigational Use Requirements

Under Stage 2, FDA expects laboratories to comply with investigational use requirements under 21 U.S.C. 360j(g) and 21 CFR part 812. Investigational medical devices (i.e., that are the object of a clinical investigation or research involving one or more subjects to determine device safety and/or effectiveness) that have an approved investigational device exemption (IDE) application, that are considered to have an approved IDE under 21 CFR part 812.2(b), or that are exempt from most of the requirements in 21 CFR part 812 under 21 CFR 812.2(c), are

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

exempted from various other requirements under the FD&C Act and FDA's regulations, such as premarket approval. 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.[64]

We expect the cost of developing an IDE application for an IVD offered as an LDT to be $48,000 (Ref. [60])[65].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. [28]). NYSDOH receives IVD submission packages for IVDs offered as LDTs that are not "designated as FDA-cleared, approved, or exempt," (Ref. [29]) 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.[66] 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

[64] The ICR package of investigational device exemptions (OMB control number 0910-0078) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202210-0910-013

[65] 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. These costs may be overestimated as the cited source reflects costs of IDE applications for all devices.

[66] Investigations of certain categories of devices are exempt from most requirements in 21 CFR part 812. 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).

offered as LDTs that would later be subject to premarket review would first submit an IDE application. We estimate that 50% of IVDs are exempt from premarket notification and 50% 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.

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 $2.56 million and $10.25 million, with a primary estimate of $5.13 million. Table 26 shows the estimated annual costs, which range from $6.20 million to $24.79 million, with a primary estimate of $12.40 million.

Table 26. Costs of Complying with Investigational Use Requirements

		Primary	Low	High
One-time				
Total cost of preparing/	Inflation-adjusted estimate from literature	$48,000	$48,000	$48,000

submitting IDE	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	79,114	39,557	158,227
	One-time Subtotal (millions)	*$5.13*	*$2.56*	*$10.25*
Annual				
Total cost of preparing/ submitting IDE	Inflation-adjusted estimate from literature	$48,000	$48,000	$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	7,652	3,826	15,303
	Annual Subtotal (millions)	*$12.40*	*$6.20*	*$24.79*
Total One-time Costs (millions)		**$7.45**	**$3.73**	**$14.90**
Total Annual Costs (millions)		**$18.02**	**$9.01**	**$36.03**

Notes: Total one-time and recurring costs include both costs to industry and FDA. See section II.G for FDA review costs of IDEs.

3. Costs Under Stage 3

Beginning 3 years after the publication of this final rule, FDA will expect compliance with the device current good manufacturing practices (CGMP) requirements of the QS requirements under 21 U.S.C. 360j(f) and 21 CFR part 820 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1).

However, for LDTs, FDA expects compliance with some, but not all, of the QS requirements. As described in section V.C.3 of the preamble, for these LDTs, FDA expects 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 (including requirements regarding complaint files under 21 CFR 820.198, for which FDA expects compliance during stage 1 of the phaseout policy).

As further described in section V.C.3 of the preamble, for IVDs that are within the scope of the phaseout policy but for which all manufacturing activities do not occur within a single laboratory, or which are transferred outside of that single laboratory, FDA also expects compliance with the other QS requirements under 21 U.S.C. 360j(f) and 21 CFR part 820. We lack evidence to quantify the numbers of such IVDs. To account for uncertainty, we consider different assumptions for low, primary, and high estimates. To estimate a lower bound estimate, we first assume that for all IVDs within the scope of the phaseout policy, all manufacturing activities occur within a single laboratory and, therefore, have zero costs associated with the QS requirements other than those listed above. 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 phaseout policy and, therefore, have costs associated with all QS requirements. Since we expect there to be a mix of these two extremes within the scope of the phaseout policy, we use an average of the lower and upper bound estimates for our primary estimate.

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 27).[67] Table 28 shows the number of labor hours for compliance with each provision of Part 820 (Ref. [57]). 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.[68]

Since FDA generally intends to exercise enforcement discretion with respect to QS requirements (other than requirements regarding records) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in the preamble, we anticipate one-time costs of compliance with records requirements other than complaint files from existing IVDs offered as LDTs and recurring costs from new IVDs offered as LDTs under this stage. In addition, we estimate that the number of affected entities for Stage 3 is lower than Stages 1 and 2 as FDA intends to exercise enforcement discretion with respect to QS requirements (other than requirements regarding records) for LDTs manufactured and performed by a laboratory integrated within a health care system to meet an unmet need of patients receiving care within the same healthcare system. Further, it is our understanding, based on consultation with NYS CLEP, that compliance with NYS CLEP's clinical laboratory standards (which exceed CLIA requirements in certain respects) and its premarket review requirements collectively could generally satisfy these subparts of the QS regulations except as to certain aspects of design control documentation. Therefore, FDA does not anticipate significant additional burden with respect to compliance with these QS requirements for laboratories offering LDTs approved by NYS CLEP. As discussed in appendix A, we estimate 12.1 percent of new premarket submissions for affected tests will be

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

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

reviewed by NYS CLEP. For the purpose of estimating costs associated with compliance with Quality System requirements, we extrapolate this to the affected laboratories, estimating that 12.1 percent of affected laboratories (1,181) will have their LDTs reviewed by NYS CLEP. We also estimate that 40 to 70 percent of LDTs from the high complexity laboratories integrated within health care systems (459) are likely to be for unmet needs. We therefore estimate the affected laboratories incurring costs under Stage 3 to be 786 (=1,181 – 1,181*0.121 – 459*0.55).

We expect the total one-time costs for QS requirement (records other than complaint files under 21 CFR 820.198) in Stage 3 of the phaseout policy to range from $0.40 million to $4.02 million, with a primary estimate of $1.41 million. The total recurring costs are estimated to range from $1.94 million to $124.01 million, with a primary estimate of $24.66 million. See Table 28.

Table 27. Medical and Diagnostic Laboratories Industry Wage Rates for Selected Labor Categories

Labor Category	Wages (/hour)	NAICS	OCC Code
Vice president	$59.68	621500	11-1000
Upper management	$76.38	621500	11-2000
Middle management	$66.83	621500	11-3000
Technical	$30.36	621500	29-0000
Admin support	$32.67	621500	43-6011
Clerical	$18.37	621500	43-4000

Table 28. 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 Complaint Files	Hours	14	8	20
Entities affected		786	393	1,571
New entities per year		63	31	126
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 Complaint Files	Hours	2	1	2
New entities per year		63	31	126
Total One-time Costs (millions)		**$1.41**	**$0.40**	**$4.02**
Total Recurring Costs (millions)		**$24.66**	**$1.94**	**$124.01**

We note that on February 2, 2024, FDA issued a final rule amending the device QS regulation, part 820, to align more closely with international consensus standards for devices (87 FR 10119). Specifically, FDA withdrew the majority of the current requirements in part 820 and instead incorporated 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 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 the regulations promulgated through that rulemaking.

The amended QS requirements will take effect on February 2, 2026, before the 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 expects compliance with the QS requirements that are in effect at that time.[69] For further information on the QS requirements established pursuant to the amendments to the QS regulation, please refer to 89 FR 7496. Notably, the requirements relating to design controls, purchasing controls, acceptance activities, CAPA, and

[69] As noted in the preamble, FDA intends to phase out the general enforcement discretion approach with respect to requirements under 21 CFR 820.198 (complaint files) during stage 1 of the phaseout policy. However, upon the start of stage 1, and prior to the effective date of the amended QS regulation, FDA intends to exercise enforcement discretion and generally not enforce requirements under 21 CFR 820.198 for laboratories that are in compliance with Subclause 8.2.2 of ISO 13485. Following the effective date of the amended QS regulation (February 2, 2026), laboratories must comply with the QS requirements that are in effect at that time.

records requirements are set forth in the following ISO 13485 clauses as modified by the 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 8.2.2, Subclause 8.2.5, Subclause 8.2.6, and Subclause 8.3.

To the extent amended QS requirements are in effect, we do not expect the total costs for compliance with QS requirements in Stage 3 to substantially change (89 FR 7496, February 2, 2024).

4. Costs Under Stages 4 and 5

Beginning 3½ years after the publication of this final rule, FDA will expect laboratories to comply with premarket review requirements for high-risk IVDs offered as LDTs (21 U.S.C. 360e and 21 CFR part 814). Laboratories will face costs of preparing and submitting premarket approval (PMA) applications and PMA supplements as well as greater annual reporting burdens associated with premarket approval. FDA will 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 will be expected to comply with 510(k) requirements or De Novo requirements beginning 4 years after the publication of the

phaseout policy. Under this stage, we anticipate costs associated with preparing and submitting 510(k) premarket notifications or De Novo classification requests, and FDA review costs.

FDA generally intends to continue to exercise enforcement discretion with respect to premarket review for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in the preamble. FDA also generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs that receive approval through NYS CLEP. In addition, FDA generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

a. Number of Premarket Submissions

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 offers 67 IVDs as LDTs and will offer 6 new IVDs as LDTs per year. Of the 67 IVDs as LDTs currently offered per laboratory, we assume that, on average, two will be modified in such a way as to require premarket review per year until they all are FDA authorized. As mentioned above, FDA

generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the health care system. We therefore exclude the number of LDTs from high complexity laboratories integrated within healthcare systems that are likely to be for such unmet needs. We also exclude premarket reviews for LDTs that receive approval through NYS CLEP. In addition, on January 31, 2024, FDA announced its intent to initiate the reclassification process for most IVDs that are currently class III into class II and, therefore, considered the impact of this reclassification process on our estimates of premarket submissions, reducing the number of expected PMAs and increasing the number of expected De Novos and 510(k)s. We explain details of the calculations in appendix A and Table 29.

Because FDA generally intends to exercise enforcement discretion with respect to premarket review for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in the preamble, we only include costs from modified and new IVDs offered as LDTs under Stages 4 and 5.

Table 29. Number of Premarket Submissions Under Stage 4 and Stage 5

	Primary	Low	High
PMA	101	51	203
PMA supplements	31	15	61
510(k) Total	2,179	1,090	4,359
510(k) with method comparison study	1,286	643	2,572
510(k) with moderately complex clinical study	894	447	1,787
De Novo	267	134	534
Total number of new premarket submissions per year for affected tests	**2,578**	**1,289**	**5,157**

Notes: The numbers of tests include currently marketed tests that would be modified per year and new tests from both affected labs and new labs entering the market per year.

b. 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 Eastern Research Group (ERG) (Ref. [61]) [70]. 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.[71]

Devices subject to premarket approval typically require premarket and post-market procedures that are not typically associated with 510(k) clearance, such as premarket 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, such as for 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. [61]). 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

[70] Another study by ERG used the same source for an analytical framework for examining the value of antibacterial products: https://aspe.hhs.gov/reports/analytical-framework-examining-value-antibacterial-products-0.
[71] We may under- or over-estimate the costs of premarket preparation since the estimates by ERG are not specific to IVDs. We have revised some of the estimates based on FDA professional judgement and historical knowledge.

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 $4.10 million to $9.29 million, with a primary estimate of $4.36 million. Multiplying the estimates by the numbers of new IVDs per year and IVDs from new entities per year that are subject to premarket approval, excluding those that would be under enforcement discretion policies, we expect recurring cost of submission and preparation for PMAs to range from $207.60 million to $1,881.11 million, with a primary estimate of $441.47 million.

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. [62]) to estimate the recurring preparation cost.[72] The current estimate after adjustment for inflation is $11,798 per PMA. Multiplying the estimates by the numbers of PMA submissions per year, we expect total recurring costs of PMA annual reporting requirements to range from $0.60 million to $2.39 million, with a primary estimate of $1.19 million.

Overall, we estimate the total recurring costs to industry of PMA requirements in Stage 4 to range between $208.20 million and $1,883.50 million, with a primary estimate of $442.67 million. See Table 30.

Table 30. Costs to Industry of Premarket Approval Application

	Primary	Low	High
Cost of Submission and Preparation			

[72] The ICR package of premarket approval of medical devices (OMB control number 0910-0231) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202211-0910-010

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
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	*$4,359,857*	*$4,100,439*	*$9,288,800*
No. PMA submissions per year for affected tests	101	51	203
*Recurring Subtotal (millions)**	*$441.47*	*$207.60*	*$1,881.11*
Recurring Annual			
Annual Report preparation for existing PMAs	$11,798	$11,798	$11,798
No. PMA submissions per year for affected tests	101	51	203
*Recurring Subtotal (millions)**	*$1.19*	*$0.60*	*$2.39*
Total Recurring Costs (millions)	**$442.67**	**$208.20**	**$1,883.50**

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 numbers of PMA submissions per year include currently marketed tests that would be modified per year and new tests from both affected entities currently on the market and new entities entering the market per year. Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of Q-submissions and PMAs.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

Some IVDs with PMAs might require a PMA supplement under 21 CFR 814.39 when certain modifications are made.[73] There are several types of PMA supplements (see Table 31; 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 supplements per PMA[74] and the share of supplements by supplement type.[75] We also multiply by the Remaining PMA Rate (Table A.4, Column F) to adjust for potential

[73] 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.
[74] 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.
[75] We use the FDA internal information on the total number of supplement submissions received by FDA from 2017 to 2023, as of July 2023.

reclassification of Class III IVDs into Class II IVDs. We assume that entities would submit PMA supplements in year 4. See Table 31 for the expected number of annual 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[76] 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 $6.28 million to $56.89 million, with a primary estimate of $13.35 million. See Table 32.

Table 31. Number of PMA Supplements by Submission Type

Submission Type	Cumulative share of supplements by type	Primary	Low	High
135 Review Track	0.053	2	1	5
Normal 180-day track	0.205	5	3	11
Normal 180-day track - No user fee	0.128	4	2	7
Panel-Track	0.067	2	1	4
Real-Time Process	0.374	14	7	28
Special CBE	0.095	4	2	7

Table 32. Costs to Industry of PMA Supplements

Submission Type	Adjusted FTE weights over PMA	Primary	Low	High
135 Review Track	0.033	$0.42	$0.20	$1.79
Normal 180-day track	0.033	$0.98	$0.46	$4.18
Normal 180-day track - No user fee	0.033	$0.67	$0.32	$2.88
Panel Track	1.000	$9.85	$4.63	$41.98
Real Time Process	0.010	$0.79	$0.37	$3.35
Special CBE	0.033	$0.64	$0.30	$2.71
Total Recurring Costs (millions)		**$13.35**	**$6.28**	**$56.89**

Note: Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of PMA supplements.

[76] This cost reflects hours spent in CDRH substantive review of devices, required to determine whether they meet the standard to be approved. 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.

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.[77] We use the ERG estimates of 510(k) with small or simple clinical trials for 510(k) submissions with method comparison studies (see Table 33) (Ref. [61]). We use the ERG estimates of 510(k) with moderately complex clinical trials for 510(k) submissions with moderately complex clinical studies (see Table 34).[78]

For any 510(k) submission (or De Novo request[79]), we expect it will take one operations specialist manager, working at a wage of $66.83 ($133.66 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 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 $215,457 to $279,157, with a primary estimate of $247,307.

FDA also anticipates that laboratories may seek to utilize FDA's 510(k) Third Party Review Program. Multiple Third Party Review Organizations (3P510k Review Organizations) are accredited to conduct reviews of 510(k) submissions for certain IVDs. Manufacturers who submit to 3P510k Review Organizations pay the 3P510k Review Organization but do not pay FDA user fees for those submissions. Each 3P510k Review Organizations sets their own rates, which are generally comparable to FDA user fees. Due to lack of data, we assume that

[77] The ICR package of premarket notification submission 510(k) (OMB control number 0910-0120) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202308-0910-018
The ICR package of De Novo classification process (OMB control number 0910-0844) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202111-0910-009

[78] Distinctions of the estimates used in Table 33 and Table 34 are based on the type of study supporting clinical validation of these tests due to differing costs.

[79] In the absence of more detailed information on De Novo costs, we extrapolate 510(k) costs to estimate De Novo costs.

laboratories will pay the same amount of FDA user fees to 3P510k Review Organizations. FDA assumes that at least 50% of the IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the 510(k) Third Party Review Program.

Multiplying by the numbers of modified and new IVDs per year and IVDs from new entities that are subject to 510(k) with method comparison studies, excluding those that would be under enforcement discretion policies per year yields the recurring submission and preparation costs for 510(k)s with method comparison studies is estimated between $142.10 million and $732.21 million, with a primary estimate of $325.15 million. See Table 33.

Table 33. Costs to Industry of 510(k)s (Method Comparison Study)

	Primary	Low	High
Cost of Submission and Preparation			
Identify predicate device			
Hours	1.5	1	2
Wage	$133.66	$133.66	$133.66
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
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	*$247,307*	*$215,457*	*$279,157*
No. 510(k) submissions with method comparison study per year for affected tests	1,286	643	2,572
Subtotal (millions)	*$317.98*	*$138.52*	*$717.87*
Fees to 3P510k Review Organizations			
MDUFA Review Fee (Adjusted fee for small entities)	$21,760 ($5,440)	$21,760 ($5,440)	$21,760 ($5,440)
IVDs Affected, non-small*	225	113	450
IVDs affected, small*	418	209	836
Subtotal (millions)	*$7.17*	*$3.58*	*$14.34*
Total Recurring Costs (millions)*	**$325.15**	**$142.10**	**$732.21**

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 numbers of 510(k) submissions per year include currently marketed tests that would be modified and new tests from both affected entities currently on the market and new entities

entering the market per year. Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of Q-submissions and 510(k) submissions.
**We calculate subtotals by multiplying the subtotal cost per submission by the number of affected IVDs.*

Table 34 presents costs of 510(k) submissions with a moderately complex clinical study. We calculate the costs using the exact same methods as in Table 33. The estimated subtotal cost of submission and preparation per submission ranges from $466,709 to $530,410, with a primary estimate of $498,560. Multiplying the estimates by the numbers of modified and new IVDs per year and IVDs from new entities per year that are subject to 510(k) with moderately complex clinical studies, excluding those that would be under enforcement discretion policies, we expect recurring submission and preparation cost to range from $211.00 million to $957.82 million, with a primary estimate of $450.45 million.

Table 34. Costs to Industry 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	$133.66	$133.66	$133.66
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
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	*$498,560*	*$466,709*	*$530,410*
No. 510(k) submissions with moderately complex clinical study per year	894	447	1,787
Subtotal (millions)	*$445.47*	*$208.51*	*$947.86*
Fees to 3P510k Review Organizations			
MDUFA Review (Adjusted fee for small entities)	$21,760 ($5,440)	$21,760 ($5,440)	$21,760 ($5,440)
IVDs Affected, non-small*	156	78	313
IVDs affected, small*	290	145	581

Subtotal (millions)	*$4.98*	*$2.49*	*$9.96*
Total Recurring Costs (millions)*	**$450.45**	**$211.00**	**$957.82**

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 numbers of 510(k) submissions per year include currently marketed tests that would be modified and new tests from both affected entities currently on the market and new entities entering the market per year. Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of Q-submissions and 510(k) submissions.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

Table 35 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. [61]).[80] 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 34. The estimated subtotal cost of submission and preparation per submission ranges from $216,211 to $530,410, with a primary estimate of $527,202. Multiplying the estimates by the numbers of modified and new IVDs per year and IVDs from new entities per year that are subject to De Novo, excluding those that would be under enforcement discretion policies, we expect recurring submission and preparation cost to range from $28.88 million to $283.39 million, with a primary estimate of $140.84 million.

Table 35. Costs to Industry 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	$133.66	$133.66	$133.66
Develop necessary SOPs	$37,688	$37,688	$37,688
Hold pre-submission meeting with FDA	$2,513	$2,513	$2,513

[80] 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.

Prepare indications for use	$25,125	$25,125	$25,125
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	*$527,202*	*$216,211*	*$530,410*
No. De Novo submissions per year for affected tests	267	134	534
Total Recurring Costs (millions)*	**$140.84**	**$28.88**	**$283.39**

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 numbers of De Novo submissions per year include currently marketed tests that would be modified and new tests from both affected entities currently on the market and new entities entering the market per year. Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of Q-submissions and De Novo requests.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

5. Summary of Costs

Table 36 summarizes our estimates of the one-time and recurring costs by stage of the phaseout policy. These include costs to FDA and costs to industry. We estimate the total one-time costs to range between $11.67 million and $85.30 million, with a primary estimate of $32.45 million. We estimate the total recurring costs to range between $0.72 billion and $4.54 billion, with a primary estimate of $1.65 billion.

Table 36. Total Costs to FDA and Industry (millions 2022$)

		Primary	Low	High
One-time				
Stage 1	Reading and Understanding the Rule	$3.62	$0.81	$12.21
	Medical Device Reporting	$13.21	$5.36	$32.57
	Correction and Removal Reporting	$0.03	$0.01	$0.06
	Complaint Records	$2.11	$0.60	$6.04
Stage 2	Registration and Listing Requirements	$0.41	$0.20	$0.82
	Labeling Requirements	$4.22	$0.54	$14.69
	Investigational Use Requirements	$7.45	$3.73	$14.90
Stage 3	Quality System Requirements	$1.41	$0.40	$4.02
Total One-time Costs (millions)		**$32.45**	**$11.67**	**$85.30**
Recurring Annual				

Stage 1	Reading and Understanding the Rule	$0.29	$0.07	$0.98
	Medical Device Reporting	$82.03	$40.91	$164.55
	Correction and Removal Reporting	$0.15	$0.08	$0.30
	Complaint Records	$0.02	$0.01	$0.05
Stage 2	Registration and Listing Requirements	$0.17	$0.08	$0.34
	Labeling Requirements	$0.34	$0.04	$1.18
	Investigational Use Requirements	$18.02	$9.01	$36.03
Stage 3	Quality System Requirements	$24.66	$1.94	$124.01
Stage 4	Premarket Approval Application	$503.91	$238.82	$2,005.97
	Premarket Approval Application Supplements	$14.76	$6.98	$59.71
Stage 5	510(k) Submission	$825.47	$378.03	$1,789.77
	De Novo Classification Request	$177.50	$47.21	$356.72
Total Recurring Costs (millions)		**$1,647.32**	**$723.18**	**$4,539.61**

Notes: The estimated costs include both costs to industry and FDA. The MDRs review costs for stage 1, the IDEs review costs for stage 2, and the Q-submission and premarket review costs to FDA for stages 4 and 5 are reported in section II.G.

Table 37 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, correction and removal reporting, and complaint records 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 $47.85 million to $216.75 million, with a primary estimate of $101.46 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 $54.67 million to $233.83 million, with a primary estimate of $113.09 million.

In the third year after publication of the final rule, we expect that costs for Stage 3 associated with Quality System requirements except for complaint files 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 $175.44 million to $1.36 billion, with a primary estimate of $386.41 million.

In subsequent years, we expect that costs for Stages 4 and 5 associated with PMAs, PMA supplements, 510(k) submissions or De Novo classification requests would occur. The recurring cost for year 4 to year 20 is estimated to range between $723.18 million and $4.54 billion, with a primary estimate of $1.65 billion. We estimate the total costs over 20 years to range from $12.57 billion to $78.99 billion, with a primary estimate of $28.61 billion.

The present value of total estimated costs is $20.41 billion at a 3 percent discount rate and $13.64 billion at a 7 percent discount rate over 20 years. The annualized value of costs is $1.37 billion at a 3 percent discount rate and $1.29 billion at a 7 percent discount rate.

Table 37. Twenty-Year Timing of the Costs (millions 2022$)

	Primary	Low	High
Year 1	$101.46	$47.85	$216.75
Year 2	$113.09	$54.67	$233.83
Year 3	$386.41	$175.44	$1,364.29
Year 4-20 (costs for each year)	$1,647.32	$723.18	$4,539.61
Total Costs	$28,605.32	$12,571.97	$78,988.22
Present Value of Total Costs (3%)	$20,407.00	$8,972.00	$56,376.49
Present Value of Total Costs (7%)	$13,637.63	$5,999.18	$37,699.79
Annualized Value of Costs (3%)	**$1,371.67**	**$603.06**	**$3,789.39**
Annualized Value of Costs (7%)	**$1,287.30**	**$566.28**	**$3,558.59**

6. Other Unquantified Costs

Other unquantified social costs associated with the phaseout policy (or consequences of the costs that have been quantified) may include the impact on prices, access to diagnostics if many laboratories exit the market or discontinue offering certain IVDs rather than incur the costs of compliance with FDA requirements, and/or a decrease in the number of new LDTs due to the

increased operation costs of the phaseout policy. 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 information on the revenues or costs of production 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.

Our analysis in section III (Final small entity analysis) shows that 22% of estimated receipts from IVDs offered as LDTs 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, the enforcement discretion policies discussed here -and in the preamble- make it less likely that these smaller laboratories would reduce operations or exit the market.

However, to the extent that some small laboratories might reduce operations or exit the market, it is possible that larger laboratories might take over the production of certain IVDs offered as LDTs, reducing potential impacts on IVD availability. This might concentrate production in 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 might pass the costs of compliance to their customers by raising prices for IVDs offered as LDTs, increased FDA oversight might 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.

We also understand that the increased cost to laboratories under the phaseout policy may reduce the amount of revenue a laboratory can invest in creating and/or modifying IVDs offered as LDTs. This could lead to a reduction in the number of new IVDs offered as LDTs and/or modifications of these which incorporate the most up-to-date scientific knowledge. While this may occur, the increased FDA oversight under the phaseout policy may provide more assurance that new and/or modified IVDs offered as LDTs will provide accurate results.

Finally, it is also possible that some laboratories might decide to switch from an IVD offered as an LDT to an FDA-authorized test or to outsource their testing to other laboratories. According to comments, an FDA-authorized test could cost an additional $6 to $35 per test performed. One comment also stated that outsourcing some testing instead of offering IVDs as LDTs could cost them an additional $3,000 to $6,000 per test, while another stated that outsourcing could cost an additional $760,000 annually. An unknown number of laboratories may pursue outsourcing their testing needs or switching to use of an FDA-authorized test rather than introducing a new test that does not fall within an enforcement discretion policy in the phaseout policy. However, we assume that the cost of switching to an FDA-authorized test when available, would cost less than the cost of submitting a premarket submission. We assume that a laboratory would switch to FDA-authorized tests or outsource their testing needs only if submitting a premarket submission was more costly than either of these alternatives. Either way,

the decision would be a private decision made according to their business plan. To the extent that any number of laboratories switch to any number of FDA-authorized tests, or outsource their testing needs, our estimated costs for submitting a PMA or a 510(k) would be overestimated.

G. Budgetary Impacts

In addition to the cost to industry of preparing and submitting various submissions to FDA, including MDRs, IDEs, Q-submissions, PMAs, PMA supplements, 510(k)s, and De Novo requests, there would be incremental review costs for FDA to review these additional submissions. FDA is excluding from new review costs LDTs that are expected to be reviewed by NYS CLEP. For LDTs approved by NYS CLEP, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements. As discussed in appendix A, we estimate that 12.1% (ranging from 6.1% to 24%) of new submissions for IVDs offered as LDTs would not experience new review costs for FDA as a result of FDA's general enforcement discretion policy with respect to the premarket review requirements for LDTs approved by NYS CLEP.

As mentioned in section II.F.4, FDA assumes that at least 50% of the IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the 510(k) Third Party Review Program. Manufacturers who submit to 3P510k Review Organizations pay the 3P510k Review Organization but do not pay FDA user fees for those submissions. 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.

To estimate the review costs for FDA, we first use average costs per-page based on premarket 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. [62]). The current estimate after adjustment for inflation is $864,057 per PMA and $20,565 per 510(k) (or per De Novo).[81] We also use labor costs from estimated FTEs for FDA review of different submission types, including MDRs, Q-submissions, IDEs, and premarket submissions.[82] The 3-year average cost of all personnel compensation and benefits paid per FTE at FDA is $315,403 (Ref. [63]). 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 premarket review cost per submission (we only use the FTEs information for the MDR review cost per listing, IDE cost per submission, and Q-submission cost per submission).

We expect MDR review cost would occur in Stage 1. Multiplying the MDR review cost per listing by the number of MDR submissions yields a total one-time review cost of MDRs between $0.22 million and $0.88 million, with a primary estimate of $0.44 million. Multiplying the review cost per listing by the number of MDR submissions per year yields a total recurring review cost of MDRs between $0.03 million and $0.11 million, with a primary estimate of $0.06 million.

Under stage 2, we expect IDE review cost would incur in year 2. Multiplying the IDE review cost per listing by the number of IDE submissions yields a total one-time review costs of IDEs between $1.16 million and $4.65 million, with a primary estimate of $2.32 million.

[81] 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.

[82] This cost reflects hours spent in CDRH substantive review of devices, required to determine whether they meet the standard to be approved, cleared, or granted marketing authorization. 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.

The estimated recurring review cost of IDEs range from $2.81 million and $11.24 million, with a primary estimate of $5.62 million.

We expect review costs of Q-submission, PMA, 510(k), and De Novo submissions would incur under stages 4 and 5. To estimate the review cost of Q-submissions, we calculate the number of modified and new IVDs per year subject to premarket review by adding the number of PMA, 510(k), and De Novo submissions.[83] Multiplying the review cost per Q-submission by the number of new premarket submissions per year yields a total recurring review cost of Q-submissions between $18.63 million and $74.50 million, with a primary estimate of $37.25 million.

The total recurring review cost of PMAs is estimated to range between $29.33 million to $117.30 million, with a primary estimate of $58.65 million. The total recurring review cost of PMA supplements is estimated to range between $0.71 million and $2.82 million, with a primary estimate of $1.41 million. The total recurring review cost of 510(k)s is estimated to range from $11.02 million to $44.06 million, with a primary estimate of $22.03 million. The recurring review cost of De Novo classification requests is estimated to range from $14.92 million to $59.67 million, with a primary estimate of $29.84 million.

Overall, we estimate the total one-time FDA review costs to range between $1.38 million and $5.53 million, with a primary estimate of $2.77 million. We estimate the total recurring FDA review costs to range between $77.43 million and $309.72 million, with a primary estimate of $154.86 million. See Table 38.[84]

[83] Our estimates of review costs of Q-submissions are uncertain as we assume every premarket submission will have a Q-submission, which is unlikely, and we do not account for the fact that some premarket submissions have multiple Q-submissions or that we receive some Q-submissions that are not tied to a premarket submission. Further, we do not account for the likelihood of receiving Q-submissions prior to Stage 3 as laboratories prepare in advance for premarket submissions.

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

Table 38. FDA Review Costs by Submission Type

		Primary	Low	High
MDR	FDA review costs using FTE	$5.58	$5.58	$5.58
	Affected IVDs offered as LDTs on the market	79,114	39,557	158,227
	*Subtotal, one-time (millions)**	*$0.44*	*$0.22*	*$0.88*
	MDR submissions per year for affected tests	10,013	5,007	20,026
	*Subtotal, recurring (millions)**	*$0.06*	*$0.03*	*$0.11*
IDE	FDA review costs using FTE	$21,763	$21,763	$21,763
	Affected IVDs offered as LDTs currently on the market	107	53	214
	*Subtotal, one-time (millions)**	*$2.32*	*$1.16*	*$4.65*
	New IDE submissions per year for affected tests	258	129	516
	*Subtotal, recurring (millions)**	*$5.62*	*$2.81*	*$11.24*
Q-submission	FDA review costs using FTE	$25,548	$25,548	$25,548
	Premarket submissions per year (PMAs, 510(k)s, and De Novos) for affected tests	1,454	727	2,908
	*Subtotal, recurring (millions)**	*$37.14*	*$18.57*	*$74.28*
PMA	FDA review costs using page numbers	$864,057	$864,057	$864,057
	FDA review costs using FTE	$294,429	$294,429	$294,429
	Average FDA review costs	*$579,243*	*$579,243*	*$579,243*
	PMA Submissions per year for affected tests	101	51	203
	*Subtotal, recurring (millions)**	*$58.65*	*$29.33*	*$117.30*
PMA Supplements	*Average FDA review costs*	$110,319	$110,319	$110,319
	Supplements per year for affected tests	31	15	61
	*Subtotal, recurring (millions)***	*$1.41*	*$0.71*	*$2.82*
510(k)	FDA review costs using page numbers	$20,565	$20,565	$20,565
	FDA review costs using FTE	$19,870	$19,870	$19,870
	Average FDA review costs	*$20,218*	*$20,218*	*$20,218*
	510(k) submissions per year for affected tests	1,090	545	2,179
	*Subtotal, recurring (millions)**	*$22.03*	*$11.02*	*$44.06*
De Novo	FDA review costs using page numbers	$20,565	$20,565	$20,565

	FDA review costs using FTE	$202,804	$202,804	$202,804
	Average FDA review costs	*$111,685*	*$111,685*	*$111,685*
	De Novo submissions per year for affected tests	267	134	534
	*Subtotal, recurring (millions)**	*$29.84*	*$14.92*	*$59.67*
Total one-time costs (millions)		**$2.77**	**$1.38**	**$5.53**
Total recurring costs (millions)		**$154.86**	**$77.43**	**$309.72**

Notes: The number of submissions per year include currently marketed tests that would be modified and new tests from both affected entities currently on the market and new entities entering the market per year. The number of premarket submissions per year for Q-submission review costs include all premarket submission types (PMA, 510(k), and De Novo). Totals may not add due to rounding.
**We calculate subtotals by multiplying average FDA review costs by the number of submissions per year.*
***We multiply the average FDA review cost per PMA by the FTE weights to calculate the review cost per PMA supplement.*

H. Transfers

With this phaseout policy, laboratories will pay fees to FDA for establishment registration, premarket submissions (where applicable), and periodic reporting for IVDs with a PMA. While these fees are 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 double-count effects on net social benefits.[85]

See Table 39 for the estimated transfers associated with the phaseout policy. All anticipated fees are public information published by FDA.[86] Each laboratory is expected to pay an annual registration fee, at a cost of $7,653 per laboratory. Laboratories will also pay for submission of a report annually to FDA for each IVD that has received premarket approval,

[85] 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. Industry and the FDA are both members of society.
[86] We cite FY24 fees; the fees are updated every summer for the upcoming fiscal year. https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa

which costs $16,925 per report. Laboratories will pay $483,560 to FDA for each PMA they submit. For PMA supplements, they will pay $72,534 for each 180-day supplement, $386,848 for each panel-track supplement, and $33,849 for each real-time supplement they submit. They will pay $21,760 for each 510(k) they submit and $145,068 for each De Novo request they submit.

As mentioned in sections II.F.4 and II.G, we assume that at least 50% of the IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the 510(k) Third Party Review Program. We consider the fees paying to 3P510k Review Organizations as costs to industry, as described in section II.F.4 (see Table 33 and Table 34).

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 ($5,440 per submission),
- De Novo requests ($36,267 per submission),
- PMAs ($120,890 per submission),
- PMA supplements ($18,134 for each 180-day supplement, $96,712 for each panel-track supplement, and $8,462 for each real-time supplement), and
- PMA annual reports ($4,231 per submission).

Small businesses with sales of $30 million or less are eligible to have the fee 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 percent) to estimate the number of small businesses IVDs. Multiplying these fees by the relevant number of laboratories

and IVDs, we expect total annual transfers to range from $34.13 million to $137.09 million, with a primary estimate of $68.54 million.

Table 39. Transfers

			Primary	Low	High
Recurring Annual	Registration Annual Fee	Fee	$7,653	$7,653	$7,653
		Entities affected	1,275	638	2,551
		Subtotal (millions)	*$9.76*	*$4.88*	*$19.52*
	Annual reporting on PMA	Fee (Adjusted fee for small entities)	$16,925 ($4,231)	$16,925 ($0)	$16,925 ($4,231)
		IVDs affected, non-small*	35	18	71
		IVDs affected, small*	66	33	132
		Subtotal (millions)	*$0.88*	*$0.30*	*$1.76*
One-time /Annual	PMA	MDUFA Review (Adjusted fee for small entities)	$483,560 ($120,890)	$483,560 ($120,890)	$483,560 ($120,890)
		IVDs affected, non-small*	35	18	71
		IVDs affected, small*	66	33	132
		Subtotal (millions)	*$25.09*	*$12.55*	*$50.19*
	PMA Supplements –180-day track	MDUFA Review (Adjusted fee for small entities)	$72,534 ($18,134)	$72,534 ($18,134)	$72,534 ($18,134)
		IVDs affected, non-small*	2	1	4
		IVDs affected, small*	4	2	7
		Subtotal (millions)	*$0.20*	*$0.10*	*$0.40*
	PMA Supplements – Panel-track	MDUFA Review (Adjusted fee for small entities)	$386,848 ($96,712)	$386,848 ($96,712)	$386,848 ($96,712)
		IVDs affected, non-small*	1	0	1
		IVDs affected, small*	1	1	2
		Subtotal (millions)	*$0.36*	*$0.18*	*$0.71*
	PMA Supplements – Real-Time	MDUFA Review (Adjusted fee for small entities)	$33,849 ($8,462)	$33,849 ($8,462)	$33,849 ($8,462)
		IVDs affected, non-small*	5	2	10
		IVDs affected, small*	9	4	18
		Subtotal (millions)	*$0.24*	*$0.12*	*$0.48*
	510(k)	MDUFA Review (Adjusted fee for small entities)	$21,760 ($5,440)	$21,760 ($5,440)	$21,760 ($5,440)
		IVDs Affected, non-small*	381	191	763
		IVDs affected, small*	708	354	1,417
		Subtotal (millions)	*$12.15*	*$6.08*	*$24.30*
	De Novo	MDUFA Review (Adjusted fee for small entities)	$145,068 ($36,267)	$145,068 ($36,267)	$145,068 ($36,267)

		IVDs affected, non-small*	94	47	187
		IVDs affected, small*	174	87	347
		Subtotal (millions)	*$19.86*	*$9.93*	*$39.72*
Total Recurring Transfers (millions)			**$68.54**	**$34.13**	**$137.09**

**The numbers of tests include currently marketed tests that would be modified in such a way as to require premarket review as well as new tests subject to premarket review from existing and new entities per year.*

I. Stream of Benefits, Costs, and Transfers

We describe how we estimate the benefits, costs, and transfers in sections II.E, II.F, II.G and II.H. See Table 40 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.

Table 40. Undiscounted Twenty-year Flow of Benefits, Costs, and Transfers (millions 2022 USD)

Year	Benefits		Costs to Industry	Costs to FDA	Transfers
	VSLY based on 3% discounting	VSLY based on 7% discounting			
1	$0.00	$0.00	$101	$0	$0
2	$0.00	$0.00	$105	$8	$10
3	$3,111	$2,725	$332	$54	$23
4	$3,151	$2,760	$1,492	$155	$68
5	$4,420	$3,871	$1,492	$155	$69
6	$4,613	$4,041	$1,492	$155	$69
7	$4,786	$4,192	$1,492	$155	$69
8	$4,939	$4,326	$1,492	$155	$69
9	$5,075	$4,446	$1,492	$155	$69
10	$5,197	$4,552	$1,492	$155	$69
11	$5,305	$4,647	$1,492	$155	$69
12	$5,403	$4,732	$1,492	$155	$69
13	$5,490	$4,808	$1,492	$155	$69
14	$5,568	$4,877	$1,492	$155	$69
15	$5,638	$4,938	$1,492	$155	$69
16	$5,701	$4,994	$1,492	$155	$69
17	$5,758	$5,044	$1,492	$155	$69
18	$5,810	$5,089	$1,492	$155	$69

19	$5,856	$5,130	$1,492	$155	$69
20	$5,899	$5,167	$1,492	$155	$69

Table 40 shows that for most years in the twenty-year time horizon, FDA review costs are greater than transfers. The total annualized values of FDA review costs, transfers, and the differences are presented in Table 41. These estimates are conducted using our current fiscal year 2024 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 phaseout policy, FDA does not intend to 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. October 1, 2027, is the start of the next medical device user fee program (i.e., MDUFA VI).[87]

Table 41. Summary of FDA Review Costs and Transfers (Annualized over 20 years, in millions 2022$)

	Discount rate	Primary	Low	High
FDA Review Costs	3%	$129.30	$64.65	$258.59
	7%	$121.39	$60.69	$242.77
Transfers	3%	$57.50	$28.65	$115.05
	7%	$40.60	$20.24	$81.27
Difference (=FDA Costs - Transfers)	3%	$71.80	$36.00	$143.54
	7%	$80.78	$40.45	$161.51

[87] Note that under the phaseout policy, FDA intends to 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) will 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 three and seven percent discount rates. See Table 42.

Table 42. Summary of Present and Annualized Values (in millions 2022$)

	Benefits	Costs*	Transfers
Present Value 7%	$37,176.54	$13,637.63	$430.15
Present Value 3%	$64,583.82	$20,407.00	$855.46
Annualized Value 7%	$3,509.20	$1,287.30	$40.60
Annualized Value 3%	$4,341.05	$1,371.67	$57.50

*The estimated costs include both costs to industry and FDA.

J. Analysis of Regulatory Alternatives to the Final Phaseout Policy

We consider four different regulatory alternatives as described below. In our analysis of alternatives, we compare total costs, benefits, and transfers with two options that would be more stringent and one option that would be less stringent. We also consider one alternative of taking no new action. Table 43 summarizes our analysis of the alternatives of the phaseout policy.

Table 43. Annualized Values of Regulatory Alternatives Over a 20 Year Period (in billions 2022$)

	Final Phaseout Policy		Alternative 2		Alternative 3		Alternative 4	
	3%	7%	3%	7%	3%	7%	3%	7%
Total Benefits	$4.34	$3.51	$4.39	$3.57	$3.94	$3.10	$5.14	$4.21
Total Costs	$1.37	$1.29	$1.45	$1.39	$1.20	$1.09	$5.58	$5.83
Net Benefits	$2.97	$2.22	$2.94	$2.18	$2.74	$2.01	-$0.44	-$1.62
Transfers	$0.06	$0.04	$0.06	$0.06	$0.05	$0.03	$0.28	$0.23

Notes: We report primary estimates. There would be no additional costs or benefits under Alternative 1.

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 will 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 publication date of the final rule:
    - Stage 1: beginning 1 year after the publication date of this final rule, FDA will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files).
    - Stage 2: beginning 2 years after the publication date of this final rule, FDA will expect compliance with requirements not covered during other stages of the phaseout policy, including registration and listing, labeling, investigational use requirements, and QS requirements under part 820 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1).
    - Stage 3: beginning 3 years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for high-risk IVDs and other premarket review requirements (for moderate-risk and low-risk IVDs that require premarket submissions).

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 $1.39 billion, which is $99 million higher than the estimated costs associated with the phaseout policy. The estimated annualized transfers of this alternative would be $58 million, which is $17 million higher than the estimated transfers associated with the phaseout policy. The shorter phaseout period would

result in higher annualized benefits because they would begin earlier than under the phaseout policy. The estimated annualized benefits of this alternative would be $3.57 billion, which is $56 million higher than the benefits associated with the phaseout policy. However, a shorter phaseout period means that, among other things, affected laboratories, including small laboratories, would have less time to prepare and it might be less feasible for them to come into compliance.

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: beginning 1 year after the publication date of this final rule, FDA will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files).
    - Stage 2: beginning 4 years after the publication date of this final rule, FDA will expect compliance with requirements other than MDR, correction and removal reporting, and QS requirements under part 820 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1).
    - Stage 3: beginning 5 years (7 years for small laboratories) after the publication date of this final rule, FDA will expect compliance with respect to premarket review requirements for high-risk IVDs.
    - Stage 4: beginning 6 years (10 years for small laboratories) after the publication date of this final rule, FDA will expect compliance with respect to premarket review requirements for moderate risk and low risk IVDs that require premarket submissions.

Compared to the final phaseout policy, 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

phaseout policy (including compliance with registration and listing, labeling, and investigational use requirements) would occur in year 2, and costs for Stage 3 under the phaseout policy (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 phaseout policy) 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 issuance of the final phaseout policy. The estimated annualized costs of this alternative would be approximately $1.09 billion, which is $202 million less than the estimated costs associated with the phaseout policy. Out of the estimated annualized costs, the estimated annualized costs to FDA would be approximately $96 million under this alternative, which is $25 million less than the estimated FDA review costs with the phaseout policy. 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 $411 million because extending the phaseout period to six years (and ten years for small laboratories) will reduce the number of avoided harms from problematic IVDs.

4. In the fourth alternative, we assume the same phaseout policy as proposed in the preamble to the proposed rule. Under this alternative, there would be one-time costs of the QS requirements and premarket review requirements because FDA would be phasing out the general enforcement discretion approach for currently marketed IVDs offered as LDTs under stages 3 through 5.

The affected laboratories would thus have higher total costs. The estimated annualized costs of this alternative would be approximately $5.83 billion, which is $4.55 billion higher than the estimated costs associated with the final phaseout policy. This alternative would also increase annualized transfers by $194 million. Since this alternative does not consider premarket reviews by third parties or NYSDOH, the costs to FDA would be higher than the estimated costs of the final phaseout policy. We estimate that costs to FDA with this alternative would increase by $552 million, from $121 million to $673 million.

The benefits would increase because the number of affected tests under stages 3 through 5 would be higher than under the final phaseout policy. We estimate that the benefits associated with this alternative would be approximately $4.21 billion, which is $703 million higher than the estimated benefits of the final phaseout policy. Table 44 below summarizes primary estimates of the costs by stage of the phaseout policy and alternative 4. The cost reduction of the final phaseout policy compared to this alternative is primarily due changes in stages 3 through 5 due to the enforcement discretion policies. See Table 19 for the impact of the enforcement discretion policies on the benefits.

Table 44. Costs of the Final Phaseout Policy and Alternative 4 (millions 2022$)

		Final Phaseout Policy	Alternative 4
Stage 1	Reading and Understanding the Phaseout Policy	$3.91	$3.91
	Medical Device Reporting	$95.24	$95.24
	Correction and Removal Reporting	$0.18	$0.18
	Complaint Records	$2.13	-
Stage 2	Registration and Listing Requirements	$0.58	$0.58
	Labeling Requirements	$4.55	$4.55
	Investigational Use Requirements	$25.47	$25.47
Stage 3	Quality System Requirements	$26.06	$472.19
Stage 4	Premarket Approval Application	$503.91	$21,589.11
	Premarket Approval Application Supplements	$14.76	$289.24
Stage 5	510(k) Submission	$825.47	$13,746.59

	De Novo Classification Request	$177.50	$2,882.49

Notes: We only report primary estimates. The estimated costs include one-time costs and recurring costs per year. The estimated costs include both costs to industry and FDA.

K. Distributional Effects

Phasing out the general enforcement discretion approach for LDTs might generate benefits and costs that accrue differentially to establishments and segments of society. In this section, we discuss 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 phaseout policy to increase the accuracy of laboratory test results, reducing the incidence of patient diagnostic error and resulting in more appropriate treatments and improved health outcomes, among other benefits. While we would not expect the benefits of the phaseout policy – in isolation – to differentially affect certain population segments, existing inequities in healthcare access might result in differential accrual of benefits across the general population. For example, there is evidence of disparities in access to tests (Ref. [64]) which might impact the patient populations that the benefits of the phaseout policy would reach. FDA also recognizes that IVDs offered as LDTs might serve communities in rural, medically underserved areas with disparities in access to diagnostic tests.

However, the benefits of test access depend on the ability of tests to work as intended, and the harms of unsafe or ineffective IVDs offered as LDTs might disproportionately occur among medically underserved patient populations that such tests might aim to reach. Without appropriate oversight, IVDs offered as LDTs might exacerbate health disparities. Research reports higher rates of inaccurate results among underrepresented patient populations, particularly racial and ethnic minorities undergoing genetic tests (Refs. [65, 66, 67, 68, 69]).

Additionally, some IVDs offered as LDTs have not been validated for use in all patient populations who may have the relevant health condition, across ages or ethnicities, meaning that it is unknown how well the test might perform across diverse patient populations expected to use the test, and tests might be less accurate in underrepresented patient populations, which could contribute to health disparities (Ref. [70]).

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 the phaseout policy is intended to help assure. By increasing its oversight, FDA might better prevent and mitigate harms disproportionately realized among underrepresented, medically underserved populations. As such, the benefits of phasing out the general enforcement discretion approach for LDTs might differentially reach these populations.

When IVDs are subject to increased FDA oversight, FDA will 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. With new FDA authorities under the Food and Drug Omnibus Reform Act of 2022 (FDORA), sponsors will generally be required to submit diversity action plans to FDA, including the sponsor's goals for enrollment in device clinical studies, to help improve the generalizability of the results to the intended use population. In contrast, with limited oversight over these IVDs, FDA does not know whether validation studies for these IVDs include diverse patient populations. 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 phasing out the general enforcement discretion approach for LDTs might 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.6, pass-through of costs to provide IVDs offered as LDTs might in turn create additional costs to society. If laboratories pass through the cost of compliance to the costs of IVDs offered as LDTs, test frequency might decrease for areas that rely on IVDs offered as LDTs for easy, rapid access to tests.[88] If laboratories or healthcare facilities respond to increased compliance costs by increasing the prices of IVDs offered as LDTs or reducing the availability of IVDs offered as LDTs, there might thus be an increase in health inequity. Vulnerable populations that rely on IVDs offered as LDTs for diagnosis might have less access to diagnostic tests in general after the implementation of the phaseout policy.

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.

We do not expect the phaseout policy to result in an increase in health inequity in isolation. Though we do have evidence of existing health inequities in diagnostic tests and clinical trials across sociodemographic populations, we lack the evidence to quantify the effect of the phaseout policy on these existing health inequities, and thus cannot determine whether the

[88] 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. [27]).

phaseout policy will ameliorate or exacerbate health inequity. By increasing oversight over IVDs offered as LDTs, FDA may better prevent and mitigate harm to patients that might result from inaccurate and unreliable tests, including patients in underserved populations.

L. International Effects

While the phaseout policy 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 the phaseout of the general enforcement discretion approach for LDTs, if those laboratories 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 January 2024, there are 74 international laboratories certified under CLIA to perform non-waived testing.[89] Based on available information and professional judgment, we assume that 100% of CLIA-certified international laboratories are performing high complexity testing and have IVDs offered as LDTs. While our historical experience indicates that these laboratories likely offer a smaller number of IVDs offered as LDTs, as they are typically offering more specialized tests, for the cost estimates, we use the same assumption described in section II.D that each laboratory would have 67 IVDs offered as LDTs, and thus we expect 496 (= 74 x 67) international IVDs offered as LDTs to be affected by the phaseout policy. We also assume 592 (74 x (6+2)) modified (an additional 2 annually) and new (an additional 6 annually) international IVDs offered as LDTs to be affected annually, consistent with assumptions in section II.D.

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

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 74 international laboratories, then search the National Bureau of Economic Research (NBER) Occupational Wages around the World (OWW) database for wage information for the relevant countries.[90] 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 45 for a summary of international costs, organized by stage and part of the phaseout policy.

Table 45. International Costs

		Primary	Low	High
One-time				
Stage 1	Reading and Understanding the Rule	$165,541	$74,494	$279,351
	Medical Device Reporting	$612,171	$498,064	$752,796
	Correction and Removal Reporting	$1,850	$1,850	$1,850
	Complaint Records	$96,644	$55,225	$138,062
Stage 2	Registration and Listing Requirements	$18,669	$18,669	$18,669
	Labeling Requirements	$192,916	$49,785	$336,048

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

	Investigational Use Requirements	$466,943	$466,943	$466,943
Stage 3	Quality System Requirements	$96,644	$55,225	$138,062
Total One-time Costs		**$1,651,379**	**$1,220,255**	**$2,131,781**
Recurring Annual				
Stage 1	Medical Device Reporting	$3,707,098	$3,707,090	$3,707,106
	Correction and Removal Reporting	$6,845	$6,845	$6,845
Stage 2	Re-registration	$6,223	$6,223	$6,223
	Investigational Use	$1,129,027	$1,129,027	$1,129,027
Stage 4	Premarket Approval Application	$59,172,917	$56,088,281	$117,781,004
	Premarket Approval Application Supplements	$1,733,605	$1,640,318	$3,506,047
Stage 5	510(k) Submission	$104,382,781	$96,222,502	$112,543,060
	De Novo Classification Request	$20,842,241	$11,086,707	$20,942,297
Total Recurring Costs		$190,980,737	$169,886,993	$259,621,610

See Table 46 for a summary of the expected timing and annualized value of international costs. At a three percent discount rate, we expect the annualized value of international costs to range from $140.29 million to $214.98 million, with a primary estimate of $157.50 million. At a seven percent discount rate, we expect the annualized value of international costs to range from $131.23 million to $201.26 million, with a primary estimate of $147.26 million.

Table 46. Twenty-Year Timing of International Costs (millions 2022$)

	Primary	Low	High
Year 1	$4.59	$4.34	$4.89
Year 2	$5.53	$5.38	$5.67
Year 3	$35.40	$33.77	$65.63
Year 4-20 (costs for each year)	$190.98	$169.89	$259.62
Total Costs of the Phaseout Policy	$3,292.19	$2,931.58	$4,489.76
Present Value of Total Costs (3%)	$2,343.16	$2,087.14	$3,198.30
Present Value of Total Costs (7%)	$1,560.07	$1,390.28	$2,132.20
Annualized Value of Costs (3%)	$157.50	$140.29	$214.98
Annualized Value of Costs (7%)	$147.26	$131.23	$201.26

III. Final 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 will be affected by the phaseout of the general enforcement discretion approach for LDTs are defined as small businesses and the phaseout policy is likely to impose a substantial burden on the affected small entities, we find that the phaseout policy will have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document and the final rule, serves as the Final 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 the phaseout policy on small entities. The Small Business Administration (SBA) considers Medical Laboratories (NAICS code 621511) to be small if their annual receipts are less than $41.5 million.[91] 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 47). Of the 1,181 laboratories, 1,085 laboratories (those with less than $41.5 million in annual receipts), or 92 percent of the total, would be small according to the 2023 SBA size standard. We estimate

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

that small businesses also manufacture 22% of IVDs offered as LDTs currently on the market.[92] We provide more detail on these estimates in Appendix B.

Table 47. 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	166	56
$151 - $999	933	327	625
$1000 - $1,999	413	145	754
$2,000 - $3,999	481	169	1,948
$4,000 - $5,999	343	120	3,061
$6,000 - $9,999	146	51	2,150
$10,000 - $14,999	77	27	1,489
$15,000 - $19,999	115	40	3,114
$20,000 - $24,999	79	28	2,920
$25,000 - $29,999	21	7	951
$30,000 - $39,999	43	15	2,270
$40,000 - $49,999	15	5	1,151
$50,000 - $99,999	67	24	5,475
$100,000 +	194	68	63,163
Total	3,365	1,193	89,127
< $41.5 million	3,091	1,097	19,510
Percent Small	92%	92%	22%

B. Description of the Potential Impacts of the Phaseout Policy on Small Entities

We compiled the costs and transfers associated with the phaseout policy and compared them to the estimated share of annual receipts of the laboratories offering IVDs as LDTs. In Table 48, 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 $4,395 to $3,045,766 per laboratory, depending on its size

[92] From Table 47 an estimated 17,318 of 79,114 IVDs or 22% offered as LDTs are from small businesses.

classification.[93] As shown in Table 48, the annualized costs per small entity averages $232,618 represent 5.8 percent of receipts for the small laboratories (with annual receipts of less than $41,500,000). Because we don't know how costs would be distributed across entities, we estimate average costs per laboratory by their receipt size categories using the assumption that costs are distributed proportionally to receipts and for this reason costs as a percent of receipts appear to be constant across all receipt size categories.

The extent in which smaller laboratories may be disproportionately impacted by the phaseout of the general enforcement discretion approach for LDTs, is dependent on the number of IVD's offered as LDTs per lab. FDA anticipates that the enforcement discretion policies discussed in the preamble of the final rule will moderate these concerns and help to avoid complete disruption to the test market. As noted in Appendix B-Table 8, the average costs per LDT are smallest for stages 1 through 3 of the phaseout policy representing 10% of costs and up to 59% of affected tests, whereas average costs per LDT for stages 4 and 5 represent 90% of costs affecting 3% of tests. The percentage of tests that may experience costs under stages 4 and 5 will increase as new laboratories and tests enter the market during and after stages 4 and 5, as they will fall within the enforcement discretion policy for currently marketed tests. However, they may still fall within the scope of other enforcement discretion policies described in the preamble to the final rule, including those for unmet needs and LDTs approved by NYS CLEP. However, in the event that a new lab does not fall within the scope of other enforcement discretion policies, costs under stages 4 and 5 could present as a potential barrier to entry in the LDT market for new laboratories. In Table B7 of Appendix B, total costs and transfers of the phaseout policy are estimated to be on average anywhere between about 2.54, 5.8 and 16 percent

[93] The average annualized cost per small entity ranges from $4,395 per laboratory with annual receipts that are less than $150,000 and to $3,045,766 per laboratory with annual receipts between $40 and $49.99 million.

for all entities. We do not have the information about labs to determine how the average estimates are distributed among the firms according to their size categories. Depending on profit margins with respect to revenue, the costs of this rule may be prohibitive for some small labs, making it likely for some small entities in this size category to exit the market, reduce operations, sell the business, be subject to acquisitions by larger firms or not enter the market. If profit margins were too small for many small firms considering the costs, it is possible that selling to large entities, would further cause industry consolidation and contribute to the growth of monopolies in the industry which would hinder competition. As we explained in Comment 17 (small entities), we do not have the information about labs to determine how the average estimates are distributed among the firms according to their size categories. Also, costs would be higher for a lab that has several IVDs offered as LDTs but sells fewer units tests whereas costs would be smaller for labs with only one IVD offered as LDTs selling a large number of unit tests. In the same manner, profit margins could be higher for labs with a smaller number of IVDs offered as LDTs but with high volume unit tests sold, compared to labs with a larger number of IVDs offered as LDTs but with low volume units tests sold.

While we do not have the data on profit margins to properly estimate the number of labs that would be adversely impacted by this rule, we estimate that small laboratories make fewer IVDs offered as LDTs than large firms. We estimate that small labs make up 92 percent of all labs, and that they also hold a 24 percent share of IVDs offered as LDTs. With the low number of IVDs offered as LDTs per small lab, it is more likely that the percent of costs over receipts per lab would be closer to our low average estimate 2.5 percent. Furthermore, for the final rule, as explained in comments 17 and 18, FDA intends to exercise enforcement discretion with respect to premarket review and QS requirements (except for applicable requirements under 21 CFR

820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule and that are not modified, or that are modified as described in the preamble and for LDTs developed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system (as described in section V.B.3 of the preamble), we do not expect significant market concentration or market exit to result from the phaseout policy.

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.[94] The estimated average recurring transfer for small businesses is $4,069. As seen in Table 48, the percentage of receipts that are additional transfers associated with the phaseout policy are estimated to be 0.10 percent for 166 laboratories (15 percent of the small entities) with their annual receipts less than $150,000.

Table 48. Small Business Costs and Transfers as a Percentage of Receipts

Receipts Size ($1,000)	Labs	Average Receipts	Total Costs per Lab	Costs as a % of Receipts	Total Transfers per Lab	Transfers as a % of Receipts
< $150	166	$75,755	$4,395	5.8%	$76	0.10%
$151 - $999	327	$430,532	$24,978	5.8%	$434	0.10%
$1000 - $1,999	145	$1,172,533	$68,026	5.8%	$1,181	0.10%
$2,000 - $3,999	169	$2,601,807	$150,947	5.8%	$2,621	0.10%
$4,000 - $5,999	120	$5,733,410	$332,631	5.8%	$5,775	0.10%
$6,000 - $9,999	51	$9,459,407	$548,799	5.8%	$9,528	0.10%
$10,000 - $14,999	27	$12,425,958	$720,908	5.8%	$12,516	0.10%
$15,000 - $19,999	40	$17,395,652	$1,009,231	5.8%	$17,521	0.10%

[94] Although businesses with gross receipts of $100 million or less are eligible to pay a reduced fee, we estimate the transfers per firm by receipts size category using the total transfers paid proportional to the share of IVDs offered as LDTs per receipt category in Table B.3 column D in Appendix B. For example, for firms making less than $150,000 in annual revenues, their share of total annual fees would be equivalent to 0.12% or $95 divided by $81,816 of the low estimate of total annualized fees of $2331 million.

$20,000 - $24,999	28	$23,750,766	$1,377,930	5.8%	$23,922	0.10%
$25,000 - $29,999	7	$29,082,108	$1,687,235	5.8%	$29,292	0.10%
$30,000 - $39,999	15	$33,924,383	$1,968,166	5.8%	$34,169	0.10%
$40,000 - $49,999	5	$49,317,674	$2,861,227	5.8%	$92,157	0.19%
$50,000 - $99,999	24	$52,498,495	$3,045,766	5.8%	$106,083	0.20%
$100,000 +	68	$209,184,656	$12,136,110	5.8%	$422,695	0.20%
Total	1,193	$16,841,846	$977,101	5.8%	$30,296	0.18%
<$41.5 M	1,097	$4,009,525	$232,618	5.8%	$4,069	0.10%
Percent small	92%	24%	24%	100%	13%	56.42%

C. Alternatives to Minimize the Burden on Small Entities

Regulatory alternative 3, described in section II.J, would reduce costs for all laboratories by extending the phaseout period to ten years for small entities and six years for other entities. Below we show how the reduction in cost under the alternative would reduce the cost on small laboratories, if it were implemented.

The 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.J.3 ("third alternative"). Compared with the final phaseout policy, 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 issuance of the final phaseout policy.

We estimate this option would reduce total costs by $690 to $478,302 per small entity.[95] For all laboratories, total recurring costs are estimated to be 4,9 percent of their average receipts. This alternative would also reduce transfers for all laboratories offering IVDs as LDTs from an average of $4,069 to $2,055 per entity for laboratories with their annual receipts below $41.5 million, which is $2,014 less than the estimated transfers of the phaseout policy. For the smallest laboratories (with annual receipts lower than $150,000), total transfers would be 0.05% percent of receipts. See Table 49.

Table 49. 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
< $150	166	$75,755	$3,705	4.9%	$38	0.05%
$151 - $999	327	$430,532	$21,055	4.9%	$217	0.05%
$1000 - $1,999	145	$1,172,533	$57,343	4.9%	$591	0.05%
$2,000 - $3,999	169	$2,601,807	$127,243	4.9%	$1,312	0.05%
$4,000 - $5,999	120	$5,733,410	$280,395	4.9%	$2,890	0.05%
$6,000 - $9,999	51	$9,459,407	$462,617	4.9%	$4,769	0.05%
$10,000 - $14,999	27	$12,425,958	$607,697	4.9%	$6,264	0.05%
$15,000 - $19,999	40	$17,395,652	$850,743	4.9%	$8,769	0.05%
$20,000 - $24,999	28	$23,750,766	$1,161,542	4.9%	$11,973	0.05%
$25,000 - $29,999	7	$29,082,108	$1,422,274	4.9%	$14,660	0.05%
$30,000 - $39,999	15	$33,924,383	$1,659,088	4.9%	$17,101	0.05%
$40,000 - $49,999	5	$49,317,674	$2,411,904	4.9%	$71,741	0.15%
$50,000 - $99,999	24	$52,498,495	$2,567,464	4.9%	$85,176	0.16%
$100,000 +	68	$209,184,656	$10,230,275	4.9%	$339,391	0.16%
Total	1,193	$16,841,846	$823,658	68.5%	$23,202	0.14%
<$41.5 M	1,097	$4,009,525	$196,088	4.9%	$2,055	0.05%

[95] The difference in average costs per small lab between the final phaseout policy and the alternative 3 is from subtracting costs per lab column Table 49 from costs per lab column in Table 47. For example, taking $5,104 from Table 48 minus $4,305 in Table 49 equals $799.

IV. **References**

[1] "Preliminary Regulatory Impact Analysis; Initial Regulatory Flexibility Analysis; Unfunded Mandates Reform Act Analysis," 2023. [Online]. Available: https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.

[2] J. Rychert, R. Schmidt and J. Genzen, "Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System," *American journal of clinical pathology,* vol. 160, no. 3, p. 297–302, 2023.

[3] J. Hooftman, A. Dijkstra, I. Suurmeijer, A. van der Bij, E. Paap and L. Zwaan, "Common contributing factors of diagnostic error: A retrospective analysis of 109 serious adverse event reports from Dutch hospitals," *BMJ Quality & Safety,* 2023.

[4] L. Zwaan, M. de Brujine, C. Wagner, A. Thijs, M. Smits, G. van der Wal and D. Timmermans, "Patient record review of the incidence, consequences, and causes of diagnostic adverse events," *Archives of internal medicine,* vol. 170, no. 12, pp. 1015-1021, 2010.

[5] C. van Moll, T. Egberts, C. Wagner, L. Zwaan and M. Berg, "The Nature, Causes, and Clinical Impact of Errors in the Clinical Laboratory Testing Process Leading to Diagnostic Error: A Voluntary Incident Report Analysis," *Journal of Patient Safety,* vol. 19, no. 8, pp. 573-579, 2023.

[6] A. K. Stroobants, H. M. J. Goldschmidt and M. Plebani, "Error budget calculations in laboratory medicine: linking the concepts of biological variation and allowable medical errors," *Clinica chimica acta,* vol. 333, no. 2, pp. 169-176, 2003.

[7] G. D. Schiff and L. L. Leape, "Commentary: how can we make diagnosis safer?," *Academic Medicine,* vol. 87, no. 2, pp. 135-138, 2012.

[8] G. D. Schiff, S. Kim, R. Abrams, K. Cosby, B. Lambert, A. Elstein, S. Hasler, N. Krosnjar, R. Odwazny, M. Wisniewski and R. McNutt, "Diagnosing diagnosis errors: lessons from a multi-institutional collaborative project," *Advances in patient safety: from research to implementation,* vol. 2: concepts and methodology, 2005.

[9] ECRI, "Deep Dive: Laboratory Testing," [Online]. Available: https://web.archive.org/web/20140714191534/https:/www.ecri.org/Press/Pages/ECRI-Institute-PSO-Study-on-Lab-Test-related-Safety-Events-Finds-Most-Occurred-Outside-the-Laboratory.aspx.

[10] M. L. Graber, N. Franklin and R. Gordon, "Diagnostic error in internal medicine," *Archives of internal medicine,* vol. 165, no. 13, pp. 1493-1499, 2005.

[11] H. Singh, A. Meyer and E. Thomas, "The frequency of diagnostic errors in outpatient care: estimations from three large observational studies involving US adult populations," *BMJ Quality and Safety,* vol. 23, no. 9, pp. 727-731, 2014.

[12] New York State Department of Health, "Public Comment: Re: Food and Drug Administration Docket No. FDA-2023-N-2177 (88 FR 68006)," 22 November 2023. [Online]. Available: https://www.regulations.gov/comment/FDA-2023-N-2177-4963. [Accessed 22 December 2023].

[13] J. C. Hopewell, S. Parish, R. Clarke, J. Armitage, L. Bowman, J. Hager, M. Lathrop and R. Collins, "No Impact of KIF6 Genotype on Vascular Risk and Statin Response Among 18,348 Randomized Patients in the Heart Protection Study," *Journal of the American College of Cardiology,* vol. 57, no. 20, pp. 2000-2007, 2011.

[14] T. Assimes , H. Hólm , S. Kathiresan, M. P. Reilly, G. Thorleifsson, B. F. Voight, J. Erdmann, C. Willenborg, D. Vaidya, C. Xie, C. C. Patterson, T. M. Morgan, M. S. Burnett, M. Li, M. A. Hlatky, J. W. Knowles, J. R. Thompson, D. Absher, C. Iribarren, A. Go, S. P. Fortmann, S. Sidney and N. T. Risch, "Lack of Association Between the Trp719Arg Polymorphism in Kinesin-Like Protein-6 and Coronary Artery Disease in 19 Case-Control Studies," *J American College of Cardiology,* pp. 1552-1563, 2010.

[15] S. Kliff and A. Bhatia, "When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong," *New York Times,* 1 January 2022.

[16] Centers for Disease Control and Prevention, "Division of Laboratory Systems (DLS): Strengthening Clinical Laboratories," 15 November 2018. [Online]. Available: https://www.cdc.gov/csels/dls/strengthening-clinical-labs.html. [Accessed 21 August 2023].

[17] Grand View Research, "Laboratory Developed Tests Market Size, Share & Trends Analysis Report By Technology (Immunoassay, Molecular Diagnostics), By Application (Oncology, Nutritional & Metabolic Disease), By Region, And Segment Forecasts, 2023 - 2030," Grand View Research, San Francisco, 2023.

[18] Centers for Medicare & Medicaid Services, "Clinical Laboratory Improvement Amendments (CLIA) Post-Public Health Emergency (PHE) Guidance," 11 May 2023. [Online]. Available: https://www.cms.gov/files/document/qso-23-15-clia.pdf. [Accessed 21 August 2023].

[19] Centers for Medicare and Medicaid Services, "CLIA Overview," 22 October 2013. [Online]. Available: https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf. [Accessed 18 January 2024].

[20] U.S. Food and Drug Administration, "Memorandum to File from Brittany Schuck Re: Examples of In Vitro Diagnostic Products (IVDs) Offered as Laboratory Developed Tests

(LDTs) that Raise Public Health Concerns," 2023. [Online]. Available: https://www.regulations.gov/document/FDA-2023-N-2177-0076.

[21] J. D. Pfeifer, R. Loberg, C. Lofton-Day and B. A. Zehnbauer, "Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics," *American Journal of Clinical Pathology,* pp. 157(4):628-638, 2022.

[22] U.S. Food and Drug Administration, "Letter to deCODEme Complete Scan," 2010. [Online]. Available: https://www.fda.gov/media/79216/download.

[23] U.S. Food and Drug Administration, "Letter to 23andMe Personal Genome Service," 2010. [Online]. Available: http://web.archive.org/web/20191214010336/https:/www.fda.gov/media/79205/download.

[24] American Association for Cancer Research, "Re: Request for Information Regarding 21st Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests," 5 January 2015. [Online]. Available: https://www.aacr.org/wp-content/uploads/2019/11/AACR-Comments-Modernized-Framework-Diagnostics-Jan-5-2015.pdf. [Accessed 24 August 2023].

[25] U.S. Government Publishing Office, "Laboratory Testing in the Era of Precision Medicine," 20 September 2016. [Online]. Available: https://www.govinfo.gov/content/pkg/CHRG-114shrg21906/pdf/CHRG-114shrg21906.pdf. [Accessed 24 August 2023].

[26] U.S. Food and Drug Administration, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs); Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories," 3 October 2014. [Online]. Available: https://www.fda.gov/media/89841/download. [Accessed 23 August 2023].

[27] Pew Research Center, "The Role of Lab-Developed Tests in the In Vitro Diagnostics Market.," 22 10 2021. [Online]. Available: https://www.pewtrusts.org/en/research-and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics-market.

[28] U.S. Food and Drug Administration, "Memo to File: Information from the New York State Department of Health (NYSDOH) for the Preliminary Regulatory Impact Analysis for the Laboratory Developed Tests Proposed Rule and Certain Related Analysis," 2023.

[29] Department of Health, Wadsworth Center, "Clinical Laboratory Evalualation Program: Clinical Laboratories: Obtain a Permit: Test Approval," [Online]. Available: https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval. [Accessed 21 August 2023].

[30] Congressional Budget Office, "Federal Policies in Response to Declining Entrepreneurship," 29 December 2020. [Online]. Available: https://www.cbo.gov/publication/56945. [Accessed 21 August 2023].

[31] AstuteAnalytica India Pvt. Ltd., "United States Clinical Laboratory Services Market to Generate Revenue of US$ 125.6 Billion by 2030: Astute Analytica," 13 March 2023. [Online]. Available: 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. [Accessed 21 August 2023].

[32] U.S. Food and Drug Administration, "Performance Report to Congress: Medical Device User Fee Amendments, FY 2022, page 21," 2022. [Online]. Available: www.fda.gov/media/167825/download. [Accessed 21 August 2023].

[33] D. E. Newman-Toker, Z. Wang, Y. Zhu, N. Nassery, A. S. Saber Tehrani, A. C. Schaffer, C. W. Yu-Moe, G. D. Clemens, M. Fanai and D. Siegal, "Rate of diagnostic errors and serious misdiagnosis-related harms for major vascular events, infections, and cancers: toward a national incidence estimate using the “Big Three”," *Diagnosis,* vol. 8, no. 1, pp. 67-84, 2021.

[34] D. Newman-Toker, N. Nassery, A. Schaffer, C. W. Yu-Moe, G. D. Clemens, Z. Wang, Y. Zhu, A. S. S. Tehrani, M. Fanai, A. Hassoon and D. Siegal, "Burden of serious harms from diagnostic error in the USA," *BMJ Quality & Safety,* 2023.

[35] D. Newman-Toker, A. Schaffer, W. Yu-Moe, N. Nassery, A. S. Tehrani, G. Clemens, Z. Wang, Y. Zhu, M. Fanai and D. Siegal, "Serious misdiagnosis-related harms in malpractice claims: The "Big Three" - vascular events, infections, and cancers," *Diagnosis,* vol. 6, no. 3, pp. 227-240, 2019.

[36] U.-P. Rohr, C. Binder, T. Dieterle, F. Giusti, C. G. M. Messina, E. Toerien, H. Moch and H. H. Schafer, "The Value of In Vitro Diagnostic Testing in Medical Practice: A Status Report," *PLOS One,* vol. 11, no. 3, pp. 1-16, 2016.

[37] M. M. Ward, F. Ullrich, K. Matthews, G. Rushton, M. A. Goldstein, D. F. Bajorin, A. Hanley and C. F. Lynch, "Who Does Not Receive Treatment for Cancer?," *Journal of Oncology Practice,* vol. 9, no. 1, pp. 20-6, 2013.

[38] National Cancer Institute, "Cancer Stat Facts: Common Cancer Sites," 2023. [Online]. Available: https://seer.cancer.gov/statfacts/html/common.html. [Accessed 21 August 2023].

[39] National Cancer Institute, "Age and Cancer Risk," National Institutes of Health, 5 March 2021. [Online]. Available: https://www.cancer.gov/about-cancer/causes-prevention/risk/age. [Accessed 18 August 2023].

[40] P. A. Johnstone, M. S. Norton and R. H. Riffenburgh, "Survival of patients with untreated breast cancer," *Journal of Surgical Oncology,* vol. 73, no. 4, pp. 273-277, 2000.

[41] H. Wao, R. Mhaskar, A. Kumar, B. Miladinovic and B. Djulbegovic, "Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis," *Systematic Reviews,* vol. 2, no. 10, 2013.

[42] U.S. Department of Health and Human Services, "Guidelines for Regulatory Impact Analysis," 12 Jan 2017. [Online]. Available: https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis.

[43] American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee, "Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association," American Heart Association, 2023.

[44] Centers for Disease Control and Prevention, "Heart Disease Facts," 15 May 2023. [Online]. Available: https://www.cdc.gov/heartdisease/facts.htm#print. [Accessed 27 November 2023].

[45] Z. Raisi-Estabragh, O. Kobo, A. Elbadawi, P. Velagapudi, G. Sharma, R. Bullock-Palmer, S. Petersen, L. Mehta, W. Ullah, A. Roguin, L. Sun and M. Mamas, "Differential Patterns and Outcomes of 20.6 Million Cardiovascular Emergency Department Encounters for Men and Women in the United States," *Journal of the American Heart Association,* vol. 11, no. 19, p. e026432, 2022.

[46] J. Conly, F. Clement, M. Tonelli, B. Hemmlgarn, S. Klarenbach, A. Lloyd and F. McAlister, "Cost-effectiveness of the use of low- and high-potency statins in people at low cardiovascular risk.," *CMAJ,* 2011.

[47] U.S. Department of Health and Human Services, "Contractor Project Report: International Prescription Drug Price Comparisons: Estimates Using 2022 Data," U.S. Department of Health and Human Services, 2024.

[48] Centers for Disease Control and Prevention, "National Notifiable Diseases Surveillance System. 2019 annual tables of infectious disease data," 2021. [Online]. Available: https://www.cdc.gov/nchs/hus/contents2020-2021.htm#Table-IDNotif. [Accessed 31 January 2024].

[49] Y. Li, S. You, K. Lee, R. Yaesoubi, K. Hsu, T. Gift, H. Chesson, A. Berruti, J. Salomon and M. Ronn, "The Estimated Lifetime Quality-Adjusted Life-Years Lost Due to Chlamydia, Gonorrhea, and Trichomoniasis in the United States in 2018," *The Journal of Infectious Diseases,* vol. 227, no. 8, pp. 1007-1018, 2023.

[50] A. Malek, C.-C. Chang, D. Clark and R. Cook, "Delay in Seeking Care for Sexually Transmitted Diseases in Young Men and Women Attending a Public STD Clinic," *Open AIDS Journal,* vol. 14, no. 7, pp. 7-13, 2013.

[51] Blue Cross and Blue Shield of Minnesota, "Blue Cross and Blue Shield of Minnesota Files Lawsuit Against GS Labs," 1 March 2022. [Online]. Available:

https://www.bluecrossmn.com/about-us/newsroom/news-releases/blue-cross-and-blue-shield-minnesota-files-lawsuit-against-gs-labs. [Accessed 21 August 2023].

[52] APM Reports, "GS Labs' responses to questions from APM Reports," APM Reports, 28 7 2022. [Online]. Available: https://www.apmreports.org/story/2022/07/28/gs-labs-responses-to-questions-from-apm-reports. [Accessed 10 1 2024].

[53] T. Scheck, J. Lu, W. Callan and A. Canny, "Private COVID lab created headaches for Minnesota consumers, health officials," 28 July 2022. [Online]. Available: https://www.mprnews.org/story/2022/07/28/gs-labs-covid-testing-minnesota. [Accessed 21 August 2023].

[54] D. McKnight and P. Hinton, "Tort Costs in America: An Empirical Analysis of Costs and Compensation of the U.S. Tort System," 22 November 2022. [Online]. Available: https://instituteforlegalreform.com/research/tort-costs-in-america-an-empirical-analysis-of-costs-and-compensation-of-the-u-s-tort-system/. [Accessed 21 August 2023].

[55] U.S. Food and Drug Administration, "Summary; Medical Device Reporting: Electronic Submission Requirements Final Regulatory Impact Analysis," 14 Feb 2014. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/summary-medical-device-reporting-electronic-submission-requirements-final-rule.

[56] U.S. Food and Drug Administration, "Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals," 11 Aug 2023. [Online]. Available: https://www.regulations.gov/document/FDA-2023-N-1006-0002.

[57] U.S. Food and Drug Administration, "Medical Devices; Quality System Regulation Amendments (Proposed Rule) Preliminary Regulatory Impact Analysis," 02 03 2022. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/medical-devices-quality-system-regulation-amendments-proposed-rule-preliminary-regulatory-impact. [Accessed 25 01 2024].

[58] U.S. Food and Drug Administration, "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," Aug 2016. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/requirements-foreign-and-domestic-establishment-registration-and-listing-human-drugs-including-drugs.

[59] U.S. Food and Drug Administration, "Summary: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling Final Regulatory Impact Analysis," Dec 2014. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/summary-

content-and-format-labeling-human-prescription-drug-and-biological-products-requirements.

[60] J. V. Batavia and S. J. Goldenberg, "Strategic Planning and Costs of FDA Regulation," *Academic Entrepreneurship for Medical and Health Scientists,* vol. 1, no. 2, 2019.

[61] I. Eastern Research Group, "Economic Analysis of CDRH Submission Requirements," 2012.

[62] U.S. Food and Drug Administration, "Microbiology Devices; Reclassification of Nucleic Acid-Based Systems for Mycobacterium tuberculosis complex Final Regulatory Impact Analysis," 2014. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/summary-microbiology-devices-reclassification-nucleic-acid-based-systems-mycobacterium-tuberculosis.

[63] U.S. Food and Drug Administration, "Food Safety Modernization Act Domestic and Foreign Facility Reinspection, Recall, and Importer Reinspection Fee Rates for Fiscal Year 2024," 28 July 2023. [Online]. Available: https://www.federalregister.gov/documents/2023/07/28/2023-15927/food-safety-modernization-act-domestic-and-foreign-facility-reinspection-recall-and-importer. [Accessed 20 October 2023].

[64] U.S. Food and Drug Administration, "Discussion Paper on Laboratory Developed Tests (LDTs)," 13 January 2017. [Online]. Available: https://www.fda.gov/media/102367/download. [Accessed 30 March 2023].

[65] G. S. Gerhard, S. G. Fisher and A. M. Feldman, "Genetic Testing for Inherited Cardiac Diseases in Underserved Populations of Non-European Ancestry: Double Disparity," *JAMA Cardiology,* pp. 3(4):273-274, 2018.

[66] A. K. Manrai, B. H. Funke, H. L. Rehm, M. S. Olesen, B. A. Maron, P. Szolovits, D. M. Margulies, J. Loscalzo and I. S. Kohane, "Genetic Misdiagnoses and the Potential for Health Disparities," *New England Journal of of Medicine,* pp. 375:655-665, 2016.

[67] A. R. Martin, M. Kanai, Y. Kamatani, Y. Okada, B. M. Neale and M. J. Daly, "Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities," *Nature Genetics,* pp. 51,584-591, 2019.

[68] Y. Wang, K. Tsuo, M. Kanai, B. M. Neale and A. R. Martin, "Challenges and Opportunities for Developing More Generalizable Polygenic Risk Scores," *Annual Review of Biomedical Data Science,* pp. 5:293-320, 2022.

[69] L. Duncan, H. Shen, B. Gelaye, J. Meijsen, K. Ressler, M. Felman, R. Peterson and B. Domingue, "Analysis of Polygenic Risk Score Usage and Performance in Diverse Human Populations," *Nature Communications,* p. 10(1):3328, 2019.

[70] K. F. Hoskins, O. C. Danciu, N. Y. Ko and G. S. Calip, "Association of Race/Ethnicity and the 21-Gene Recurrence Score With Breast Cancer–Specific Mortality Among US Women," *JAMA Oncology,* pp. 7(3):370-378, 2021.

[71] J. Gruber, " Chapter2," in *PublicFinanceandPublicPolicy,*, WorthPublishers,, 2016.

[72] Federal Reserve Bank of San Francisco, "Federal Reserve Bank of San Francisco Education Publications," November 2002. [Online]. Available: https://www.frbsf.org/education/publications/doctor-econ/2002/november/private-social-costs-pollution-production/#fn. [Accessed 21 August 2023].

[73] Congressional Research Service, "FDA Regulation of Laboratory-Developed Tests (LDTs)," 7 December 2022. [Online]. Available: https://crsreports.congress.gov/product/pdf/IF/IF11389. [Accessed 23 August 2023].

[74] J. K. Hammitt and J.-T. Liu, "Effects of Disease Type and Latency on the Value of Mortality Risk," *Journal of Risk and Uncertainty,* vol. 28, pp. 73-95, 2004.

[75] J. Hickner, P. Thompson, T. Wilkinson, P. Epner, M. Shaheen, A. Pollock, J. Lee, C. Duke, B. Jackson and J. Taylor, "Primary Care Physicians' Challenges in Ordering Clinical Laboratory Tests and Interpreting Results," *The Journal of the American Board of Family Medicine,* vol. 27, no. 2, pp. 268-274, 2014.

Appendix A. Estimation of the Number of Affected Labs and Tests

Number of Affected Labs

To obtain the number of laboratories and tests affected by the phaseout policy, we use data from the Centers for Medicare & Medicaid Services (CMS) that shows the number of laboratories by laboratory type (column A in Table A.1).[96] Only laboratories that are certified under CLIA and meet the regulatory requirements under CLIA to perform high complexity testing are affected by the phaseout policy since LDTs are high complexity. To determine the number of affected high complexity laboratories, we must first determine the number of non-waived laboratories (column C in Table A.1) and then estimate how many of those can perform high complexity testing versus only moderate complexity testing. We determine the number of non-waived laboratories by excluding the number of laboratories whose certificate type is microscopy or waiver (column B in Table A.1). Since laboratories are certified only as waived or non-waived, without specific notation on whether they meet the regulatory requirements for high complexity testing or only moderate complexity testing, the estimate for how many of the non-waived laboratories can perform high complexity testing is based on FDA professional judgement and historical knowledge. Therefore, we estimated the percent of each laboratory type that was likely to be high complexity to determine the high complexity rate (column D). We then estimate the number of high complexity laboratories affected by the phaseout policy by multiplying column C times high complexity rate in column D (column E). We estimate that there are 11,808 high complexity CLIA laboratories. This is close to our original estimate of 12,000 used in the preliminary analysis (Ref. [1]) and a 2021 report from the Pew Charitable

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

Trust (Ref. [12]) that also estimated that there are approximately 12,000 CLIA-certified laboratories performing high complexity testing.

As explained in section II.D.1, we rely on the information about laboratories and tests in NYS to estimate the percent of high complexity laboratories that make IVDs offered as LDTs. From the NYSDOH data, we calculate that approximately 10% of laboratories located in NYS that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing are developing IVDs offered as LDTs. We assume that NYS is representative of the U.S. laboratory community. We therefore estimate that approximately 10% of 11,808 (or 1,181) 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 potential variability across the country, we estimate the proportion of high complexity laboratories making IVDs offered as LDTs to vary from 5% of 11,808 (or 590) laboratories to a high estimate of 20% of 11,808 (or 2,362) affected laboratories by reducing the primary estimate by 50% and doubling the primary estimate, respectively. In addition, we assume that there would be new laboratories entering the market every year (approximately 8 percent of the affected high complexity laboratories making IVDs offered as LDTs, ranging from 47 to 189, with a primary estimate of 94). While there are also likely laboratories that exit the market each year, we have not subtracted expected departing laboratory numbers from our cost estimates.

Table A.1 Number of Affected Laboratories by Laboratory Type

Laboratory Type	(A) Total	(B) Waiver and Microscopy	(C) Difference (A) - (B)	(D) High Complexity Rate	(E) No. HC Labs (C) x (D)	(F) Integrated Healthcare System Rate	(G) No. HC Labs within Healthcare System (E) x (F)
Physician Office **	123,726	108,696	15,030	0	-		-
Other **	39,524	36,162	3,362	0.5	1,681	0	-

Pharmacy**	29,120	29,110	10	0	-		-
Intermediate Care Facility *	28,758	28,705	53	0	-		-
Skilled Nursing/ Nursing Facility	15,154	15,109	45	0	-		-
Home Health Agency	13,824	13,809	15	0	-		-
Assisted Living Facility	12,019	12,015	4	0	-		-
Hospital	9,399	2,599	6,800	0.5	3,400	1	3,400
Independent	9,198	3,602	5,596	0.75	4,197	0	-
Community Clinic	8,165	6,686	1,479	0.5	740	0.66	488
End Stage Renal Disease Dialysis	7,301	7,294	7	0	-		-
Ambulatory Surgery Center	7,150	6,719	431	0.75	323	0.5	162
Other Practitioner	6,868	6,653	215	0	-		-
School/Student Health Service	6,729	6,599	130	0	-		-
Ambulance	5,968	5,917	51	0	-		-
Hospice	5,100	5,091	9	0	-		-
Federally Qualified Health Center	4,556	4,332	224	0.5	112	0	-
Ancillary Test Site	3,700	2,811	889	0.75	667	0.5	333
Mobile Lab	3,219	3,131	88	0.25	22	0.75	17
Rural Health Care Clinic	2,726	2,512	214	0.25	54	0.25	13
Industrial	1,771	1,751	20	0.5	10	0	-
Comprehensive Outpatient Rehab	1,230	1,214	16	0.5	8	0.5	4
Prison	1,204	1,168	36	0.5	18	0	-
Public Health Laboratory	1,015	777	238	1	238	0	-
Health Maintenance Org	695	536	159	0.5	80	0.5	40
Health Fair	617	608	9	0	-		-
Blood Banks	426	167	259	1	259	0.5	130
Insurance	45	42	3	0	-		-
Total	**349,207**	**313,815**	**35,392**		**11,808**		**4,586**

Number of Affected Tests

We estimate the number of affected tests using information from NYSDOH. We then estimate the number of affected tests subject to different requirements and that would fall under different enforcement policies by adjusting the number of tests to account for the number that are

currently marketed, the number expected to be impacted by potential reclassification of Class III IVDs to Class II IVDs, the number of LDTs expected to be for unmet needs in an integrated health care system, and the number of LDTs estimated to be reviewed by NYS CLEP each year.

1) Using NYSDOH information

Using the NYSDOH information, FDA calculates that each laboratory that manufactures IVDs offers an average of 67 IVDs as LDTs and introduces an average of 6 new IVDs offered as LDTs per year (see section II.D.1 for details of the calculation). Multiplying 67 IVDs per lab by the number of affected laboratories, it is estimated that the number of affected currently marketed IVDs offered as LDTs ranges from 39,557 (=590 x 67) to 158,227 (=2,362 x 67), with a primary estimate of 79,114 (=1,181 x 67). Multiplying 6 new IVDs offered as LDTs per laboratory by the number of affected laboratories, we estimate 3,542, 7,085, or 14,170 new IVDs offered as LDTs may be affected per year.[97] We also estimate new IVDs offered as LDTs from new laboratories entering the market every year (8 percent of affected laboratories). The total number of new IVDs offered as LDTs per year is estimated to range from 3,826 to 15,303, with a primary estimate of 7,652.

FDA generally intends to exercise enforcement discretion with respect to premarket review requirements for currently marketed IVDs offered as LDTs and LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. To estimate the number of high complexity laboratories within integrated healthcare systems which may fall under the enforcement discretion policy for unmet needs (column G in Table A.1 above), we first multiply

[97] As mentioned in Section D.1, we only rely on the NYSDOH information to extrapolate estimates for affected tests across the country and assume that the laboratories in NYS are representative of the U.S. laboratory community. The estimates thus may be biased upwards if the costs associated with premarket review of IVDs offered as LDTs result in fewer new IVDs per year.

the number of high complexity laboratories in each laboratory type in each row in Column E by the estimated rate of integrated healthcare system in Column F for that laboratory type. As with the high complexity rate, to determine the estimated rate of integrated healthcare system laboratories, we used professional judgement and historical knowledge to estimate the percent of high complexity laboratories we expect would be part of an integrated healthcare system for each laboratory type. We estimate that there are approximately 4,586 high complexity laboratories that may be part of an integrated healthcare system. Applying the proportion of high complexity laboratories making IVDs offered as LDTs (5%, 10%, 20%) to this estimate, we estimate the number of high complexity laboratories with LDTs within integrated healthcare systems to range from 229 (=5% x 4,586) to 917 (=20% x 4,586), with a primary estimate of 459 (=10% x 4,586). We assume that about 40 to 70 percent of LDTs from these high complexity laboratories integrated within healthcare systems are likely to be for unmet needs. The estimated number of LDTs that are likely to be for unmet needs range from 10,755 to 24,582, with a primary estimate of 16,900 (see Table A.2).

Table A.2 Number of Affected Laboratories and LDTs For Unmet Needs

Number of affected labs and tests	Primary	Low	High	Calculation
Affected labs **(A)**	1,181	590	2,362	11,808 * 5-20%
Affected IVDs offered as LDTs on the market **(B)**	79,114	39,557	158,227	A * 67
New IVDs offered as LDTs per year **(C)**	7,652	3,826	15,303	A * 1.08 * 6
Affected labs for unmet needs **(D)**	459	229	917	4,586 * 5-20%
Affected LDTs on the market for unmet needs **(E)**	16,900	10,755	24,582	D * 67 * 40-70%
New LDTs for unmet needs **(F)**	1,635	1,040	2,377	D * 1.08 * 6 * 40-70%
Affected IVDs offered as LDTs on the market excluding LDTs for unmet needs	62,213	28,802	133,645	B - E
New IVDs offered as LDTs excluding LDTs for unmet needs	6,017	2,786	12,926	C - F

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

Table A.3 shows the number of affected IVDs offered as LDTs by submission type, excluding tests for unmet needs, using the primary estimates from Table A.2. As explained in section II.D.1, we also expect that among currently-marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the rule, 2 IVDs will be modified per laboratory per year in a manner that falls outside of the enforcement discretion policy for currently marketed IVDs offered as LDTs and will thus be expected to undergo premarket review (2,362 = 1,181 affected labs * 2). We then add this number to the number of new tests (10,013 = 2,362 + 7,652) to estimate total number of new tests in column A of Table A.3. We further break down these estimates by submission type to estimate compliance costs. As mentioned in section II.F.2, we estimate that approximately 50 percent of IVDs currently undergo premarket review (5,007 = 10,013 * 0.5). In addition, we assume that about 40 percent are offered after 510(k) clearance (4,005 = 10,013 * 0.40), 5 percent after De Novo classification (501 = 10,013 * 0.05), and 5 percent after premarket approval (501 = 10,013 * 0.05). We assume these estimated percentages also apply to IVDs offered as LDTs and apply these shares to the estimated total number of affected tests, minus the number of affected tests expected to be offered under an enforcement policy without premarket submission, to estimate the number of IVDs offered as LDTs by submission type. For 2,139 LDTs for unmet needs (2,139 = 459 * 2 * 55% + 1,635)[98], we estimate that approximately 10 percent are offered after premarket approval (214 = 2,139 * 0.10), 80 percent after 510(k) clearance (1,711 = 2,139 * 0.80), and 10 percent after De Novo classification (214 = 2,139 * 0.10). We then subtract the number of new LDTs for unmet needs (column B of Table A.3) from the number of new IVDs offered as LDTs (column A of Table A.3) to calculate the number of new IVDs offered as LDTs excluding LDTs for unmet needs.

[98] We assume that about 40 to 70 percent of LDTs from these high complexity laboratories integrated within a healthcare system are likely to be for unmet needs. We use 55% for the primary estimate.

Table A.3 Number of IVDs offered as LDTs Per Year Excluding LDTs For Unmet Needs

	No. IVDs offered as LDTs, total A	No. LDTs for unmet needs B	No. IVDs offered as LDTs excluding LDTs for unmet needs A - B
Total	10,013	2,139	7,874
Exempt	5,007	-	5,007
PMA	501	214	287
510 (k)	4,005	1,711	2,294
De Novo	501	214	287

2) Reclassification adjustment

On January 31, 2024, FDA announced its intent to initiate the reclassification process for most IVDs that are currently Class III into Class II. The majority of these tests are infectious disease and companion diagnostic IVDs. Reclassification would allow manufacturers of certain types of tests to seek marketing clearance through the less burdensome 510(k) pathway rather than the PMA pathway. FDA also intends to continue taking a risk-based approach in the initial classification of IVDs to determine the appropriate level of regulatory controls and whether a new test may be classified into Class II through De Novo classification (and special controls established), rather than being class III and subject to the PMA pathway. Based on our experience, we believe that special controls could be developed that, along with general controls, could provide a reasonable assurance of safety and effectiveness for most future companion diagnostic and infectious disease IVDs. As such, first of a kind submission for such tests would be expected to submit a De Novo, with follow-on IVDs submitting 510(k) notifications. Therefore, our estimates for the number of affected IVDs that will be subject to certain requirements were adjusted based on the anticipated number of submissions following the potential reclassifications and considering that most future companion diagnostic and infectious disease IVDs would be reviewed through the De Novo and 510(k) pathways.

To estimate anticipated rates of submissions going forward, we rely on historical data for total IVD original and supplemental PMA submissions where FDA review started in the last ten fiscal years (FY 2014-2023). We use information for IVD PMA submissions received per fiscal year for certain CDRH-regulated infectious disease and companion diagnostic tests that have either been recently down classified or for which FDA intends to propose reclassification (Table A.4). The number of estimated De Novo submissions per year going forward is estimated based on the number of "first of a kind (FOAK)" original PMA submissions since, going forward, we would expect new FOAK tests to submit a De Novo instead of a PMA. The number of estimated 510(k) submissions per year going forward is estimated by considering the number of non-FOAK original PMA submissions as well as PMA supplements since, going forward, we would expect these submissions to be 510(k)s instead. (We excluded "135-Day Review Track for 30-Day Notice" and "Special CBE" PMA supplement types from our counts since no 510(k) would be expected for these types of modifications for Class II devices).

We use these data to calculate the reduction in anticipated PMA submissions and the increase in anticipated De Novo and 510(k) submissions going forward, following potential reclassification and considering that most future companion diagnostic and infectious disease IVDs would be Class II. This is represented by the last three columns of Table A.4, showing the rate of remaining PMAs, the rate of new De Novos, and the rate of new 510(k)s anticipated per year, respectively. Then we use these rates to determine the new estimates, as shown in Table A.5. For example, we multiply the remaining PMA rate (Column F of Table A.4) of 0.40 by the estimated number of PMAs before potential reclassification (Table A.5) to obtain the number of PMAs expected after potential reclassification (287 * 0.40 = 115) (Table A.5). We then multiply the De Novo rate of 0.06 (Column G of Table A.4) by the number of PMAs before potential

reclassification and add to the number of De Novo submissions before potential reclassification to estimate the number of De Novo submissions after potential reclassification (287 * 0.06 + 287 = 304) (Table A.5).

Table A.4 Rate of Potential Reclassification of PMA Submission Per Fiscal Year (FY 2014-2023)

Review Track	**(A)** Average Historical IVD submissions per Year	**(B)** # from column A that fall into procodes considered for reclassification	**(C)** Average FOAK used to estimate future # De Novo per Year	**(D)** Average non-FOAK used to estimate future # 510(k) per Year	**(E)** Estimated # Remaining PMA per year in future	**(F) Remaining PMA Rate =(E)/(A)**	**(G) De Novo Rate =(C)/(A)**	**(H) 510(k) Rate =(D)/(A)**
PMA Original	11.7	7.0	0.7	6.3	4.7	0.40	0.06	0.54
135 Review Track For 30-Day Notice	13.7	5.3	0.0	0.0	8.4	0.61	0.00	0.00
Normal 180 Day Track	27.4	17.3	0.0	17.3	10.1	0.37	0.00	0.63
Normal 180 Day Track No User Fee	15.8	9.4	0.0	9.4	6.4	0.41	0.00	0.59
Panel Track	7.7	4.8	0.0	4.8	2.9	0.38	0.00	0.62
Real-Time Process	53.3	25.9	0.0	25.9	27.4	0.51	0.00	0.49
Special CBE	11.3	5.5	0.0	0.0	5.8	0.51	0.00	0.00

Table A.5 Number of Submissions for IVDs offered as LDTs Before and After Potential Reclassification

Submission Type	**Before Potential Reclassification**			**After Potential Reclassification**		
	Primary	Low	High	Primary	Low	High
PMA	287	143	574	115	58	230
510(k)	2,294	1,147	4,588	2,479	1,239	4,958
De Novo	287	143	574	304	152	608
PMA supplements	67	33	133	35	17	70

3) NYS CLEP review adjustment

As discussed in the preamble, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs that are approved by NYS CLEP. Therefore, we reduce the estimated number of premarket submissions to FDA by the number of premarket submissions expected to go to NYS CLEP. We use an estimate of the number of

premarket submissions expected to be reviewed by NYS CLEP, rather than an estimate of the number of LDTs expected to be approved by NYS CLEP, due to the assumption that neither NYS CLEP nor FDA will approve/authorize 100% of the submissions reviewed, and workload costs are based on the number of submissions reviewed, not the number approved/authorized.

NYSDOH provided information indicating that they review an average of 888 LDTs per year, including high risk, moderate risk, low risk, and clinical trial IVDs based on NYSDOH criteria. Accounting for FDA's assumption that 50% of IVDs offered as LDTs will be low risk and not subject to premarket review and that 21% of new IVDs offered as LDTs per year will fall within the enforcement discretion policy for unmet needs (0.21 = 1,635 new LDTs for unmet needs per year / 7,652 new IVDs offered as LDTs per year; see Table A.2), we estimate that an average of 351 (= [100% - 21%] x 50% x 888) new IVDs offered as LDTs per year that would normally be submitted to FDA for premarket review would not undergo FDA premarket review as a result of the enforcement discretion policy with respect to LDTs approved by NYS CLEP . We then estimate that 12.1% of premarket submissions for IVDs offered as LDTs would be reviewed by NYS CLEP (and that these would not be submitted to FDA for review) by dividing 351 by 2,898 (the total number of new PMAs, 510(k)s, and De Novo submissions per year for affected tests, see Table A.5), excluding those that would be under the unmet needs enforcement discretion policy (0.121 = 351 / 2,898).

We thus exclude 12.1% from the number of affected tests after potential reclassification (Table A.5). Table A.6 below shows the final number of premarket submissions for IVDs offered as LDTs, excluding tests for unmet needs and submissions for LDTs expected to be reviewed by NYS CLEP, when estimating the costs of Stages 4 and 5 in section II.F.4. For example, we estimate the number of PMAs to be 101 (=115 – 115*0.121).

Table A.6 Number of IVD Submissions After Potential Reclassification and Excluding Tests for Unmet Needs and LDTs Reviewed by NYS CLEP

Submission Type	Primary	Low	High
PMA	101	51	203
510(k)	2,179	1,090	4,359
De Novo	267	134	534
PMA supplements	31	15	61

Appendix B. Final Small Entity Analysis Estimates

The purpose of this Appendix is to explain the steps for calculating the number of laboratories and existing IVDs offered as LDTs per receipt size category that was used for Section III. Final Small Entity Analysis. In Table 48 of Section III. Final 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 the phaseout policy on small entities. We initially use our estimated total market revenue for IVDs offered as LDTs of $14 billion in the bottom of column E in Table B.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 based on the assumption that 35% of revenue for this NAICS category is from IVDs offered as LDTs.[99] We also re-classify enterprise size categories given our new estimated average receipts per lab (Table B.2).

Table B.1 Growth Adjusted Annual Receipts from IVDs Offered as LDTs by Enterprise Size (2022, U.S. Dollars)		
Number of Firms and Receipts by Enterprise Receipt Size 2017	**Receipts Only IVDs Offered as**	**Calculation**

[99] This is also explained in detail in section II.D.3 Baseline Market Revenue.

I	Enterprise Size ($1,000)	Firms	Receipts ($1,000) D	LDTs ($1,000) in 2022 dollars adjusted for growth since 2017 E	
1	< $150	438	$22,315	$12,575	E Total * D1/D Total
2	$151 - $999	933	$250,134	$140,954	E Total * D2/D Total
3	$1000 - $1,999	413	$301,551	$169,929	E Total * D3/D Total
4	$2,000 - $3,999	481	$779,302	$439,148	E Total * D4/D Total
5	$4,000 - $5,999	343	$1,224,596	$690,078	E Total * D5/D Total
6	$6,000 - $9,999	146	$860,008	$484,627	E Total * D6/D Total
7	$10,000 - $14,999	77	$595,808	$335,747	E Total * D7/D Total
8	$15,000 - $19,999	115	$1,245,731	$701,988	E Total * D8/D Total
9	$20,000 - $24,999	79	$1,168,397	$658,409	E Total * D9/D Total
10	$25,000 - $29,999	21	$380,304	$214,307	E Total * D10/D Total
11	$30,000 - $39,999	43	$908,377	$511,884	E Total * D11/D Total
12	$40,000 - $49,999	15	$460,659	$259,588	E Total * D12/D Total
13	$50,000 - $99,999	67	$2,190,319	$1,234,278	E Total * D13/D Total
14	$100,000 +	194	$25,270,700	$14,240,421	E Total * D14/D Total
	Total	**3,365**	$35,658,201	$20,093,935	

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 1,275 (total LDT labs) to obtain 166 (438/3,365*1,275 = 166). We repeat this calculation for the rest of the rows. We then estimate the average receipts per laboratory by receipt size category.

Table B.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 IVDs Offered as LDTs Only ($1,000) in 2022 dollars adjusted for growth since 2017	LDT Labs (1,181)	Average Receipts per lab
1	< $150	438	$22,315	$12,575	166	$76
2	$151 - $499	933	$250,134	$140,954	354	$399
3	$500 - $999	413	$301,551	$169,929	157	$1,086
4	$1,000 - $2,999	481	$779,302	$439,148	182	$2,409
5	$3,000 - $5,999	343	$1,224,596	$690,078	130	$5,309

6	$6,000 - $7,999	146	$860,008	$484,627	55	$8,759
7	$8,000 - $9,999	77	$595,808	$335,747	29	$11,506
8	$10,000 - $14,999	115	$1,245,731	$701,988	44	$16,107
9	$15,000 - $19,999	79	$1,168,397	$658,409	30	$21,991
10	$20,000 - $23,999	21	$380,304	$214,307	8	$26,928
11	$24,000 - $29,999	43	$908,377	$511,884	16	$31,411
12	$30,000 - $35,999	15	$460,659	$259,588	6	$45,665
13	$36,000 - $99,999	67	$2,190,319	$1,234,278	25	$48,610
14	$100,000 +	194	$25,270,700	$14,240,421	74	$193,689
	Total	3,365	$35,658,201	$20,093,935	1,275	$15,757

We obtain the number of IVDs offered as LDTs per receipts size category in column D by multiplying column C times 79,114 (which is our estimated number of affected IVDs offered as LDTs currently on the market, as described in section II.D.1). See Table B.3.

Table B.3 Share of LDTs Offered as LDTs and IVDs Offered as LDTs per Receipt Category

i	**Enterprise Size ($1,000)**	**Percent Firms by Receipt Size A**	**LDT LABS B =Ai x 1,181)**	**Percent Receipts by Receipt Size C**	**IVDs offered as LDTs per receipt category * D**
1	< $150	13%	166	0.06%	56
2	$151 - $999	28%	354	0.70%	625
3	$1000 - $1,999	12%	157	0.85%	754
4	$2,000 - $3,999	14%	182	2.19%	1,948
5	$4,000 - $5,999	10%	130	3.43%	3,061
6	$6,000 - $9,999	4%	55	2.41%	2,150
7	$10,000 - $14,999	2%	29	1.67%	1,489
8	$15,000 - $19,999	3%	44	3.49%	3,114
9	$20,000 - $24,999	2%	30	3.28%	2,920
10	$25,000 - $29,999	1%	8	1.07%	951
11	$30,000 - $39,999	1%	16	2.55%	2,270
12	$40,000 - $49,999	0%	6	1.29%	1,151
13	$50,000 - $99,999	2%	25	6.14%	5,475
14	$100,000 +	6%	74	70.87%	63,163
	Total	100%	1,275		89,127

* Column D is the product of each row in Column C and 79,114.

The following four tables show detailed calculations leading to estimating cost as a percent of receipts using the primary, low and high estimates.

Table B.4 Detailed Calculations for Percent Receipts and Average Receipts per Lab

i	**Enterprise Size ($1,000)**	**LDT Labs**	**Receipts by Size Category**	**Percent Receipts by Receipt Category**	**Average Receipts per Lab**
	Calculation	*A*	*B*	$C_i = B_i / B_{total}$	$D = B_i / A_i$
1	< $150	166	$12,574,839	0.06%	$75,755
2	$151 - $999	327	$140,954,286	0.70%	$430,532
3	$1000 - $1,999	145	$169,928,542	0.85%	$1,172,533
4	$2,000 - $3,999	169	$439,148,446	2.19%	$2,601,807
5	$4,000 - $5,999	120	$690,078,339	3.43%	$5,733,410
6	$6,000 - $9,999	51	$484,627,495	2.41%	$9,459,407
7	$10,000 - $14,999	27	$335,746,806	1.67%	$12,425,958
8	$15,000 - $19,999	40	$701,988,231	3.49%	$17,395,652
9	$20,000 - $24,999	28	$658,409,354	3.28%	$23,750,766
10	$25,000 - $29,999	7	$214,307,047	1.07%	$29,082,108
11	$30,000 - $39,999	15	$511,884,157	2.55%	$33,924,383
12	$40,000 - $49,999	5	$259,588,303	1.29%	$49,317,674
13	$50,000 - $99,999	24	$1,234,277,833	6.14%	$52,498,495
14	$100,000 +	68	$14,240,421,072	70.87%	$209,184,656
	Total	1,193	$20,093,934,751		$16,841,846

Table B.5 Annualized Costs by Receipt Category - Primary, Low and High Estimates

i	**Enterprise Size ($1,000)**	**Annualized Cost by Receipt Category Primary, Low and High Estimates (7%)**		
	Calculation	$E_{(primary)}$ = $1,165,774,775 x C_i	$E_{(low)}$ = $510,386,965 x C_i	$E_{(high)}$ = $3,222,662,070 x C_i
1	$151 - $999	$729,545	$319,402	$2,016,751
2	$1000 - $1,999	$8,177,639	$3,580,246	$22,606,226
3	$2,000 - $3,999	$9,858,617	$4,316,194	$27,253,113
4	$4,000 - $5,999	$25,477,747	$11,154,393	$70,430,558
5	$6,000 - $9,999	$40,035,759	$17,528,025	$110,674,655
6	$10,000 - $14,999	$28,116,271	$12,309,563	$77,724,481
7	$15,000 - $19,999	$19,478,771	$8,527,986	$53,847,019
8	$20,000 - $24,999	$40,726,726	$17,830,537	$112,584,761
9	$25,000 - $29,999	$38,198,443	$16,723,631	$105,595,588
10	$30,000 - $39,999	$12,433,292	$5,443,410	$34,370,530
11	$40,000 - $49,999	$29,697,600	$13,001,884	$82,095,900

12	$50,000 - $99,999	$15,060,340	$6,593,556	$41,632,731
13	$100,000 +	$71,608,173	$31,350,720	$197,953,283
14	Total	$826,175,853	$361,707,420	$2,283,876,474
	Total	$1,165,774,775	$510,386,965	$3,222,662,070

Table B.6 Annualized Costs per Lab Receipt Category - Primary, Low and High Estimates

i	**Enterprise Size ($1,000)**	**Annualized Cost per lab by Receipt Category Primary, Low and High Estimates (7%)**		
	Calculation	$F_{(primary)} = E_{(primary)} / A_i$	$F_{(low)} = E_{(low)} / A_i$	$F_{(high)} = E_{(high)} / A_i$
1	< $150	$4,395	$1,924	$12,150
2	$151 - $999	$24,978	$10,936	$69,049
3	$1000 - $1,999	$68,026	$29,782	$188,051
4	$2,000 - $3,999	$150,947	$66,086	$417,277
5	$4,000 - $5,999	$332,631	$145,629	$919,523
6	$6,000 - $9,999	$548,799	$240,269	$1,517,098
7	$10,000 - $14,999	$720,908	$315,620	$1,992,873
8	$15,000 - $19,999	$1,009,231	$441,850	$2,789,912
9	$20,000 - $24,999	$1,377,930	$603,271	$3,809,144
10	$25,000 - $29,999	$1,687,235	$738,687	$4,664,184
11	$30,000 - $39,999	$1,968,166	$861,681	$5,440,787
12	$40,000 - $49,999	$2,861,227	$1,252,671	$7,909,561
13	$50,000 - $99,999	$3,045,766	$1,333,464	$8,419,700
14	$100,000 +	$12,136,110	$5,313,301	$33,549,002
	Total	$977,101	$427,784	$2,701,093

Table B.7 Costs as a Percent of Receipts - Primary, Low and High Estimates

i	**Enterprise Size ($1,000)**	**Annualized Cost as a Percent of Receipts per lab Primary, Low and High Estimates (7%)**		
	Calculation	$G_{(primary)} = F_{(primary)} / D_i$	$G_{(low)} = F_{(low)} / D_i$	$G_{(high)} = F_{(high)} / D_i$
1	$151 - $999	5.80%	2.54%	16.04%
2	$1000 - $1,999	5.80%	2.54%	16.04%
3	$2,000 - $3,999	5.80%	2.54%	16.04%
4	$4,000 - $5,999	5.80%	2.54%	16.04%
5	$6,000 - $9,999	5.80%	2.54%	16.04%
6	$10,000 - $14,999	5.80%	2.54%	16.04%
7	$15,000 - $19,999	5.80%	2.54%	16.04%
8	$20,000 - $24,999	5.80%	2.54%	16.04%
9	$25,000 - $29,999	5.80%	2.54%	16.04%

10	$30,000 - $39,999	5.80%	2.54%	16.04%
11	$40,000 - $49,999	5.80%	2.54%	16.04%
12	$50,000 - $99,999	5.80%	2.54%	16.04%
13	$100,000 +	5.80%	2.54%	16.04%
14	Total	5.80%	2.54%	16.04%

Table B.8 below, describes total discounted costs to industry along with the percent share of costs by stage, LDTs affected, costs per LDT along with percent affected tests, entities affected and cost per lab.

Table B.8 Discounted Costs to Industry and Percentage, by affected LDTs, by Entity and by Stage

Stage	Discounted Costs ($ Millions, 7%, 20 years)	Percent Costs	LDTs Affected	Costs per LDT	Percent Tests Affected	Entities Affected	Costs per Lab
Stage 1	$83	7%	10,013	$8,335	11%	1,275	$65,457
Stage 2	$12	1%	10,013	$1,187	11%	1,275	$9,326
Stage 3	$21	2%	52,641	$391	59%	849	$24,216
Stage 4	$361	31%	132	$2,735,305	0.1%	849	$424,763
Stage 5	$689	59%	2,446	$281,807	3%	849	$812,045
Total	**$1,166**	**100%**		**$3,027,025**			**$1,335,807**