

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

Economics Staff  
Office of Economics and Analysis  
Office of Policy, Legislation, and International Affairs  
Office of the Commissioner



## **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 most 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.<sup>1,2</sup> 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 applicable statutory and regulatory requirements. Additional costs include costs to FDA, which we include in our estimates. We estimate that the annualized benefits over 20 years range from \$18.34 billion to \$198.51 billion at a seven percent discount rate, with a primary estimate of \$63.77 billion, and from \$12.14 billion to \$130.52 billion at a three percent discount rate, with a primary estimate of \$41.9 billion. The annualized costs range from \$563 million to \$3.56 billion at a seven percent discount rate, with a primary estimate of \$1.28 billion, and from \$600 million to \$3.79 billion at a three percent discount rate, with a primary estimate of \$1.37 billion.

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<sup>1</sup> See discussion of “problematic IVDs” in section I.B below.

<sup>2</sup> See discussion of “IVDs offered as LDTs” in section V.A 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 most 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 most 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 inaccurate or 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 FDA's general enforcement discretion approach for most 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 applicable 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 class III 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 \$18.34 billion to \$198.51 billion, with a primary estimate of \$63.77 billion per year. At a three percent discount rate, 20-year annualized benefits range from \$12.14 billion to \$130.52 billion, with a primary estimate of \$41.9 billion per year. At a seven percent discount rate, 20-year annualized costs range from about \$563 million to \$3.56 billion, with a primary estimate of \$1.28 billion per year. At a three percent discount rate, annualized costs range from about \$600 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 \$24 million to \$95 million, with a primary estimate of \$48 million per year. At a three percent discount rate, 20-year annualized transfers range from \$34 million to \$136 million, with a primary estimate of \$68 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 \$59 million to \$235 million, with a primary estimate of \$117 million per year. At a three percent discount rate, 20-year annualized costs to FDA range from \$62 million to \$250 million, with a primary estimate of \$125 million per year. Factoring in offsets from user fees at current levels, estimated costs to FDA are reduced to \$35 million to \$139 million at a seven percent discount rate, with a primary estimate of \$70 million, and to \$29 million to \$114 million at a three percent discount rate, with a primary estimate of \$57 million, covering approximately half 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) | \$63,765         | \$18,344     | \$198,513     | 2022         | 7%            | 20 years       |  |
|             |                                 | \$41,903         | \$12,141     | \$130,521     | 2022         | 3%            | 20 years       |  |
|             | Annualized Quantified           |                  |              |               |              | 7%            |                |  |
|             |                                 |                  |              |               |              | 3%            |                |  |
| Qualitative |                                 |                  |              |               |              |               |                |  |
| Costs       | Annualized Monetized (\$m/year) | \$1,283          | \$563        | \$3,558       | 2022         | 7%            | 20 years       | A portion of foreign costs will be passed on to domestic consumers. We estimate that up to \$124.53 million in annualized costs (7%, 20 years) to foreign facilities could be passed on to domestic consumers. |
|             |                                 | \$1,367          | \$600        | \$3,788       | 2022         | 3%            | 20 years       |  |
|             | Annualized Quantified           |                  |              |               |              | 7%            |                |  |
|             |                                 |                  |              |               |              | 3%            |                |  |
| Qualitative |                                 |                  |              |               |              |               |                |  |

| Category  |  | Primary Estimate | Low Estimate | High Estimate | Units        |               |                | Notes |
|-----------|--|------------------|--------------|---------------|--------------|---------------|----------------|-------|
|           |  |                  |              |               | Year Dollars | Discount Rate | Period Covered |       |
| Transfers | Federal Annualized Monetized (\$m/year)  | \$48             | \$24         | \$95          | 2022         | 7%            | 20 years       |       |
|           |  | \$68             | \$34         | \$136         | 2022         | 3%            | 20 years       |       |
|           | From: Device Industry  |                  |              | To: FDA       |              |               |                |       |
|           | Other Annualized Monetized (\$m/year)  |                  |              |               |              | 7%            |                |       |
|           |  |                  |              |               |              | 3%            |                |       |
|           |  | From:            |              |               | To:          |               |                |       |
| Effects   | State, Local, or Tribal Government:<br>Small Business: The phaseout policy will have a significant economic impact on a substantial number of small laboratories that manufacture IVDs offered as LDTs.<br>Wages:<br>Growth: |                  |              |               |              |               |                |       |

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) document 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 IVDs offered as LDTs per year, whereas smaller laboratories may focus on fewer IVDs overall and may not introduce many or any new IVDs every 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. 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).<sup>3</sup> 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 applicable 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 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

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<sup>3</sup> 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>.

policies for other types of tests (see section V.A of the preamble) and we have revised our estimates accordingly. Our updated estimates are addressed in section 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%.

**Response:** While we no longer directly estimate this parameter in our final analysis, 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 650,000 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. [3]). Our primary estimate thus represents about five to six 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.2.a “Cancer.” Using statistics from the NYS Department of Health Clinical Laboratory Evaluation Program (CLEP) (Ref. [4]) and FDA’s 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests,<sup>27</sup> 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 a problematic IVD. 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<sup>4</sup> Tests)

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.” Relatedly, 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

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<sup>4</sup> 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.

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 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.B.2.a “Cancer,” 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 E.2, 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.B.2.a "Cancer," 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. For additional discussion of this comment please see our response to Comment 271 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. [5] [6]). 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. [7]). 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 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.<sup>5</sup> 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. In including the example of NIPS in this final analysis, we consider our expectation that phasing out enforcement discretion will create opportunities for greater regulatory oversight to ensure tests are appropriately safe and effective for their intended use and truthful, accurate, and clear statements about test use and performance to prevent patient and provider misunderstanding.

## **11. Comments (Innovation)**

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

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<sup>5</sup> Available at: <https://www.fda.gov/medical-devices/safety-communications/genetic-non-invasive-prenatal-screening-tests-may-have-false-results-fda-safety-communication>

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 contested that predetermined change control plans (PCCPs) would 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 IDTs 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:** FDA does not agree that the phaseout policy will hinder the timely development and deployment of innovative IVDs offered as LDTs. First, we do not consider unsafe or ineffective products to be beneficial innovation. 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 genuine innovation. By applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, FDA will reduce regulatory uncertainty, which will give stakeholders clarity and confidence, and facilitate investment in the development of innovative IVDs. Additionally, FDA's phaseout approach 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 genuine 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 preventative 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. In addition, we note that in the final phaseout policy, which would also affect small laboratories and Academic Medical Centers (AMCs), the number of laboratories that scale back operations or exit the market may be reduced in comparison to the estimates in our preliminary analysis.

FDA generally 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 this rule and that are not modified, or that are modified in certain limited ways as described in the preamble . FDA also generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs approved by NYS CLEP.<sup>6</sup>

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<sup>6</sup> 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.A.3.b 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.A.3.b of the preamble. For additional discussion of the NYS CLEP premarket review program, see section V.A.3.b of the preamble.

FDA also intends to exercise enforcement discretion and generally not enforce ~~respect to~~ premarket review requirements and QS requirements (except for applicable 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 will help to support coverage and reimbursement determinations for IVDs offered as LDTs, which we anticipate will make certain IVDs offered as LDTs for which there is a reasonable assurance of safety and effectiveness more affordable for patients. As a result, FDA does not agree that patients will necessarily be disincentivized from seeking preventative care resulting in increased costs to the healthcare system as a result of the phaseout policy.

In addition, phasing out the general enforcement discretion approach for most 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. FDA therefore does not agree that ending the general enforcement discretion approach for most LDTs as described in the final phaseout policy will necessarily increase costs to individuals, insurers such as Medicare and Medicaid, or the overall healthcare system. While 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.A 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 applicable 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.A of the preamble, which means laboratories would 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 and cost of SOPs.

**Response:** FDA has revised the phaseout policy to include several enforcement discretion policies for certain types of tests as described in section V.A of the preamble. For example, FDA intends to exercise enforcement discretion for premarket review and QS requirements (except for applicable 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 tests as described in section V.A of the preamble. For example, FDA intends to exercise enforcement discretion for 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. 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 VI.A 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- 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 subject to 510(k) requirements 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, though we note that both FDA and CMS have long considered their roles not to be redundant, but to be 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 all requirements for LDTs manufactured and used within the Veterans Health Administration (VHA) and the Department of Defense (DoD). See section II.G of this analysis.

#### **17. Comment (Firm Exit, Small Entities, and Market Concentration)**

As discussed in section VI.F 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, resulting in laboratory closures, consolidation of smaller entities, and monopolies in the testing space as large laboratories take more of the market share. Several comments stated that large laboratories will be advantaged as they have the resources to afford the necessary staffing and other costs related to test development and

regulatory submission and emphasized the thin financial margins with which small laboratories operate.

Other comments have claimed that certain laboratories, such as academic, small, public health, and specialty laboratories, will disproportionately exit the market relative to their counterparts. For small laboratories specifically, some comments claimed that many do not have the revenue to cover the increased cost of meeting applicable requirements if the phaseout policy is finalized and will have to exit the market.

Other comments stated that by reducing the availability of IVDs offered as LDTs, the phaseout policy would lead to delays in testing, including by potentially increasing reliance on reference laboratories which may increase the time individuals obtained test results. Some comments expressed concern that the remaining laboratories 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. One comment discussed small labs within a medical system closing, stating that the removal of pathologists due to this kind of lab exit would decrease the quality of patient care. Two comments have addressed the exit of academic labs as particularly concerning given their role in diagnosing and monitoring rare diseases.

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. Further, many comments stated that a potential increase in

firms exiting the market could increase unemployment among laboratory technicians, increase market concentration in the healthcare industry, and decrease the availability of laboratory tests.

**Response:** FDA appreciates the concerns regarding financial and administrative challenges for smaller laboratories. To the extent smaller laboratories may be disproportionately impacted by the phaseout of the general enforcement discretion approach for most LDTs, FDA anticipates that the enforcement discretion policies discussed in the preamble of the final rule will sufficiently address these concerns and help to avoid undue disruption to the test market. As noted in Table 51, costs and transfers of the phaseout policy are estimated to be about 3 percent of small laboratories' yearly receipts. We therefore believe that the likelihood that the phaseout policy will cause widespread, significant market exit of small laboratories is low.

In particular, given that FDA generally 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.A of the preamble), we do not expect significant market concentration to result from the phaseout policy.

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.

#### D. Summary of Changes

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 enforcement discretion policies:

- FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of applicable 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.A.3.c 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 applicable 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 all requirements for LDTs manufactured and used 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 applicable 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.

## 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.

## 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 increased due to quantifying benefits that we previously discussed qualitatively or only addressed incompletely. In particular, 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 fifth of the preliminary estimate, we now also use this information to include general, yearly estimates of morbidity avoidable in cardiovascular and infectious diseases. Primarily as a result of the broader treatment of these other disease categories, enabled by additional information, estimated total annualized benefits in this final estimate are about twice the preliminary estimate.

In response to comments, and as described in section II.E.2 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. [4]) and FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests.<sup>27</sup>

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]) now supplanted

by broader analysis of health benefits in section II. E of this analysis. 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.4, we adjust estimates of benefits to account for existing review by NYS CLEP and enforcement discretion 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 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, FDA generally has exercised enforcement discretion such that it generally has not enforced applicable 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 tests;
- 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 regulatory 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 run in large volumes in reference laboratories for patients from different institutions around the world and are sometimes assembled using components intended for research use only. Some LDTs are manufactured by corporations that market the tests nationwide as they accept specimens from patients across the country and run their tests in very large volumes in a single laboratory.<sup>7</sup> 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. [8]). IVDs offered as LDTs are a growing sector of that market (Ref. [9]). 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

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<sup>7</sup> See, e.g., Pew Research Center (Ref. [19]), Grand View Research (Ref. [9]), and Congressional Research Service (Ref. [72]). 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.

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.

While laboratories that offer IVDs are regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA),<sup>8</sup> 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. [10]). 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;

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<sup>8</sup> 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>.

- 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 tests 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. [11]).”

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.<sup>9</sup> 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.<sup>10</sup>

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<sup>9</sup> 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.

<sup>10</sup> Memorandum to File from Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs,

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. [12]). 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. [13]).

News and other outlets have also reported on problems with IVDs offered as LDTs, including the New York Times (Ref. [7]), and lawsuits have been filed relating to pharmacogenomic and non-invasive prenatal screening IVDs offered as LDTs.<sup>11</sup>

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 happened to date, even though the disparity between IVDs offered as

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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

<sup>11</sup> 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).



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, and would be complicated by the rapidly changing market, with new tests introduced regularly. As for patients, ability to internalize the relevant risks may be precluded by not knowing the 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. [14] and [15]). 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. [16] and [17]). 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 most 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.<sup>12</sup> 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.<sup>13</sup>

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<sup>12</sup> 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 under the First Fundamental Theorem of Welfare Economics. Related concepts include market failure, government failure or behavioral bias (Ref. [67]).

<sup>13</sup> 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. [68]).

In order to curtail offering of problematic tests, FDA is phasing out the general enforcement discretion for most 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.

### 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 most LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs. In developing the phaseout policy, FDA has considered a number of factors, including:

- the public health importance of better assuring the safety and effectiveness of IVDs offered as LDTs;
- the need to avoid undue disruption to clinical testing;
- the time it might take for laboratories to come into compliance with FDA requirements; and

- the need for adequate resources to implement the phaseout policy in a manner that does not undermine reasonable expectations with regards to premarket review timing (per the current Medical Device User Fee Amendments (MDUFA) V agreement).

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

#### 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 most 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. [18]).<sup>14</sup> 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

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<sup>14</sup> This includes laboratories operating under State licensure programs deemed exempt from CLIA.

LDT because they are not designed, manufactured, and used within a single laboratory.<sup>1516</sup>

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.A 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
- 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,

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<sup>15</sup> 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.

<sup>16</sup> 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. [10]).

- for HLA antibody screening and monitoring, or
- for conducting real and “virtual” HLA crossmatch tests.

FDA will also continue enforcement discretion 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 exercise enforcement discretion for LDTs manufactured and used 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.

In addition, tests exclusively used for public health surveillance are not affected by the phaseout policy. These tests are distinct from other tests where: (1) they are intended solely for use on systematically collected samples for analysis and interpretation of health data in connection with disease prevention and control, and (2) tests results are not reported to patients or their healthcare providers.

We lack information to quantify the number of tests that fall in the above categories and thus they are not included 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 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 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.

FDA also generally intends to exercise enforcement discretion with respect to premarket review for two categories of IVDs manufactured by laboratories:

- LDTs approved by NYS CLEP; and
- LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

For 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 test for the disease/condition; (2) there is an FDA-authorized test for the disease/condition but it is not indicated for use on the patient, or a unique attribute needs to be added to the test to meet the patient's needs; or (3) there is an FDA-authorized test but it is not available to the patient. This is discussed further in section V.A of the preamble.

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.A 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 would 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 would 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. [19]). 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. [20]). 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. [21]) 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. [20]). 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. [22]). 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.<sup>17</sup>

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. [21]). 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. [20]), 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 that laboratories within NYS that manufacture IVDs offered as LDTs introduce an average of 6

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<sup>17</sup> 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.

new IVDs offered as LDTs per year.<sup>18</sup> 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.<sup>19</sup> In addition, we expect 50 percent of currently marketed IVDs offered as LDTs ( $34 \text{ IVDs offered as LDTs per laboratory} = 67 * 0.5$ ) 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 ( $2 = 34 / 20 \text{ years}$ ). 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).

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.

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<sup>18</sup> 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.

<sup>19</sup> We use an average of firms' entry and exit rates from 2010 to 2018 in the U.S. (8 percent) (Ref. [22]).

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

|  | <b>Primary Estimate</b> | <b>Low Estimate</b> | <b>High Estimate</b> |
|--|-------------------------|---------------------|----------------------|
| 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.<sup>20</sup> 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).<sup>21</sup>

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. [9] [23]).<sup>22</sup>

<sup>20</sup> 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 621511 which 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>

<sup>21</sup> 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.

<sup>22</sup> The calculation for future value in 6 years using a CAGR of 4.2% is:

$$\text{Future Value (FV)} = \text{Present Value (PV)} \times (1+4.2\%)^6 = \$15 \text{ billion} \times (104.2\%)^6 = \$19 \text{ billion.}$$

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

| Year | <b>Low</b><br>Projection (\$1,000)<br>(4.2% CAGR) | <b>Primary</b><br>(Average between low<br>and high projection) | <b>High</b><br>Projection (\$1,000)<br>(6% CAGR) |
|------|---|--|--|
| 2023 | \$19,062,398                                      | \$20,093,935   | \$21,125,471                                     |
| 2030 | \$25,424,450                                      | \$28,594,674   | \$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 (Ref. [24]). The estimated annual reviews for premarket submissions/applications are adjusted for the enforcement discretion polices, 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<br>Average<br>(FY 2017 to<br>2021) | Estimated Annual Reviews for New IVDs<br>Offered as LDTs |     |       |
|---|---|--|-----|-------|
|   |   | Primary  | Low | High  |
| Original PMAs, PDPs, Panel-Track<br>PMA Supplements | 73  | 104*   | 52* | 207*  |
| 510(k) Premarket Notifications                      | 3,877                                     | 957  | 479 | 1,914 |
| De Novo Classification Requests                     | 66  | 269  | 135 | 539   |

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 41.

\* The estimated reviews include original PMAs and panel-track PMA supplements. See Table 32 and Table 34 for estimated numbers of original PMAs and panel-track PMA supplements, respectively.

### 4. Baseline Risk of Problematic IVDs

We measure benefits of phasing out the general enforcement discretion approach for most LDTs against a baseline scenario in which FDA continues exercising enforcement discretion

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 most LDTs.

To estimate the baseline incidence of harms that can be avoided by phasing out the general enforcement discretion approach for most 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. [25]). 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.2, 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 most 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 reviewed by the NYSDOH review program NYS CLEP 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 that enforcement discretion policy for LDTs approved by NYS CLEP applies only to premarket review requirements and 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.

Using a case study, we additionally consider that, without the phaseout policy, problematic IVDs offered as LDTs would also likely see use during future public health emergencies similar to the COVID-19 pandemic.

Finally, in section II.E.4 “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 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, 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 tests under enforcement discretion versus active enforcement. We note, however, as described in section V.A.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 most 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 unauthorized 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 most 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. [25]). Using a case study, we additionally consider that, without the rule, problematic IVDs offered as LDTs would also likely see use during future public health emergencies similar to the COVID-19 pandemic.

##### *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 would 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. [26]).<sup>23</sup> With a correct diagnosis, death can be delayed to a later date than one following an incorrect diagnosis. However, depending on when a misdiagnosis occurs, death might still be delayed to a degree depending on how soon a patient seeks follow-up and receives a correct diagnosis at a later time. Life expectancy in this case would still be shortened compared to if the initial diagnosis had been correct, but this would not necessarily be counted as a death due to misdiagnosis.<sup>24</sup> 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. [25]).

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<sup>23</sup> From Newman-Toker (2023), annual US incidence was 6.0 M vascular events, 6.2 M infections and 1.5 M cancers. Per ‘Big Three’ dangerous disease case, weighted mean error and serious harm rates were 11.1% and 4.4%, respectively. Extrapolating to all diseases (including non-‘Big Three’ dangerous disease categories), the authors estimated 795,000 total serious harms annually in the USA (plausible range 598 000–1 023 000). Sensitivity analyses using more conservative assumptions estimated 549 000 serious harms. Results were compatible with setting-specific serious harm estimates from inpatient, emergency department and ambulatory care (Ref. [26]).

<sup>24</sup> 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. [75]).

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. [27]) 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. Because heart disease will be assessed in a separate section of this regulatory impact analysis, we exclude 22% of these cases (range: 11% to 33%), reflecting an assumption that 50% of vascular events are heart disease (range: 25% to 75%) and 44% (= 6.0M / 13.7M) of misdiagnosis-related fatalities are associated with vascular events.<sup>25</sup> As we are uncertain exactly how many deaths relate to misdiagnosis of cancer, we use a range of 0.09 million, 0.16 million and 0.24 million.

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<sup>25</sup> 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.

Excluding the state of New York proportionally by population,<sup>26</sup> we assume that about 150,554 U.S. misdiagnosis-related cancer deaths occur outside of NY could thus potentially involve tests not covered by NYS CLEP. It is likely that some patients outside of the state of New York are also tested with tests covered 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. [28]). 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 ( $= 150,554 \times 0.91 \times 0.10$ ).

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 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:

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<sup>26</sup> 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>.

- 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. [4]).

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. [4])

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.<sup>27</sup> 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

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<sup>27</sup> 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.

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 5,200 cancer patients 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 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 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. [29]). 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 26,600 harms from diagnostic error among cancer patients.

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

|   | Low    | Primary | High    |
|---|--------|---------|---------|
| a) Deaths from Misdiagnosis (Non-NYS)   | 84,686 | 150,554 | 225,831 |
| b) Percent Tested with IVDs   | 91%    | 91%     | 91%     |
| c) Probability of IVD Being Offered as an LDT   | 3.9%   | 10.0%   | 45.0%   |
| d) Patients Tested with IVDs Offered as LDTs<br>(= a * b * c)                             | 3,006  | 13,700  | 92,478  |
| e) Percent of IVDs offered as LDTs Not Authorized by FDA Following a Premarket Submission | 22%    | 38%     | 54%     |
| f) Tests Using Problematic IVDs Offered as LDTs (= d * e)                                 | 661    | 5,206   | 49,938  |
| g) Percent Leading to Diagnostic Error  | 25%    | 50%     | 75%     |
| h) Treatment-to-Diagnosis Ratio   | 0.88   | 0.9     | 0.92    |
| i) Harms Avoidable by the Phaseout Policy (= f * g * h)                                   | 145    | 2,343   | 34,457  |

### 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. [30]). 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.<sup>28</sup> We then use the RSR to estimate the absolute survival rate (of individuals with cancer who are diagnosed) further down below.

At the bottom of column D, we obtain the average five-year RSR across cancer sites, weighting by percent of total new cancer cases. For example, the weight on the RSR for breast cancer is the number of breast cancers divided by the sum of all new cancer cases (290,560 /

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<sup>28</sup> Relative survival is a net survival measure representing cancer survival in the absence of other causes of death. Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals. The formulation is based on the assumption of independent competing causes of death. The relative survival adjusts for the general survival of the U.S. population for that race, sex, age, and date at which the age was coded.

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)<br>A | Relative Survival (%) (2012–2018)<br>B | % New Cases<br>C | RSR x Percent weight<br>D<br>(=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                                    |
| <b>Sum</b>                       | <b>1,818,030</b>                |  | 100%             | <b>68.60%</b>                           |

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

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. [31]). Per CDC life tables, the 5-year survival rate for all age-66 individuals is approximately 91.13%.<sup>29</sup> 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

<sup>29</sup> 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>



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. [32]) and 11.94 months, or 0.995 years, in cases of lung cancer (Ref. [33]). 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.

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. A reduction in current mortality risk implies a corresponding increase in life expectancy. We use VSLYs derived from the value of a statistical life (VSL) under assumptions of three and seven percent discounting.<sup>30,31</sup> 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 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<br>(3% discounting) | (b) Value Per Case<br>(VSLY 3%)<br>(= a * 3.018) | (c) VSLY<br>(7% discounting) | (d) Value Per Case<br>(VSLY 7%)<br>(= c * 2.708) |
|---------|------------------------------|--|------------------------------|--|
| Low     | \$255,143                    | \$770,084  | \$427,203                    | \$1,157,020                                      |
| Central | \$546,735                    | \$1,650,181                                      | \$915,435                    | \$2,479,329                                      |
| High    | \$832,253                    | \$2,511,942                                      | \$1,393,495                  | \$3,774,090                                      |

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

<sup>30</sup> 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. [34]).

<sup>31</sup> We note that VSLY depends on the choice of discount rate per OMB Circular A-4 (2003).

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

|   | Low           | Primary         | High              |
|---|---------------|-----------------|-------------------|
| a) Harms Avoidable by the Phaseout Policy     | 145           | 2,343           | 34,457            |
| b) Value Per Harm (VSLY using 3% discounting) | \$770,084     | \$1,650,181     | \$2,511,942       |
| c) Value Per Harm (VSLY using 7% discounting) | \$1,157,020   | \$2,479,329     | \$3,774,090       |
| d) Percent Not Internalized at Baseline       | 90%           | 95%             | 100%              |
| e) Total Benefit (VSLY using 3% discounting)  | \$100,819,857 | \$3,672,687,757 | \$86,554,364,622  |
| f) Total Benefit (VSLY using 7% discounting)  | \$151,477,688 | \$5,518,062,262 | \$130,044,372,030 |

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, mode, and maximum taken from row (a) of Table 5;
- 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 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 uniform distributions defined by the low and high estimates in 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. [34]), the low, primary, and high benefit estimates in Table 10 represent the 5<sup>th</sup>, 50<sup>th</sup>, and 95<sup>th</sup> 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

|  | Low | Primary | High |
|--|-----|---------|------|
|--|-----|---------|------|

|  |                 |                 |                  |
|--|-----------------|-----------------|------------------|
| e) Total Benefit (VSLY using 3% discounting) | \$1,225,801,108 | \$4,315,080,594 | \$13,734,584,742 |
| f) Total Benefit (VSLY using 7% discounting) | \$1,843,600,785 | \$6,489,037,557 | \$20,589,623,000 |

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.

*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. [35]). 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. [36]).

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 most LDTs to avoid.

According to the American Heart Association (2023), in the U.S. in 2020, 127.9 million adults 20 years of age or older have some form of cardiovascular disease (Ref. [35]). Excluding the state of New York proportionally by population,<sup>32</sup> we assume that about 120,349,000 such cases are outside of NY and could thus potentially be managed using tests not covered by NYS

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<sup>32</sup> 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>.

CLEP. It is likely that some patients outside of the state of New York are also tested with tests covered 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. [28]). 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 7,462,000 U.S. (non-NY) patients with cardiovascular disease would rely on IVDs offered as LDTs ( $= 120,348,840 \times 0.62 \times 0.10$ ).

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 2,835,000 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. Based on statistics reported by the American Heart Association on treatment rates of high cholesterol (44.9%), hypertension (52%), and diabetes (22%) (Ref. [29]), we estimate that diagnostic error has treatment implications for 22% to 52% of patients, with a central estimate of 44.9%. Thus, using our central estimates, we expect the phaseout policy to avoid about 636,600 harms among patients with cardiovascular disease.

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

|   | Low         | Primary     | High        |
|---|-------------|-------------|-------------|
| a) US Adults 20 or Older with Cardiovascular Disease (Non-NYS)                            | 120,348,840 | 120,348,840 | 120,348,840 |
| b) Percent Tested with IVDs   | 62%         | 62%         | 62%         |
| c) Probability of IVD Being Offered as an LDT   | 3.9%        | 10.0%       | 45.0%       |
| d) Patients Tested with IVDs Offered as LDTs (= a * b * c)                                | 2,910,035   | 7,461,628   | 33,577,326  |
| e) Percent of IVDs Offered as LDTs Not Authorized by FDA Following a Premarket Submission | 22%         | 38%         | 54%         |
| f) Tests Using Problematic IVDs Offered as LDTs (= d * e)                                 | 640,208     | 2,835,419   | 18,131,756  |
| g) Percent Leading to Diagnostic Error  | 25%         | 50%         | 75%         |
| h) Treatment-to-Diagnosis Ratio   | 0.22        | 0.449       | 0.52        |
| i) Harms Avoidable by the Phaseout Policy (= f * g * h)                                   | 35,211      | 636,551     | 7,071,385   |

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. [5] [6]). 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. [5] [6]). If 35% of the StatinCheck test recipients were identified as having the Trp719Arg polymorphism, then 56,000 patients may have been informed that they would respond better to statin therapy than other patients. If these patients received lower-potency statin treatment than is standard, a loss of quality adjusted life years (QALY) likely occurred, though medical expenditures were likely reduced. The use of high-potency statins results in an increase of 0.13 QALYs relative to the use of low-potency statins; the use of high-potency statins costs \$1,069 more than low-potency statins (Ref. [37]). Using a Value of a Quality-Adjusted Life Year (VQALY) of \$649,215 (the central VQALY that assumes three percent discounting), the value of lost health from using low-potency statins instead of high-potency statins is \$84,398 (= \$649,215 x 0.13). The net lost benefit for each person using low-potency statins is \$83,329 (= \$84,398 - \$1,069), and the estimated total welfare losses are thus about \$4.7 billion (= \$83,329 x 56,000). Using a VQALY of \$1,070,162 (the central VQALY that assumes seven percent discounting), the value of lost health from using low-potency statins instead of high-potency statins is \$139,121 (= \$1,070,162 x 0.13). VQALYs 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 \$138,052 (= \$139,121 - \$1,069), and the estimated total welfare losses over the period 2008-2011 are thus about \$7.7 billion (= \$138,052 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 \$83,329 as our primary estimate given three percent discounting and \$138,052 as our primary estimate given seven percent discounting. Further below, also include estimates based on the low and high VQALY estimates.<sup>33</sup>

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

|  | Low             | Primary          | High                |
|--|-----------------|------------------|---------------------|
| a) Harms Avoidable by the Phaseout Policy      | 35,211          | 636,551          | 7,071,385           |
| b) Value Per Harm (VQALY using 3% discounting) | \$38,317        | \$83,329         | \$127,403           |
| c) Value Per Harm (VQALY using 7% discounting) | \$63,854        | \$138,052        | \$210,704           |
| d) Percent Not Internalized at Baseline        | 90%             | 95%              | 100%                |
| e) Total Benefit (VQALY using 3% discounting)  | \$1,214,266,667 | \$50,390,983,457 | \$900,918,275,141   |
| f) Total Benefit (VQALY using 7% discounting)  | \$2,023,557,180 | \$83,483,418,785 | \$1,489,970,932,975 |

<sup>33</sup> Available at: <https://aspe.hhs.gov/sites/default/files/documents/7f96080e2812365443347c1cca347188/standard-ria-values-2024.xlsx>

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 VQALYs that assume three and seven percent discounting follow uniform distributions defined by the low 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. [34]), the low, primary, and high benefit estimates in Table 13 represent the 5<sup>th</sup>, 50<sup>th</sup>, and 95<sup>th</sup> 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

|   | Low              | Primary          | High              |
|---|------------------|------------------|-------------------|
| e) Total Benefit (VQALY using 3% discounting) | \$16,043,560,570 | \$55,472,555,611 | \$172,687,741,835 |
| f) Total Benefit (VQALY using 7% discounting) | \$26,432,671,590 | \$92,101,808,769 | \$286,644,379,033 |

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.

*c. 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. [38]). 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,<sup>34</sup> we assume that about 2,577,300 such cases occur outside of NY and could thus potentially involve tests not covered by NYS CLEP. It is likely that some patients outside of the state of New York are also tested with tests covered 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), 66% of U.S. clinical decisions involve IVD testing (Ref. [28]). 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 170,100 U.S. (non-NY) patients with infectious disease would rely on IVDs offered as LDTs ( $= 2,577,283 \times 0.66 \times 0.10$ ).

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 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, over 63,700 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

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<sup>34</sup> 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>.

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. [39]), 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 13,000 harms among patients with infections.

Table 14. Avoidable Harms from Diagnostic Error Related to Infections

|   | Low       | Primary   | High      |
|---|-----------|-----------|-----------|
| a) Yearly U.S. Infections (Non-NYS)   | 2,577,283 | 2,577,283 | 2,577,283 |
| b) Percent Tested with IVDs   | 66%       | 66%       | 66%       |
| c) Probability of IVD Being Offered as an LDT   | 3.9%      | 10.0%     | 45.0%     |
| d) Patients Tested with IVDs Offered as LDTs<br>(= a * b *c)                              | 66,339    | 170,101   | 765,453   |
| e) Percent of IVDs Offered as LDTs Not Authorized by FDA Following a Premarket Submission | 22%       | 38%       | 54%       |
| f) Tests Using Problematic IVDs Offered as LDTs (= d * e)                                 | 14,595    | 64,638    | 413,345   |

|   |       |        |         |
|---|-------|--------|---------|
| g) Percent Leading to Diagnostic Error                  | 25%   | 50%    | 75%     |
| h) Treatment-to-Diagnosis Ratio                         | 0.30  | 0.41   | 0.50    |
| i) Harms Avoidable by the Phaseout Policy (= f * g * h) | 1,095 | 13,160 | 155,004 |

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. [39]), and assuming equal numbers of men and women patients, average QALY losses are about 0.008 from gonorrhea and 0.024 from chlamydia. Averaging between these two diseases while weighting 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 0.02. 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.<sup>35</sup>

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 \$12,900 (= \$649,215 x 0.02). Using a VQALY of \$1,070,162 (the central VQALY that assumes seven percent discounting), the value of lost health is about \$21,300. VQALYs are those projected for 2024 but using 2022 base year dollar values for consistency with the rest of this analysis.

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<sup>35</sup> See CDC on “Gonorrhea Treatment and Care” (<https://www.cdc.gov/std/gonorrhea/treatment.htm>) and “Chlamydia Treatment and Care” (<https://www.cdc.gov/std/chlamydia/treatment.htm>).

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 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

|  | Low         | Primary       | High            |
|--|-------------|---------------|-----------------|
| a) Harms Avoidable by the Phaseout Policy      | 1,095       | 13,160        | 155,004         |
| b) Value Per Harm (VQALY using 3% discounting) | \$6,017     | \$12,893      | \$19,626        |
| c) Value Per Harm (VQALY using 7% discounting) | \$9,918     | \$21,253      | \$32,352        |
| d) Percent Not Internalized at Baseline        | 90%         | 95%           | 100%            |
| e) Total Benefit (VQALY using 3% discounting)  | \$5,927,420 | \$161,189,608 | \$3,042,169,658 |
| f) Total Benefit (VQALY using 7% discounting)  | \$9,770,731 | \$265,704,203 | \$5,014,698,371 |

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 uniform distributions defined by the low 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. [34]), the low, primary, and high benefit estimates in Table 16 represent the 5<sup>th</sup>, 50<sup>th</sup>, and 95<sup>th</sup> 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

|  | Low | Primary | High |
|--|-----|---------|------|
|--|-----|---------|------|



|   |              |               |               |
|---|--------------|---------------|---------------|
| e) Total Benefit (VQALY using 3% discounting) | \$54,670,583 | \$189,393,046 | \$577,904,403 |
| f) Total Benefit (VQALY using 7% discounting) | \$90,634,571 | \$311,957,235 | \$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.

*d. Public Health Emergencies*

At baseline, without the phaseout policy, problematic IVDs offered as LDTs would also likely see use during future public health emergencies similar to the COVID-19 pandemic. During the COVID-19 pandemic, FDA reviewed emergency use authorization (EUA) requests for COVID-19 tests from laboratories. FDA’s analysis of the first 125 EUA requests for COVID-19 molecular diagnostic tests from laboratories found that 82 (66%) were not designed or validated appropriately (Ref. [40]).

Additionally, press reports indicated problematic tests beyond those in FDA’s analysis. For example, one Chicago laboratory contracted with the University of Nevada Reno and Washoe County School district to conduct COVID-19 testing using a test they offered without an EUA from FDA. A ProPublica investigation of the laboratory’s operations in Nevada led to findings that the Chicago laboratory offered a test that was unreliable. According to ProPublica, the Chicago laboratory’s test missed 96% of the positive cases from the university campus. The test’s errors routinely sent people infected with COVID-19 back into the community (Ref. [41]). Despite growing evidence of the laboratory telling infected people they had tested negative, “government managers in Nevada ignored their own scientists’ warnings and expanded the lab’s

testing beyond schools to the general public.”<sup>36</sup> The laboratory ceased commercial operations in the state before the investigation could be completed.

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

To estimate the number of people affected by this problematic IVD, we rely on an analytic model described in a study by Paltiel, Zheng, & Walensky (2020) (Ref. [42]). The purpose of the model was to assess isolation and screening programs to help decide a level of isolation and screening that would keep students at residential colleges safe from contracting COVID-19. The authors adapted a simple compartmental epidemic model to capture features of a situation facing university decision-makers that included the epidemiology of COVID-19; the natural history of COVID-19 illness; and regular mass screening to detect, isolate, and contain the presence of COVID-19 in a residential college setting. A spreadsheet implementation of the model allows the user to vary critical epidemic parameters and to examine how different test performance attributes such as frequency, sensitivity, specificity, and cost would translate to outcomes. The default model input data the authors used were obtained from a variety of published sources, adhering whenever possible to the data guidance for modelers issued by the U.S. Centers for Disease Control and Prevention and the Office of the Assistant Secretary for Preparedness and Response. For purposes of this analysis, we defined the already known

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<sup>36</sup> *Ibid.*

epidemic scenario<sup>37</sup> given the known false negative rate of 96% as an input to estimate test sensitivity. The estimated cumulative outcomes depend on the input data for the number of tests administered, number of true-positive and false-positive results, number of new infections, and person-days requiring isolation. The model estimates economic performance such as cost of initial and confirmatory tests and incremental cost-effectiveness, and budget impacts are assumed to occur during an abbreviated 80-day semester, running from Labor Day through Thanksgiving. The description of our input parameters can be found in Table 17.

Table 17. Description and Value of Input Parameters

| <b>Description Input Parameters</b>  | <b>Value</b>            |
|--|-------------------------|
| Tests sold between October 2021 and October 2022                                     | 1,738,443 <sup>38</sup> |
| Initial Susceptible  | 232,000                 |
| Initial Infected (1.5%)  | 3,450                   |
| Days **  | 80                      |
| False negative rate (FN)   | 96%                     |
| True negative rate (TN)  | 96%                     |
| True positive rate (TP)  | 4%                      |
| False positive rate (FP)   | 4%                      |
| Sensitivity = TP/(TP + FN)   | 4.0%                    |
| Specificity = TN/(TN + FP)   | 96.0%                   |
| Rate at which infected individuals recover from disease and are removed ( $\rho$ )** | 2.5                     |
| Cost per test  | \$25                    |
| Cost per confirmatory test   | \$100                   |
| Days to incubation*  | 3                       |
| Time to recovery*  | 14                      |
| Symptom case fatality rate*  | 0.05%                   |
| Probability that infection will lead to symptoms                                     | 30%                     |

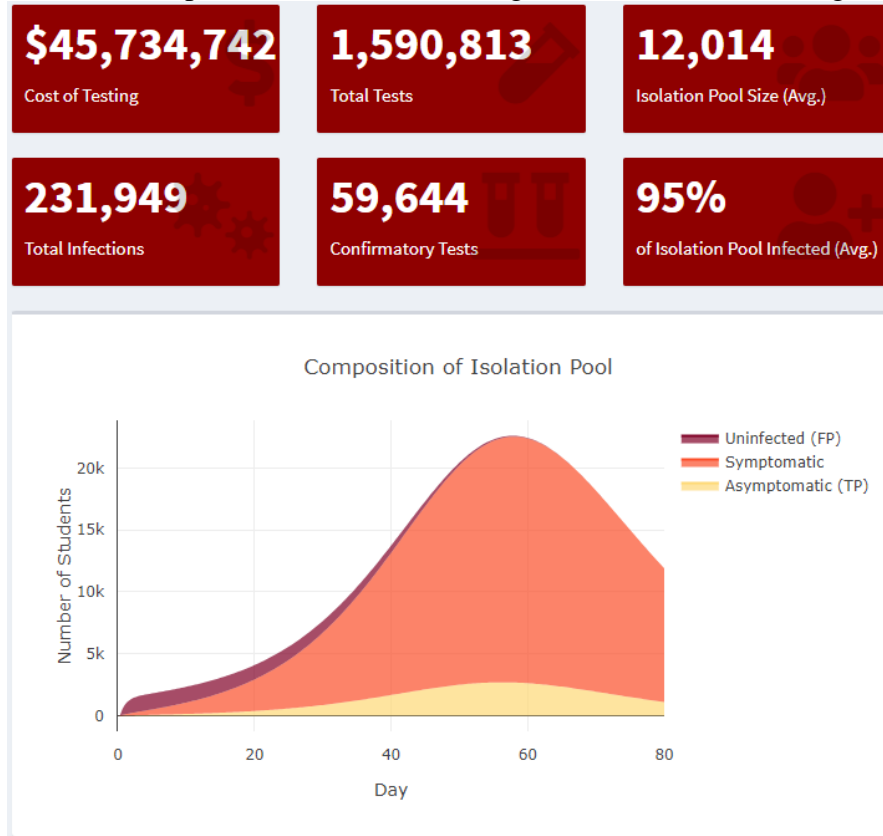
\* Model default setting

<sup>37</sup> This is dependent on the level of isolation and screening scenario that would keep students at residential colleges safe from contracting SARS-Cov-2.

<sup>38</sup> A CMS “Statement of Deficiencies” for this laboratory reported that 1,738,443 tests were administered between May 1, 2021, and December 30, 2021. CMS, Statement of Deficiencies and Plan of Correction (Dec. 29, 2021), available at <https://s3.documentcloud.org/documents/21872905/northshore-clinical-labs-14d0426602-form-cms-2567-12292021.pdf>. Thus, this number is likely an underestimate for a full year of testing.

Figure 1 below shows how cases and testing costs can grow from use of problematic IVDs. At the end of 80 days, the model shows 231,949 cases which is essentially 99.9% of the initial susceptible population estimate with the total costs of the testing program reaching \$45 million.<sup>39</sup>

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



We use the case fatality rate of 0.05%, but instead of assuming death ultimately occurs, apply this percentage to estimate critical cases,<sup>40</sup> and of the 30% probability that infection would eventually lead to observable COVID-19 symptoms, we assume that half of the 30% would be mild cases and the other half severe. We roughly reach a cumulative estimate of 231,949 cases

<sup>39</sup> The public version of the 2020 Paltiel, Zheng, & Walensky, model can be accessed at <https://data-viz.it.wisc.edu/covid-19-screening/>

<sup>40</sup> We assume no death associated with this cohort because the test was offered at schools and universities and death is rarely associated with the age-cohort being tested.

with visible symptoms, of which 116 are critical, 115,917 are with severe symptoms and 115,917 are cases with mild symptoms.

The final step in estimating benefits from this particular case study requires estimating the gains from averting COVID-19 morbidity. The gains are first estimated as Quality Adjusted Life Years (QALYs): about 0.01 per mild case averted, 0.02 QALYs per severe case, and 3.15 QALYs per critical case (Ref. [43]). Using a VQALY of \$649,215 (the central VQALY that assumes three percent discounting), these gains translate into monetary values of about \$6,000 per mild case, \$13,000 per severe case, and \$2.045 million per critical case. Using a VQALY of \$1,070,162 (the central VQALY that assumes seven percent discounting), these gains translate into monetary values of about \$11,000 per mild case, \$21,000 per severe case and \$3.371 million per critical case. We modify several inputs used in the report, including incorporating HHS’s current estimates of the VSL and VQALY, and revising the QALY losses to match estimates contained in more recent research. We present the updated values per mild, severe, and critical cases in Table 18 for VQALYs derived from VSLYs that assume three and seven percent discount rates.

In Table 18, we estimate that the benefit from avoiding the use of this particular high-volume test would have been about \$2.5 billion using a VSLY based on a three percent discount rate and about \$4.1 billion using a VSLY based on a seven percent discount rate.

Table 18. Case Study Benefits from Averting COVID-19 Cases Due to a Certain Problematic IVD (\$2022)

| Level               | Cases   | QALYs | Value /case |             | Total Benefit   |                 |
|---------------------|---------|-------|-------------|-------------|-----------------|-----------------|
|                     |         |       | 3% VQALY    | 7% VQALY    | 3% VQALY        | 7% VQALY        |
| Critical<br>(0.05%) | 116     | 3.15  | \$2,045,026 | \$3,371,012 | \$237,170,894   | \$390,951,402   |
| Severe<br>(49%)     | 115,917 | 0.02  | \$12,984    | \$21,403    | \$1,505,094,020 | \$2,480,990,010 |
| Mild<br>(49%)       | 115,917 | 0.01  | \$6,492     | \$10,702    | \$752,547,010   | \$1,240,495,005 |

|     |         |  |  |  |                 |                 |
|-----|---------|--|--|--|-----------------|-----------------|
| Sum | 231,949 |  |  |  | \$2,494,811,924 | \$4,112,436,417 |
|-----|---------|--|--|--|-----------------|-----------------|

We use the above result to estimate a recurring benefit based on the annual likelihood of a pandemic similar to COVID-19. While other unknown incidents due to other unreliable tests during the COVID-19 pandemic might also have been preventable by phasing out the general enforcement discretion approach for most LDTs, we include only one such instance, similar in scope and impacts as analyzed above, per future pandemic. According to a report from the Center for Global Development, the annual probability of a future pandemic of similar magnitude to COVID-19 is between 2.5% to 3.3% (Ref. [44]). We thus estimate the central annual likelihood of 2.9% as the midpoint between 2.5% and 3.3%. In Table 19 below, we estimate the annual benefit from preventing the use, during a pandemic, of a problematic IVD such as analyzed above by multiplying this range of annual likelihood estimates by the total benefits from Table 18. Annual estimated benefits from averted cases of a COVID-like pandemic are about \$72.3 million using a VQALY based on a three percent discount rate and \$119.3 million using a VQALY based on a seven percent discount rate.

Table 19. Recurring Annual Benefits from Averted Cases of a COVID-Like Pandemic Due to Faulty Tests

|         | Annual likelihood | Health (by VQALY assumption) |                |                |
|---------|-------------------|------------------------------|----------------|----------------|
|         |                   | 0% discounting               | 3% discounting | 7% discounting |
| Low     | 0.025             | \$36,482,395                 | \$62,370,298   | \$102,810,910  |
| Central | 0.029             | \$42,319,578                 | \$72,349,546   | \$119,260,656  |
| High    | 0.033             | \$48,156,762                 | \$82,328,793   | \$135,710,402  |

## 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 most 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 [7]). However, the five most common microdeletion tests screen for conditions that affect only one in 5,000-20,000 births.<sup>41</sup> 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.”<sup>42</sup> 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. [7]). Misunderstanding by

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<sup>41</sup> Ibid.

<sup>42</sup> Ibid.

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. In this analysis, we use information in the NY Times<sup>43</sup> to estimate payment for such problematic NIPS tests. 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.<sup>44</sup> Taking the product of 400,000 and \$654 gives us an estimated \$262 million in cost saving benefits from averting future overpayment.

*b. Reduction in Expenses from Lawsuits.*

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 most 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.

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<sup>43</sup> Ibid.

<sup>44</sup> Ibid.



On March 1<sup>st</sup>, 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. [45]). 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 [46]). The case is currently ongoing (Refs. [45] and [47]).

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. [48]). We assume total litigation and risk transfer costs would be the opportunity costs of having problems prevented by compliance with applicable requirements instead of corrected via litigation. In a \$10 million dollar case, 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 cancers, cardiovascular disease, and infections, as well as future use of problematic IVDs offered as LDTs during a public health emergency similar to COVID-19. The public health emergency case study represents a single select case where likely others occurred, and therefore yields a minimum estimate.

Quantified non-health benefits are one-time costs savings from avoiding payment for problematic IVDs, namely NIPS tests. The one-time (non-health) benefit estimate of \$262 million is based on only a select case and should be considered a minimum estimate.

Unquantified benefits include, among others, 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 20.

Table 20. Total Undiscounted Benefits (millions 2022\$)

| <b>Health Benefits (VSLY – 3%)</b>          |              | <b>One Time Benefits (minimum)</b> | <b>Recurring Annual Benefits</b> |          |           |
|---|--------------|------------------------------------|----------------------------------|----------|-----------|
| <b>Type</b>                                 | <b>Level</b> |                                    | Low                              | Central  | High      |
| Cancer                                      | Generalized  |                                    | \$1,226                          | \$4,315  | \$13,735  |
| Cardiovascular Disease                      | Generalized  |                                    | \$16,044                         | \$55,473 | \$172,688 |
| Infections                                  | Generalized  |                                    | \$55                             | \$189    | \$578     |
| Public Health Emergencies                   | Case study   |                                    | \$62                             | \$72     | \$82      |
| <b>Subtotal Health Benefits (VSLY – 3%)</b> |              |                                    | \$17,386                         | \$60,049 | \$187,083 |
| <b>Health Benefits (VSLY – 7%)</b>          |              | <b>One Time Benefits (minimum)</b> | <b>Recurring Annual Benefits</b> |          |           |
| <b>Type</b>                                 | <b>Level</b> |                                    | Low                              | Central  | High      |
| Cancer                                      | Generalized  |                                    | \$1,844                          | \$6,489  | \$20,590  |

|   |             |       |          |          |           |
|---|-------------|-------|----------|----------|-----------|
| Cardiovascular Disease                      | Generalized |       | \$26,433 | \$92,102 | \$286,644 |
| Infections                                  | Generalized |       | \$91     | \$312    | \$953     |
| Public Health Emergencies                   | Case study  |       | \$103    | \$119    | \$136     |
| <b>Subtotal Health Benefits (VSLY – 7%)</b> |             |       | \$28,470 | \$99,022 | \$308,323 |
| <b>Non health Benefits</b>                  |             |       |          |          |           |
| NIPS  | Case Study  | \$262 |          |          |           |
| <b>Subtotal Non-Health Benefits</b>         |             |       | \$262    |          |           |
| <b>Total Sum of Benefits (VSLY – 3%)</b>    |             |       | \$262    | \$17,386 | \$60,049  |
| <b>Total Sum of Benefits (VSLY – 7%)</b>    |             |       | \$262    | \$28,470 | \$99,022  |

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 21).

Table 21. 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    | \$87                            | \$30,025  | \$30,112  | \$87                            | \$49,511    | \$49,598    |
| 3 & 4      | 1/3      | 3/4       | 4    | \$59                            | \$30,405  | \$30,464  | \$59                            | \$50,139    | \$50,197    |
| 4 & 5      | 1/3      | 1         | 5    | \$62                            | \$42,648  | \$42,710  | \$62                            | \$70,327    | \$70,389    |
|            | 0        | 1         | 6    | \$0                             | \$44,519  | \$44,519  | \$0                             | \$73,413    | \$73,413    |
|            | :        | :         | :    |                                 |           |           |                                 |             |             |
|            | 0        | 1         | 20   | \$0                             | \$56,920  | \$56,920  | \$0                             | \$93,861    | \$93,861    |
| <b>Sum</b> |          |           |      | \$208                           | \$885,065 | \$885,273 | \$208                           | \$1,459,482 | \$1,459,690 |

However, as a result of exercising enforcement discretion with respect to premarket review and QS requirements, with the exception of 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, 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.A.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 tests, only half of the estimated potential benefits will be realized. 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:

$$\text{adjustment} = \text{prop. of IVDs NOT under ED} + 0.5 * \text{prop. of IVDs under ED}$$

In Table 22, the resulting adjusted annualized benefit estimates using three and seven percent discounting are approximately \$41.9 billion and \$63.8 billion, respectively.

Table 22. Expected Benefits Over Time Accounting for Exercising Enforcement Discretion  
(Primary Estimate in Millions 2022\$, 20 years)

| Stage                                       | Year | Proportions of IVDs by enforcement status (premarket review and most QS requirements) |           | c) Effect of ED on benefits | d) Adj. factor (= b + c*a) | Benefits (3% VSLY) |                | Benefits (7% VSLY) |                |
|---|------|---|-----------|-----------------------------|----------------------------|--------------------|----------------|--------------------|----------------|
|   |      | a) ED   | b) Not ED |                             |                            | e) Without ED      | With ED (=d*e) | f) Without ED      | With ED (=d*f) |
|   | 1    | 0.918   | 0.082     | 0.5                         | 0.541                      | \$0                | \$0            | \$0                | \$0            |
| 1   | 2    | 0.818   | 0.182     | 0.5                         | 0.591                      | \$0                | \$0            | \$0                | \$0            |
| 2   | 3    | 0.729   | 0.271     | 0.5                         | 0.636                      | \$30,112           | \$30,112       | \$49,598           | \$49,598       |
| 3 & 4                                       | 4    | 0.650   | 0.350     | 0.5                         | 0.675                      | \$45,124           | \$30,464       | \$74,354           | \$50,197       |
| 4 & 5                                       | 5    | 0.580   | 0.420     | 0.5                         | 0.710                      | \$60,137           | \$42,710       | \$99,109           | \$70,389       |
|   | 6    | 0.517   | 0.483     | 0.5                         | 0.741                      | \$60,049           | \$44,519       | \$99,022           | \$73,413       |
|   | 7    | 0.462   | 0.538     | 0.5                         | 0.769                      | \$60,049           | \$46,182       | \$99,022           | \$76,154       |
|   | 8    | 0.413   | 0.587     | 0.5                         | 0.794                      | \$60,049           | \$47,660       | \$99,022           | \$78,592       |
|   | 9    | 0.369   | 0.631     | 0.5                         | 0.816                      | \$60,049           | \$48,976       | \$99,022           | \$80,762       |
|   | 10   | 0.330   | 0.670     | 0.5                         | 0.835                      | \$60,049           | \$50,149       | \$99,022           | \$82,696       |
|   | 11   | 0.295   | 0.705     | 0.5                         | 0.853                      | \$60,049           | \$51,196       | \$99,022           | \$84,423       |
|   | 12   | 0.264   | 0.736     | 0.5                         | 0.868                      | \$60,049           | \$52,133       | \$99,022           | \$85,968       |
|   | 13   | 0.236   | 0.764     | 0.5                         | 0.882                      | \$60,049           | \$52,973       | \$99,022           | \$87,353       |
|   | 14   | 0.211   | 0.789     | 0.5                         | 0.895                      | \$60,049           | \$53,726       | \$99,022           | \$88,595       |
|   | 15   | 0.188   | 0.812     | 0.5                         | 0.906                      | \$60,049           | \$54,403       | \$99,022           | \$89,712       |
|   | 16   | 0.168   | 0.832     | 0.5                         | 0.916                      | \$60,049           | \$55,014       | \$99,022           | \$90,718       |
|   | 17   | 0.149   | 0.851     | 0.5                         | 0.925                      | \$60,049           | \$55,564       | \$99,022           | \$91,625       |
|   | 18   | 0.133   | 0.867     | 0.5                         | 0.934                      | \$60,049           | \$56,061       | \$99,022           | \$92,446       |
|   | 19   | 0.118   | 0.882     | 0.5                         | 0.941                      | \$60,049           | \$56,511       | \$99,022           | \$93,188       |
|   | 20   | 0.104   | 0.896     | 0.5                         | 0.948                      | \$60,049           | \$56,920       | \$99,022           | \$93,861       |
| <b>Sum</b>                                  |      |   |           |                             |                            | \$1,036,113        | \$885,273      | \$1,708,392        | \$1,459,690    |
| <b>Present Value (Rate matches VSLY)</b>    |      |   |           |                             |                            |                    | \$623,408      |                    | \$675,532      |
| <b>Annualized Value (Rate matches VSLY)</b> |      |   |           |                             |                            |                    | \$41,903       |                    | \$63,765       |

F. Costs

FDA is phasing out the general enforcement discretion approach for most 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 and to foster the manufacturing of innovative IVDs, while also accounting for patient access and reliance.

FDA intends that phaseout of enforcement discretion will occur over a four-year period in five key stages as described in section V.B of the preamble. For a few categories of tests manufactured by laboratories, FDA will exercise enforcement discretion approach with respect to some or all applicable requirements as described in section V.A 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.<sup>45</sup> Specifically, we use wage information for a specific industry: medical and diagnostic laboratories.<sup>46</sup>

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

#### 1. Costs Under Stage 1

Under Stage 1, FDA expects laboratories<sup>47</sup> to comply with MDR requirements (requirements for adverse event reporting) under 21 U.S.C. 360i(a)-(c) and 21 CFR part 803 and correction and removal reporting requirements under 21 U.S.C. 360i(g) and 21 CFR part 806

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<sup>45</sup> [https://www.bls.gov/oes/current/naics4\\_621500.htm](https://www.bls.gov/oes/current/naics4_621500.htm)

<sup>46</sup> NAICS code: 621500

<sup>47</sup> 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.

one year after publication of the phaseout policy. 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,<sup>48</sup> 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.<sup>49</sup> Fully loaded wage rates are \$115.20 an hour for managers and \$160.60 an hour for lawyers (average: \$137.90).<sup>50</sup> 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 reading the rule between \$0.81 million and \$12.21 million, with a primary estimate of \$3.62

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<sup>48</sup> <https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis>

<sup>49</sup> 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](https://www.bls.gov/oes/current/naics4_621500.htm)

<sup>50</sup> Fully-loaded wages account for employee benefits and overhead on top of the hourly wage, calculated by doubling the published wage rate.

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 23).

Table 23. 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            |
| <b>Total One-time Costs (millions)</b>  | <b>\$3.62</b> | <b>\$0.81</b> | <b>\$12.21</b> |
| <b>Total Recurring Costs (millions)</b> | <b>\$0.29</b> | <b>\$0.07</b> | <b>\$0.98</b>  |

*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. [49]). 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 24.

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. [49]).<sup>51</sup> 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

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<sup>51</sup> 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.

the one-time costs of acquiring an e-certificate to range from \$0.01 million to \$0.05 million, with a primary estimate of \$0.02 million. We estimate the recurring costs to range from \$0.001 million to \$0.004 million, with a primary estimate of \$0.002 million.

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

Finally, we expect a recurring cost associated with filing and submitting MDRs. We estimate it will take computer and information system managers 430 hours,<sup>52</sup> 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 24.

Table 24. Costs of Medical Device Reporting

|                               |       | Primary | Low | High |
|-------------------------------|-------|---------|-----|------|
| <b><i>One-time/Annual</i></b> |       |         |     |      |
|                               | Hours | 10      | 8   | 12   |

<sup>52</sup> 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. [49]). 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.

|   |                                      |                |                |                 |
|---|--------------------------------------|----------------|----------------|-----------------|
| Establish SOPs                            | Wage                                 | \$122.72       | \$122.72       | \$122.72        |
|   | Employees                            | 2              | 1              | 3               |
|   | Entities affected                    | 1,181          | 590            | 2,362           |
|   | New entities per year                | 94             | 47             | 189             |
|   | <i>One-time Subtotal (millions)</i>  | <i>\$2.90</i>  | <i>\$0.58</i>  | <i>\$10.43</i>  |
|   | <i>Recurring Subtotal (millions)</i> | <i>\$0.23</i>  | <i>\$0.05</i>  | <i>\$0.83</i>   |
| 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             |
|   | <i>One-time Subtotal (millions)</i>  | <i>\$9.79</i>  | <i>\$4.52</i>  | <i>\$21.09</i>  |
|   | <i>Recurring Subtotal (millions)</i> | <i>\$0.78</i>  | <i>\$0.36</i>  | <i>\$1.69</i>   |
| 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               |
|   | <i>One-time Subtotal (millions)</i>  | <i>\$0.06</i>  | <i>\$0.03</i>  | <i>\$0.12</i>   |
|   | <i>Recurring Subtotal (millions)</i> | <i>\$0.005</i> | <i>\$0.002</i> | <i>\$0.01</i>   |
| 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             |
|   | <i>One-time Subtotal (millions)</i>  | <i>\$0.02</i>  | <i>\$0.01</i>  | <i>\$0.05</i>   |
|   | <i>Recurring Subtotal (millions)</i> | <i>\$0.002</i> | <i>\$0.001</i> | <i>\$0.004</i>  |
| <b><i>Recurring Annual</i></b>            |                                      |                |                |                 |
| Maintaining Certificates                  | Search cost                          | \$10.00        | \$10.00        | \$10.00         |
|   | Entities affected                    | 1,181          | 590            | 2,362           |
|   | <i>Recurring Subtotal (millions)</i> | <i>\$0.01</i>  | <i>\$0.01</i>  | <i>\$0.02</i>   |
| Filing and submitting MDRs                | Hours                                | 430            | 430            | 430             |
|   | Wage                                 | \$159.44       | \$159.44       | \$159.44        |
|   | Entities affected                    | 1,181          | 590            | 2,362           |
|   | <i>Recurring Subtotal (millions)</i> | <i>\$80.94</i> | <i>\$40.47</i> | <i>\$161.88</i> |
| <b>Total One-time Costs (millions)</b>    |                                      | <b>\$13.21</b> | <b>\$5.36</b>  | <b>\$32.57</b>  |
| <b>Total Recurring Costs (millions)</b>   |                                      | <b>\$82.03</b> | <b>\$40.91</b> | <b>\$164.55</b> |

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 2020 FDA notice: *Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals* (Ref. [50]). 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. [50]). 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 2020 FDA notice *Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals* acknowledged 1,033 correction and removal reports per year. In the same year (2020), the U.S. Census Statistics of U.S. Businesses (SUSB) estimated there were

approximately 9,338 medical device manufacturing establishments in the U.S.<sup>53</sup> 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 25.

Table 25. Costs of Correction and Removal Reporting

|   |                                      | Primary        | Low            | High           |
|---|--------------------------------------|----------------|----------------|----------------|
| <b><i>One-time/Annual</i></b>           |                                      |                |                |                |
| Digital Verification Certificate        | Flat fee                             | \$50.00        | \$50.00        | \$50.00        |
|   | Entities affected                    | 590            | 295            | 1,181          |
|   | New entities per year                | 47             | 24             | 94             |
|   | <i>One-time Subtotal (millions)</i>  | <i>\$0.03</i>  | <i>\$0.01</i>  | <i>\$0.06</i>  |
|   | <i>Recurring Subtotal</i>            | <i>\$2,362</i> | <i>\$1,181</i> | <i>\$4,723</i> |
| <b><i>Recurring Annual</i></b>          |                                      |                |                |                |
| 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          |
|   | <i>Recurring Subtotal (millions)</i> | <i>\$0.15</i>  | <i>\$0.07</i>  | <i>\$0.30</i>  |
| <b>Total One-time Costs (millions)</b>  |                                      | <b>\$0.03</b>  | <b>\$0.01</b>  | <b>\$0.06</b>  |
| <b>Total Recurring Costs (millions)</b> |                                      | <b>\$0.15</b>  | <b>\$0.08</b>  | <b>\$0.30</b>  |

d. Complaint Files

<sup>53</sup> 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>

Under Stage 1, FDA expects laboratories to comply with quality system (QS) requirements under 21 CFR part 820.198 (complaint files). 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. [51]).<sup>54</sup> We also use wage rates to estimate costs for affected entities (see Table 30). 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 26. Costs of Complaint Files

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

## 2. Costs Under Stage 2

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

<sup>54</sup> 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.

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).<sup>55</sup>

*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. [52]). We anticipate one-time costs associated with registration and listing requirements and recurring costs associated with re-registration.

We expect the registration and listing would 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.<sup>56</sup> We also expect that annual re-registration and listing updates would take a general/operations manager 1 hour. Multiplying by the numbers of affected entities per year, we expect total one-time costs for registration and listing requirements to range between \$0.20 million and \$0.82 million, with a 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 27.

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<sup>55</sup> 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.

<sup>56</sup> 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.

Table 27. Costs of Registration and Listing

|  |                                      | Primary       | Low           | High          |
|--|--------------------------------------|---------------|---------------|---------------|
| <b><i>One-time/Annual</i></b>                            |                                      |               |               |               |
| 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           |
|  | <i>One-time Subtotal (millions)</i>  | <i>\$0.41</i> | <i>\$0.20</i> | <i>\$0.82</i> |
|  | <i>Recurring Subtotal (millions)</i> | <i>\$0.03</i> | <i>\$0.02</i> | <i>\$0.07</i> |
| <b><i>Recurring Annual</i></b>                           |                                      |               |               |               |
| Re-registration  | Hours                                | 1             | 1             | 1             |
|  | Wage                                 | \$115.20      | \$115.20      | \$115.20      |
|  | Entities affected                    | 1,181         | 590           | 2,362         |
|  | <i>Recurring Subtotal (millions)</i> | <i>\$0.14</i> | <i>\$0.07</i> | <i>\$0.28</i> |
| <b>Total One-time Costs (millions)</b>                   |                                      | <b>\$0.41</b> | <b>\$0.20</b> | <b>\$0.82</b> |
| <b>Total Recurring Costs (millions)</b>                  |                                      | <b>\$0.17</b> | <b>\$0.08</b> | <b>\$0.34</b> |

*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),<sup>57</sup> 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. [53]). 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.<sup>58</sup> Multiplying the

<sup>57</sup> NAICS code 621500, occupation codes 11-1021 for general and operations managers. Available from: [https://www.bls.gov/oes/current/naics4\\_621500.htm](https://www.bls.gov/oes/current/naics4_621500.htm)

<sup>58</sup> 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.



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 28.

Table 28. 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            |
|   | <i>One-time Subtotal (millions)</i>  | <i>\$4.22</i> | <i>\$0.54</i> | <i>\$14.69</i> |
|   | <i>Recurring Subtotal (millions)</i> | <i>\$0.34</i> | <i>\$0.04</i> | <i>\$1.18</i>  |
| <b>Total One-time Costs (millions)</b>  |                                      | <b>\$4.22</b> | <b>\$0.54</b> | <b>\$14.69</b> |
| <b>Total Recurring Costs (millions)</b> |                                      | <b>\$0.34</b> | <b>\$0.04</b> | <b>\$1.18</b>  |

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

We expect the cost of developing an IDE application for an IVD offered as an LDT to be \$48,000 (Ref. [54])<sup>59</sup>. 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. [20]). NYSDOH receives IVD submission packages for IVDs offered as LDTs that are not “designated as FDA-cleared, approved, or exempt,” (Ref. [21]) 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.<sup>60</sup> Based on the number of IVD IDE submissions and the number of IVD premarket submissions that FDA received over a four-year period, we estimate that we receive about 13.5 IVD IDE submissions for every 100 premarket submissions. Therefore, we estimate that about 13.5% of investigational IVDs offered as LDTs that would later be subject to premarket review would first submit an IDE application. 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.

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<sup>59</sup> 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.

<sup>60</sup> IDE requirements in 21 CFR part 812 do not apply to investigations of certain types of devices. See 21 CFR 812.2(c). Moreover, certain categories of investigations are considered to have an approved IDE application. See 21 CFR 812.2(b).

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 29 shows the estimated annual costs, which range from \$6.20 million to \$24.79 million, with a primary estimate of \$12.40 million.

Table 29. Costs of Complying with Investigational Use Requirements

|   |  | Primary       | Low           | High           |
|---|--|---------------|---------------|----------------|
| <b><i>One-time</i></b>                        |  |               |               |                |
| Total cost of preparing/<br>submitting<br>IDE | Inflation-adjusted estimate from literature  | \$48,000      | \$48,000      | \$48,000       |
|   | Percent of IVDs offered as LDTs that are investigational                                   | 2             | 2             | 2              |
|   | Percent of investigational IVDs offered as LDTs that require submission of IDE application | 6.75          | 6.75          | 6.75           |
|   | IVDs currently offered as LDTs affected  | 79,114        | 39,557        | 158,227        |
|   | <i>One-time Subtotal (millions)</i>  | <i>\$5.13</i> | <i>\$2.56</i> | <i>\$10.25</i> |
| <b><i>Annual</i></b>                          |  |               |               |                |

|   |  |                |               |                |
|---|--|----------------|---------------|----------------|
| Total cost of preparing/<br>submitting<br>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         |
|   | <i>Annual Subtotal (millions)</i>  | <i>\$12.40</i> | <i>\$6.20</i> | <i>\$24.79</i> |
| <b>Total One-time Costs (millions)</b>        |  | <b>\$7.45</b>  | <b>\$3.73</b> | <b>\$14.90</b> |
| <b>Total Annual Costs (millions)</b>          |  | <b>\$18.02</b> | <b>\$9.01</b> | <b>\$36.03</b> |

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

Under Stage 3, at the three-year mark, FDA expects 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 (except for requirements regarding complaint files under 21 CFR 820.198, for which FDA expects compliance under stage 1 of the phaseout policy).

However, for LDTs, FDA expects compliance with some, but not all, of the QS requirements. As described in section V.B.3 of the preamble, for these IVDs, 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.B.3 of the preamble, for any 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 30).<sup>61</sup> Table 31 shows the number of labor hours for compliance with each provision of Part 820 (Ref. [51]). 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.<sup>62</sup>

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<sup>61</sup> All wage rates are doubled to account for overhead costs. Available from: [https://www.bls.gov/oes/current/naics4\\_621500.htm](https://www.bls.gov/oes/current/naics4_621500.htm)

<sup>62</sup> 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.

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 mentioned in appendix A, we estimate 11.4 percent of the affected tests will be 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 11.4 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  $794 (=1,181 - 1,181*0.114 - 459*0.55)$ .

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 \$0.41 million to \$4.06 million, with a primary estimate of \$1.42 million. The total recurring costs are estimated to range from \$1.96 million to \$125.32 million, with a primary estimate of \$24.92 million. See Table 31.

Table 30. Medical and Diagnostic Laboratories Industry Wage Rates for Selected Labor Categories

| <b>Labor Category</b> | <b>Wages (/hour)</b> | <b>NAICS</b> | <b>OCC Code</b> |
|-----------------------|----------------------|--------------|-----------------|
| 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 31. Costs of Compliance with Quality System Requirements

|  |       | <b>Primary</b> | <b>Low</b> | <b>High</b> |
|--|-------|----------------|------------|-------------|
| <b><i>One-time/Annual</i></b>  |       |                |            |             |
| 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          |
| 820.20I Quality System Procedures  | Hours | 14             | 0          | 40          |
| 820.22 Quality Audit   | Hours | 8              | 0          | 24          |
| 820.25 Personnel, establish procedures for identifying training needs        | Hours | 8              | 0          | 24          |
| 820.25 Personnel, train in CGMP revisions                                    | Hours | 50             | 0          | 290         |
| 820.40 Document Controls   | Hours | 14             | 0          | 40          |
| 820.60 Identification and Traceability                                       | Hours | 8              | 0          | 24          |
| 820.72, 820.75 Inspection, measuring, and test equipment, process validation | Hours | 23             | 0          | 72          |
| 820.70(i) Automated Processes  | Hours | 14             | 0          | 40          |
| 820.90 Nonconforming Product   | Hours | 14             | 0          | 40          |
| 820.140 Handling   | Hours | 8              | 0          | 24          |
| 820.200 Servicing  | Hours | 14             | 0          | 40          |
| 820.30(a) General  | Hours | 200            | 30         | 560         |

|  |       |                |               |                 |
|--|-------|----------------|---------------|-----------------|
| 820.50(a) Assessment of Suppliers and Contractors                            | Hours | 75             | 25            | 125             |
| 820.100 Corrective and Preventive Action                                     | Hours | 28             | 16            | 40              |
| 820.150 Storage  | Hours | 15             | 8             | 24              |
| 820.198 Records  | Hours | 14             | 8             | 20              |
| Entities affected  |       | 794            | 397           | 1588            |
| New entities per year  |       | 64             | 32            | 127             |
| <b><i>Recurring Annual</i></b>   |       |                |               |                 |
| 820.20(a) Quality Policy   | Hours | 1              | 0             | 2               |
| 820.20(b) Organization   | Hours | 1              | 0             | 2               |
| 820.20(c) Management Review  | Hours | 8              | 0             | 24              |
| 820.20(d) Quality Planning   | Hours | 4              | 0             | 10              |
| 820.20(e) Quality System Procedures  | Hours | 4              | 0             | 10              |
| 820.22 Quality Audit   | Hours | 1              | 0             | 2               |
| 820.25 Personnel, maintain procedures  | Hours | 1              | 0             | 2               |
| 820.40 Document Controls   | Hours | 2              | 0             | 4               |
| 820.60 Identification and Traceability                                       | Hours | 1              | 0             | 2               |
| 820.72, 820.75 Inspection, measuring, and test equipment, process validation | Hours | 4              | 0             | 13              |
| 820.70(i) Automated Processes  | Hours | 2              | 0             | 4               |
| 820.90 Nonconforming Product   | Hours | 2              | 0             | 4               |
| 820.140 Handling   | Hours | 1              | 0             | 2               |
| 820.200 Servicing  | Hours | 2              | 0             | 4               |
| 820.30(a) General  | Hours | 20             | 3             | 56              |
| 820.30(b) Design and Development Planning                                    | Hours | 216            | 32            | 520             |
| 820.30(e) Design Review  | Hours | 942            | 82            | 2,574           |
| 820.30(f) Design Verification  | Hours | 1,681          | 249           | 4,047           |
| 820.30(h) Design Transfer  | Hours | 43             | 6             | 104             |
| 820.30(i) Design Changes   | Hours | 378            | 56            | 910             |
| 820.30(j) Design History File  | Hours | 22             | 3             | 52              |
| 820.50(a) and (b) Purchasing control   | Hours | 159            | 98            | 233             |
| 820.100 Corrective and Preventive Action                                     | Hours | 3              | 2             | 4               |
| 820.150 Storage  | Hours | 2              | 1             | 2               |
| 820.198 Records  | Hours | 2              | 1             | 2               |
| New entities per year  |       | 64             | 32            | 127             |
| <b>Total One-time Costs (millions)</b>                                       |       | <b>\$1.42</b>  | <b>\$0.41</b> | <b>\$4.06</b>   |
| <b>Total Recurring Costs (millions)</b>                                      |       | <b>\$24.92</b> | <b>\$1.96</b> | <b>\$125.32</b> |

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.<sup>63</sup> 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 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

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<sup>63</sup> 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.

- 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

Under Stage 4, FDA expects laboratories to comply with premarket review requirements for high-risk IVDs (21 U.S.C. 360e and 21 CFR part 814) beginning three and a half years after publication of the phaseout policy. 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 four years after 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 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 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. 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 32.

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 32. Number of Premarket Submissions Under Stage 4 and Stage 5

|  | Primary      | Low          | High         |
|--|--------------|--------------|--------------|
| PMA  | 102          | 51           | 204          |
| PMA supplements  | 31           | 15           | 62           |
| 510(k) Total   | 2,197        | 1,098        | 4,394        |
| 510(k) with method comparison study  | 1,296        | 648          | 2,592        |
| 510(k) with moderately complex clinical study                                | 901          | 450          | 1,801        |
| de novo  | 269          | 135          | 539          |
| <b>Total number of new premarket submissions per year for affected tests</b> | <b>2,599</b> | <b>1,300</b> | <b>5,198</b> |

*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. [55]). 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.<sup>64</sup>

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<sup>64</sup> 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.

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. [55]). For upper bound estimates, we use the ERG estimates of the PMAs with complex, extensive clinical trials. We updated the ERG estimates to account for inflation. We expect that most of the PMAs will involve complex clinical trials. We assume that of the PMAs, 95% are complex clinical trials and 5% are complex, extensive clinical trials. We take 95% of the low and 5% of the high estimates to calculate primary estimates. The total cost of submission and preparation per PMA is estimated to range from \$4.10 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 \$209.26 million to \$1,896.12 million, with a primary estimate of \$444.99 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. [56]) to estimate the recurring preparation cost. The current estimate after adjustment for inflation is \$11,798 per PMA. Multiplying the estimates by the numbers of PMA submissions per year, we expect total recurring costs of PMA annual reporting requirements to range from \$0.60 million to \$2.41 million, with a primary estimate of \$1.20 million.

Overall, we estimate the total recurring costs to industry of PMA requirements in Stage 4 to range between \$209.86 million and \$1,898.53 million, with a primary estimate of \$446.19 million. See Table 33.

Table 33. Costs to Industry of Premarket Approval Application

|  | Primary            | Low                | High               |
|--|--------------------|--------------------|--------------------|
| <b><i>Cost of Submission and Preparation</i></b> |                    |                    |                    |
| 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        |
| <i>Subtotal cost per submission</i>              | <i>\$4,359,857</i> | <i>\$4,100,439</i> | <i>\$9,288,800</i> |
| No. PMA submissions per year for affected tests  | 102                | 51                 | 204                |
| <i>Recurring Subtotal (millions)*</i>            | <i>\$444.99</i>    | <i>\$209.26</i>    | <i>\$1,896.12</i>  |
| <b><i>Recurring Annual</i></b>                   |                    |                    |                    |
| Annual Report preparation for existing PMAs      | \$11,798           | \$11,798           | \$11,798           |
| No. PMA submissions per year for affected tests  | 102                | 51                 | 204                |
| <i>Recurring Subtotal (millions)*</i>            | <i>\$1.20</i>      | <i>\$0.60</i>      | <i>\$2.41</i>      |
| <b>Total Recurring Costs (millions)</b>          | <b>\$446.19</b>    | <b>\$209.86</b>    | <b>\$1,898.53</b>  |

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*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.<sup>65</sup> There are several types of PMA supplements (see Table 34; 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<sup>66</sup> and the share of supplements by supplement type.<sup>67</sup> We also multiply by the Remaining PMA Rate (Table A.4, Column F) to adjust for potential reclassification of Class III IVDs into Class II IVDs. We assume that entities would submit PMA supplements in year 4. See Table 34 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<sup>68</sup> 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 \$6.33 million to \$57.34 million, with a primary estimate of \$13.46 million. See Table 35.

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<sup>65</sup> 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>.

<sup>66</sup> 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.

<sup>67</sup> We use the FDA internal information on the total number of supplement submissions received by FDA from 2017 to 2023, as of July 2023.

<sup>68</sup> 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.

Table 34. 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   | 8    |
| Panel-Track                        | 0.067                                   | 2       | 1   | 4    |
| Real-Time Process                  | 0.374                                   | 14      | 7   | 28   |
| Special CBE                        | 0.095                                   | 4       | 2   | 7    |

Table 35. 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        | \$1.80         |
| Normal 180-day track                    | 0.033                         | \$0.99         | \$0.46        | \$4.21         |
| Normal 180-day track - No user fee      | 0.033                         | \$0.68         | \$0.32        | \$2.90         |
| Panel Track                             | 1.000                         | \$9.93         | \$4.67        | \$42.32        |
| Real Time Process                       | 0.010                         | \$0.79         | \$0.37        | \$3.38         |
| Special CBE                             | 0.033                         | \$0.64         | \$0.30        | \$2.73         |
| <b>Total Recurring Costs (millions)</b> |                               | <b>\$13.46</b> | <b>\$6.33</b> | <b>\$57.34</b> |

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

Similar to the PMA, we use the ERG estimates of the 510(k) process to estimate the one-time submission and preparation cost of 510(k)s, adjusting for inflation. We use the ERG estimates of 510(k) with small or simple clinical trials for 510(k) submissions with method comparison studies (see Table 36) (Ref. [55]). We use the ERG estimates of 510(k) with moderately complex clinical trials for 510(k) submissions with moderately complex clinical studies (see Table 37).<sup>69</sup>

For any 510(k) submission (or de novo request<sup>70</sup>), 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

<sup>69</sup> Distinctions of the estimates used in Table 36 and Table 37 are based on the type of study supporting clinical validation of these tests due to differing costs.

<sup>70</sup> In the absence of more detailed information on De Novo costs, we extrapolate 510(k) costs to estimate De Novo costs.



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. 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 \$139.64 million and \$723.68 million, with a primary estimate of \$320.55 million. See Table 36.

Table 36. Costs to Industry of 510(k)s (Method Comparison Study)

|   | Primary                 | Low                     | High                    |
|---|-------------------------|-------------------------|-------------------------|
| <b><i>Cost of Submission and Preparation</i></b>                                |                         |                         |                         |
| 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               |
| <b><i>Subtotal cost per submission</i></b>                                      | <b><i>\$247,307</i></b> | <b><i>\$215,457</i></b> | <b><i>\$279,157</i></b> |
| No. 510(k) submissions with method comparison study per year for affected tests | 1,296                   | 648                     | 2,592                   |
| <b>Total Recurring Costs (millions)*</b>  | <b>\$320.55</b>         | <b>\$139.64</b>         | <b>\$723.68</b>         |

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 37 presents costs of 510(k) submissions with a moderately complex clinical study. We calculate the costs using the exact same methods as in Table 36. 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 \$210.19 million to \$955.52 million, with a primary estimate of \$449.07 million.

Table 37. Costs to Industry of 510(k)s (Moderately Complex Clinical Study)

|  | Primary                 | Low                     | High                    |
|--|-------------------------|-------------------------|-------------------------|
| <b><i>Cost of Submission and Preparation</i></b>                       |                         |                         |                         |
| 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               |
| <b><i>Subtotal cost per submission</i></b>                             | <b><i>\$498,560</i></b> | <b><i>\$466,709</i></b> | <b><i>\$530,410</i></b> |
| No. 510(k) submissions with moderately complex clinical study per year | 901                     | 450                     | 1,801                   |
| <b>Total Recurring Costs (millions)*</b>                               | <b>\$449.07</b>         | <b>\$210.19</b>         | <b>\$955.52</b>         |

*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 38 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. [55]).<sup>71</sup> 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 37. 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 \$29.11 million to \$285.66 million, with a primary estimate of \$141.96 million.

Table 38. Costs to Industry of De Novo Classification Request

|   | Primary                 | Low                     | High                    |
|---|-------------------------|-------------------------|-------------------------|
| <b><i>Cost of Submission and Preparation</i></b>    |                         |                         |                         |
| 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                 |
| 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               |
| <b><i>Subtotal cost per submission</i></b>          | <b><i>\$527,202</i></b> | <b><i>\$216,211</i></b> | <b><i>\$530,410</i></b> |
| No. de novo submissions per year for affected tests | 269                     | 135                     | 539                     |
| <b>Total Recurring Costs (millions)*</b>            | <b>\$141.96</b>         | <b>\$29.11</b>          | <b>\$285.66</b>         |

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.

<sup>71</sup> 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.

## 5. Summary of Costs

Table 39 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 \$85.34 million, with a primary estimate of \$32.47 million. We estimate the total recurring costs to range between \$0.72 billion and \$4.54 billion, with a primary estimate of \$1.64 billion.

Table 39. Total Costs to FDA and Industry (millions 2022\$)

|  |  | Primary        | Low            | High           |
|--|--|----------------|----------------|----------------|
| <i>One-time</i>                        |  |                |                |                |
| 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                | \$1.42         | \$0.41         | \$4.06         |
| <b>Total One-time Costs (millions)</b> |  | <b>\$32.47</b> | <b>\$11.67</b> | <b>\$85.34</b> |
| <i>Recurring Annual</i>                |  |                |                |                |
| 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                | \$24.92        | \$1.96         | \$125.32       |
| Stage 4                                | Premarket Approval Application             | \$507.92       | \$240.72       | \$2,021.99     |
|  | Premarket Approval Application Supplements | \$14.88        | \$7.04         | \$60.19        |

|   |                                |                   |                 |                   |
|---|--------------------------------|-------------------|-----------------|-------------------|
| Stage 5                                 | 510(k) Submission              | \$813.43          | \$371.73        | \$1,766.80        |
|   | De Novo Classification Request | \$178.92          | \$47.59         | \$359.56          |
| <b>Total Recurring Costs (millions)</b> |                                | <b>\$1,641.07</b> | <b>\$719.23</b> | <b>\$4,537.27</b> |

*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 40 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 \$176.44 million to \$1.37 billion, with a primary estimate of \$388.75 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 \$719.23 million and \$4.54 billion, with a primary estimate of \$1.64 billion. We estimate the total costs over 20 years to range from \$12.51 billion to \$78.96 billion, with a primary estimate of \$28.50 billion.

The present value of total estimated costs is \$20.33 billion at a 3 percent discount rate and \$13.59 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 \$1.28 billion at a 7 percent discount rate.

Table 40. 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                                | \$388.75          | \$176.44        | \$1,373.88        |
| Year 4-20 (costs for each year)       | \$1,641.07        | \$719.23        | \$4,537.27        |
| Total Costs                           | \$28,501.54       | \$12,505.89     | \$78,958.10       |
| Present Value of Total Costs (3%)     | \$20,333.92       | \$8,925.38      | \$56,357.13       |
| Present Value of Total Costs (7%)     | \$13,589.79       | \$5,968.56      | \$37,689.00       |
| <b>Annualized Value of Costs (3%)</b> | <b>\$1,366.76</b> | <b>\$599.93</b> | <b>\$3,788.08</b> |
| <b>Annualized Value of Costs (7%)</b> | <b>\$1,282.78</b> | <b>\$563.39</b> | <b>\$3,557.58</b> |

#### 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 and access to diagnostics if many laboratories exit the market or discontinue offering certain IVDs rather than incur the costs of compliance with FDA requirements. There may be instances in which a laboratory may choose to exit the market or discontinue certain IVDs offered as LDTs due to compliance costs. Without 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.

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 enforcement discretion from premarket review requirements certain LDTs that are approved by NYS CLEP. Based on available information from the NYSDOH, we estimate that 11.4% (ranging from 5.7% to 22.8%) of IVDs offered as LDTs would not experience new review costs for FDA as a result of FDA leveraging the NYS CLEP.<sup>72</sup>

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<sup>72</sup> The NYSDOH may have different costs for submitting a premarket review per lab. We thus possibly overestimate costs to industry for premarket review requirements in section II.F.4. Due to lack of information on the cost difference, we assume the same preparation cost per submission for new IVDs that would be reviewed by the NYS CLEP.



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. 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. FDA assumes that at least 50% of the IVDs offered as LDTs subject to 510(k) requirements could be reviewed under the 510(k) Third Party Review Program.

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. [56]). The current estimate after adjustment for inflation is \$864,057 per PMA and \$20,565 per 510(k) (or per de novo).<sup>73</sup> We also use labor costs from estimated FTEs for FDA review of different submission types, including MDRs, Q-submissions, IDEs, and premarket submissions.<sup>74</sup> The 3-year average cost of all personnel compensation and benefits paid per FTE at FDA is \$315,403 (Ref. [57]). 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

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<sup>73</sup> 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.

<sup>74</sup> 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.

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.

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-submission, 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.<sup>75</sup> 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 \$16.97 million and \$67.88 million, with a primary estimate of \$33.94 million.

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<sup>75</sup> 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.

The total recurring review cost of PMAs is estimated to range between \$29.56 million to \$118.24 million, with a primary estimate of \$59.12 million. The total recurring review cost of PMA supplements is estimated to range between \$0.71 million and \$2.85 million, with a primary estimate of \$1.42 million. The total recurring review cost of 510(k)s is estimated to range from \$9.68 million to \$38.70 million, with a primary estimate of \$19.35 million. The recurring review cost of de novo classification requests is estimated to range from \$15.04 million to \$60.15 million, with a primary estimate of \$30.07 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 \$74.79 million and \$299.17 million, with a primary estimate of \$149.58 million. See Table 41.<sup>76</sup>

Table 41. 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        |
|              | <i>Subtotal, one-time (millions)*</i>   | <i>\$0.44</i> | <i>\$0.22</i> | <i>\$0.88</i>  |
|              | MDR submissions per year for affected tests                                     | 10,013        | 5,007         | 20,026         |
|              | <i>Subtotal, recurring (millions)*</i>  | <i>\$0.06</i> | <i>\$0.03</i> | <i>\$0.11</i>  |
| IDE          | FDA review costs using FTE  | \$21,763      | \$21,763      | \$21,763       |
|              | Affected IVDs offered as LDTs currently on the market                           | 107           | 53            | 214            |
|              | <i>Subtotal, one-time (millions)*</i>   | <i>\$2.32</i> | <i>\$1.16</i> | <i>\$4.65</i>  |
|              | New IDE submissions per year for affected tests                                 | 258           | 129           | 516            |
|              | <i>Subtotal, recurring (millions)*</i>  | <i>\$5.62</i> | <i>\$2.81</i> | <i>\$11.24</i> |
| 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 | 1,328         | 664           | 2,657          |

<sup>76</sup> The costs could be spread over time depending on the time of submission and review.

|   |   |                 |                |                 |
|---|---|-----------------|----------------|-----------------|
|   | <i>Subtotal, recurring (millions)*</i>          | \$33.94         | \$16.97        | \$67.88         |
| PMA                                     | FDA review costs using page numbers             | \$864,057       | \$864,057      | \$864,057       |
|   | FDA review costs using FTE                      | \$294,429       | \$294,429      | \$294,429       |
|   | <i>Average FDA review costs</i>                 | \$579,243       | \$579,243      | \$579,243       |
|   | PMA Submissions per year for affected tests     | 102             | 51             | 204             |
|   | <i>Subtotal, recurring (millions)*</i>          | \$59.12         | \$29.56        | \$118.24        |
| PMA Supplements                         | <i>Average FDA review costs</i>                 | \$110,319       | \$110,319      | \$110,319       |
|   | Supplements per year for affected tests         | 31              | 15             | 62              |
|   | <i>Subtotal, recurring (millions)**</i>         | \$1.42          | \$0.71         | \$2.85          |
| 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        |
|   | <i>Average FDA review costs</i>                 | \$20,218        | \$20,218       | \$20,218        |
|   | 510(k) submissions per year for affected tests  | 957             | 479            | 1,914           |
|   | <i>Subtotal, recurring (millions)*</i>          | \$19.35         | \$9.68         | \$38.70         |
| 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       |
|   | <i>Average FDA review costs</i>                 | \$111,685       | \$111,685      | \$111,685       |
|   | De novo submissions per year for affected tests | 269             | 135            | 539             |
|   | <i>Subtotal, recurring (millions)*</i>          | \$30.07         | \$15.04        | \$60.15         |
| <b>Total one-time costs (millions)</b>  |   | <b>\$2.77</b>   | <b>\$1.38</b>  | <b>\$5.53</b>   |
| <b>Total recurring costs (millions)</b> |   | <b>\$149.58</b> | <b>\$74.79</b> | <b>\$299.17</b> |

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.<sup>77</sup>

See Table 42 for the estimated transfers associated with the phaseout policy. All anticipated fees are public information published by FDA.<sup>78</sup> 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, 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.

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),

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<sup>77</sup> 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.

<sup>78</sup> 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>

- 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 \$40.49 million to \$162.53 million, with a primary estimate of \$81.26 million.

Table 42. Transfers

|                  |                                |  | Primary                  | Low                      | High                     |
|------------------|--------------------------------|--|--------------------------|--------------------------|--------------------------|
| Recurring Annual | Registration Annual Fee        | Fee  | \$7,653                  | \$7,653                  | \$7,653                  |
|                  |                                | Entities affected                              | 1,275                    | 638                      | 2,551                    |
|                  |                                | <i>Subtotal (millions)</i>                     | <i>\$9.76</i>            | <i>\$4.88</i>            | <i>\$19.52</i>           |
|                  | Annual reporting on PMA        | Fee (Adjusted fee for small entities)          | \$16,925<br>(\$4,231)    | \$16,925<br>(\$0)        | \$16,925<br>(\$4,231)    |
|                  |                                | IVDs affected, non-small*                      | 36                       | 18                       | 71                       |
|                  |                                | IVDs affected, small*                          | 66                       | 33                       | 133                      |
|                  |                                | <i>Subtotal (millions)</i>                     | <i>\$0.89</i>            | <i>\$0.30</i>            | <i>\$1.77</i>            |
| One-time /Annual | PMA                            | MDUFA Review (Adjusted fee for small entities) | \$483,560<br>(\$120,890) | \$483,560<br>(\$120,890) | \$483,560<br>(\$120,890) |
|                  |                                | IVDs affected, non-small*                      | 36                       | 18                       | 71                       |
|                  |                                | IVDs affected, small*                          | 66                       | 33                       | 133                      |
|                  |                                | <i>Subtotal (millions)</i>                     | <i>\$25.29</i>           | <i>\$12.65</i>           | <i>\$50.59</i>           |
|                  | PMA Supplements –180-day track | MDUFA Review (Adjusted fee for small entities) | \$72,534<br>(\$18,134)   | \$72,534<br>(\$18,134)   | \$72,534<br>(\$18,134)   |
|                  |                                | IVDs affected, non-small*                      | 2                        | 1                        | 4                        |
|                  |                                | IVDs affected, small*                          | 4                        | 2                        | 7                        |
|                  |                                | <i>Subtotal (millions)</i>                     | <i>\$0.20</i>            | <i>\$0.10</i>            | <i>\$0.41</i>            |
|                  | PMA Supplement                 | MDUFA Review (Adjusted fee for small entities) | \$386,848<br>(\$96,712)  | \$386,848<br>(\$96,712)  | \$386,848<br>(\$96,712)  |

|   |                             |  |                         |                         |                         |
|---|-----------------------------|--|-------------------------|-------------------------|-------------------------|
|   | s – Panel-track             | IVDs affected, non-small*                      | 1                       | 0                       | 1                       |
|   |                             | IVDs affected, small*                          | 1                       | 1                       | 2                       |
|   |                             | <i>Subtotal (millions)</i>                     | <i>\$0.36</i>           | <i>\$0.18</i>           | <i>\$0.72</i>           |
|   | PMA Supplements – Real-Time | MDUFA Review (Adjusted fee for small entities) | \$33,849<br>(\$8,462)   | \$33,849<br>(\$8,462)   | \$33,849<br>(\$8,462)   |
|   |                             | IVDs affected, non-small*                      | 5                       | 2                       | 10                      |
|   |                             | IVDs affected, small*                          | 9                       | 5                       | 18                      |
|   |                             | <i>Subtotal (millions)</i>                     | <i>\$0.24</i>           | <i>\$0.12</i>           | <i>\$0.48</i>           |
|   | 510(k)                      | MDUFA Review (Adjusted fee for small entities) | \$21,760<br>(\$5,440)   | \$21,760<br>(\$5,440)   | \$21,760<br>(\$5,440)   |
|   |                             | IVDs Affected, non-small*                      | 769                     | 384                     | 1,538                   |
|   |                             | IVDs affected, small*                          | 1,428                   | 714                     | 2,856                   |
|   |                             | <i>Subtotal (millions)</i>                     | <i>\$24.50</i>          | <i>\$12.25</i>          | <i>\$49.00</i>          |
|   | De Novo                     | MDUFA Review (Adjusted fee for small entities) | \$145,068<br>(\$36,267) | \$145,068<br>(\$36,267) | \$145,068<br>(\$36,267) |
| IVDs affected, non-small*                   |                             | 94   | 47                      | 188                     |                         |
| IVDs affected, small*                       |                             | 175  | 88                      | 350                     |                         |
| <i>Subtotal (millions)</i>                  |                             | <i>\$20.02</i>                                 | <i>\$10.01</i>          | <i>\$40.04</i>          |                         |
| <b>Total Recurring Transfers (millions)</b> |                             |  | <b>\$81.26</b>          | <b>\$40.49</b>          | <b>\$162.53</b>         |

\*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 43 for a summary of the timing of expected benefits, costs, and transfers over a twenty-year time frame, in millions of 2022 U.S. dollars. Only primary estimates are presented. For each year, we present the undiscounted benefits, costs to industry, costs to FDA, and transfers, as well as discounted estimates that account for inflation and the changing value of the dollar.

Table 43. 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  | \$30,112 | \$49,598 | \$336   | \$53  | \$23 |
| 4  | \$30,464 | \$50,197 | \$1,491 | \$150 | \$81 |
| 5  | \$42,710 | \$70,389 | \$1,491 | \$150 | \$81 |
| 6  | \$44,519 | \$73,413 | \$1,491 | \$150 | \$81 |
| 7  | \$46,182 | \$76,154 | \$1,491 | \$150 | \$81 |
| 8  | \$47,660 | \$78,592 | \$1,491 | \$150 | \$81 |
| 9  | \$48,976 | \$80,762 | \$1,491 | \$150 | \$81 |
| 10 | \$50,149 | \$82,696 | \$1,491 | \$150 | \$81 |
| 11 | \$51,196 | \$84,423 | \$1,491 | \$150 | \$81 |
| 12 | \$52,133 | \$85,968 | \$1,491 | \$150 | \$81 |
| 13 | \$52,973 | \$87,353 | \$1,491 | \$150 | \$81 |
| 14 | \$53,726 | \$88,595 | \$1,491 | \$150 | \$81 |
| 15 | \$54,403 | \$89,712 | \$1,491 | \$150 | \$81 |
| 16 | \$55,014 | \$90,718 | \$1,491 | \$150 | \$81 |
| 17 | \$55,564 | \$91,625 | \$1,491 | \$150 | \$81 |
| 18 | \$56,061 | \$92,446 | \$1,491 | \$150 | \$81 |
| 19 | \$56,511 | \$93,188 | \$1,491 | \$150 | \$81 |
| 20 | \$56,920 | \$93,861 | \$1,491 | \$150 | \$81 |

Table 43 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 resulting funding gap is presented in Table 44. 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).<sup>79</sup>

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<sup>79</sup> 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



Table 44. Summary of FDA Review Costs and Transfers (Annualized over 20 years, in millions 2022\$)

|  | Discount rate | Primary  | Low     | High     |
|--|---------------|----------|---------|----------|
| FDA Review Costs                       | 3%            | \$124.94 | \$62.47 | \$249.88 |
|  | 7%            | \$117.31 | \$58.66 | \$234.62 |
| Transfers                              | 3%            | \$67.81  | \$33.80 | \$135.67 |
|  | 7%            | \$47.71  | \$23.79 | \$95.49  |
| Difference<br>(=FDA Costs - Transfers) | 3%            | \$57.13  | \$28.67 | \$114.21 |
|  | 7%            | \$69.60  | \$34.86 | \$139.13 |

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 45.

Table 45. Summary of Present and Annualized Values (in millions 2022\$)

|                     | Benefits     | Costs*      | Transfers  |
|---------------------|--------------|-------------|------------|
| Present Value 7%    | \$675,532.46 | \$13,589.79 | \$505.47   |
| Present Value 3%    | \$623,408.08 | \$20,333.92 | \$1,008.81 |
| Annualized Value 7% | \$63,765.48  | \$1,282.78  | \$47.71    |
| Annualized Value 3% | \$41,902.81  | \$1,366.76  | \$67.81    |

\*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 46 summarizes our analysis of the alternatives of the phaseout policy.

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establishment registrations (which are distinct from user fee payments for premarket submissions) will be subject to the current MDUFA V fee structure.

Table 46. Annualized Values of Regulatory Alternatives Over a 20 Year Period (in billions 2022\$)

|                | <b>Final Phaseout Policy</b> |           | <b>Alternative 2</b> |           | <b>Alternative 3</b> |           | <b>Alternative 4</b> |           |
|----------------|------------------------------|-----------|----------------------|-----------|----------------------|-----------|----------------------|-----------|
|                | <b>3%</b>                    | <b>7%</b> | <b>3%</b>            | <b>7%</b> | <b>3%</b>            | <b>7%</b> | <b>3%</b>            | <b>7%</b> |
| Total Benefits | \$41.90                      | \$63.77   | \$42.42              | \$64.79   | \$38.06              | \$56.30   | \$49.60              | \$76.54   |
| Total Costs    | \$1.37                       | \$1.28    | \$1.45               | \$1.38    | \$1.20               | \$1.08    | \$5.57               | \$5.83    |
| Net Benefits   | \$40.54                      | \$62.48   | \$40.97              | \$63.41   | \$36.87              | \$55.22   | \$44.03              | \$70.71   |
| Transfers      | \$0.07                       | \$0.05    | \$0.07               | \$0.07    | \$0.06               | \$0.04    | \$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: Phase out the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements, one year after publication of the final phaseout policy.
  - Stage 2: Phase out the general enforcement discretion approach with respect to requirements not covered during other stages of the phaseout policy, including registration and listing, labeling, investigational use requirements, and QS requirements, two years after publication of the final phaseout policy.
  - Stage 3: Phase out the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs and other premarket review requirements (for moderate-risk and low-risk IVDs that require premarket submissions), three years after publication of the final phaseout policy.

Under this alternative, we assume that one-time and recurring costs of the QS requirements would occur in year 2 and costs of the PMA, 510(k), and de novo submissions would occur in year 3. The estimated annualized costs of this alternative would be \$1.45 billion, which is \$99 million higher than the estimated costs associated with the phaseout policy. The estimated annualized transfers of this alternative would be \$68 million, which is \$20 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 \$64.79 billion, which is \$1.02 billion 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: Phase out the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements one year after publication of the phaseout policy.
  - Stage 2: Phase out the general enforcement discretion approach with respect to requirements other than MDR, correction and removal reporting, and premarket review requirements four years after publication of the phaseout policy.

- Stage 3: Phase out the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs five years (seven years for small laboratories) after publication of the phaseout policy.
- Stage 4: Phase out the general enforcement discretion approach with respect to premarket review requirements for moderate risk and low risk IVDs that require premarket submissions six years (ten years for small laboratories) after publication of the phaseout policy.

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 \$1.08 billion, which is \$201 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 \$92 million under this alternative, which is \$26 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 \$7.46 billion 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 \$0.19 billion. 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 \$463 million, from \$117 million to \$581 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 \$76.54 billion, which is \$12.78 billion higher than the estimated benefits of the final phaseout policy. Table 47 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 22 for the impact of the enforcement discretion policies on the benefits.

Table 47. 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                   | \$26.34               | \$472.19      |
| Stage 4 | Premarket Approval Application                | \$507.92              | \$21,589.11   |
|         | Premarket Approval Application Supplements    | \$14.88               | \$285.28      |
| Stage 5 | 510(k) Submission                             | \$813.43              | \$13,746.59   |
|         | De Novo Classification Request                | \$178.92              | \$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 most 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. [58]) 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. [59, 60, 61, 62, 63]).

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. [64]).

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 most 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. 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 most 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.<sup>80</sup> 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

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<sup>80</sup> A 2021 Pew Charitable Trusts' survey of laboratory managers found that 'rapid access' and 'patient need' were top reasons why laboratory managers would choose to employ an LDT (Ref. [19]).



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 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 most 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.<sup>81</sup> 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

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<sup>81</sup> [https://qcor.cms.gov/advanced\\_find\\_provider.jsp?which=4&backReport=active\\_CLIA.jsp](https://qcor.cms.gov/advanced_find_provider.jsp?which=4&backReport=active_CLIA.jsp)

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.

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.<sup>82</sup> 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

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<sup>82</sup> <https://www.nber.org/research/data/occupational-wages-around-world-oww-database>

domestic costs of compliance. See Table 48 for a summary of international costs, organized by stage and part of the phaseout policy.

Table 48. International Costs

|                              |  | Primary              | Low                  | High                 |
|------------------------------|--|----------------------|----------------------|----------------------|
| <i>One-time</i>              |  |                      |                      |                      |
| 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            | \$49,784             | \$336,047            |
|                              | Investigational Use Requirements           | \$466,943            | \$466,943            | \$466,943            |
| Stage 3                      | Quality System Requirements                | \$96,644             | \$55,225             | \$138,062            |
| <b>Total One-time Costs</b>  |  | <b>\$1,651,379</b>   | <b>\$1,220,255</b>   | <b>\$2,131,781</b>   |
| <i>Recurring Annual</i>      |  |                      |                      |                      |
| Stage 1                      | Medical Device Reporting                   | \$3,706,891          | \$3,706,891          | \$3,706,891          |
|                              | Correction and Removal Reporting           | \$6,845              | \$6,845              | \$6,845              |
| Stage 2                      | Re-registration                            | \$6,223              | \$6,223              | \$6,223              |
|                              | Investigational Use                        | \$1,045,396          | \$1,045,396          | \$1,045,396          |
| Stage 4                      | Premarket Approval Application             | \$52,427,204         | \$49,694,217         | \$104,353,970        |
|                              | Premarket Approval Application Supplements | \$1,535,974          | \$1,453,322          | \$3,106,357          |
| Stage 5                      | 510(k) Submission                          | \$83,949,007         | \$76,730,620         | \$91,167,393         |
|                              | De Novo Classification Request             | \$18,466,225         | \$9,822,822          | \$18,554,875         |
| <b>Total Recurring Costs</b> |  | <b>\$161,143,766</b> | <b>\$142,466,336</b> | <b>\$221,947,950</b> |

See Table 49 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 \$117.87 million to \$184.03 million, with a primary estimate of \$133.11 million. At a seven percent discount rate, we expect the annualized value of international costs to range from \$110.34 million to \$172.38 million, with a primary estimate of \$124.53 million.

Table 49. Twenty-Year Timing of International Costs (millions 2022\$)

|   | Primary    | Low        | High       |
|---|------------|------------|------------|
| Year 1                                    | \$4.59     | \$4.34     | \$4.89     |
| Year 2                                    | \$5.44     | \$5.30     | \$5.59     |
| Year 3                                    | \$31.84    | \$30.39    | \$58.63    |
| Year 4-20 (costs for each year)           | \$161.14   | \$142.47   | \$221.95   |
| <i>Total Costs of the Phaseout Policy</i> | \$2,781.32 | \$2,461.97 | \$3,842.22 |
| Present Value of Total Costs (3%)         | \$1,980.33 | \$1,753.59 | \$2,737.89 |
| Present Value of Total Costs (7%)         | \$1,319.31 | \$1,168.91 | \$1,826.17 |
| <b>Annualized Value of Costs (3%)</b>     | \$133.11   | \$117.87   | \$184.03   |
| <b>Annualized Value of Costs (7%)</b>     | \$124.53   | \$110.34   | \$172.38   |

### 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 most 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.<sup>83</sup> 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 50). 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 that small businesses also manufacture 22% of IVDs offered as LDTs currently on the market.<sup>84</sup> We provide more detail on these estimates in Appendix B.

Table 50. 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  | 154  | 50                             |
| \$151 - \$999           | 933  | 327  | 555                            |
| \$1000 - \$1,999        | 413  | 145  | 669                            |
| \$2,000 - \$3,999       | 481  | 169  | 1,729                          |
| \$4,000 - \$5,999       | 343  | 120  | 2,717                          |
| \$6,000 - \$9,999       | 146  | 51   | 1,908                          |
| \$10,000 - \$14,999     | 77   | 27   | 1,322                          |
| \$15,000 - \$19,999     | 115  | 40   | 2,764                          |
| \$20,000 - \$24,999     | 79   | 28   | 2,592                          |
| \$25,000 - \$29,999     | 21   | 7  | 844                            |
| \$30,000 - \$39,999     | 43   | 15   | 2,015                          |
| \$40,000 - \$49,999     | 15   | 5  | 1,022                          |
| \$50,000 - \$99,999     | 67   | 24   | 4,860                          |
| \$100,000 +             | 194  | 68   | 56,067                         |
| <b>Total</b>            | <b>3,365</b>                                   | <b>1,181</b>                                 | <b>79,114</b>                  |
| < \$41.5 million        | 3,091  | 1,085  | 17,318                         |
| Percent Small           | 92%  | 92%  | 22%                            |

<sup>83</sup> Small Business Association. Table of Size Standards. March 17, 2023. Available from: <https://www.sba.gov/document/support-table-size-standards>

<sup>84</sup> From Table 50 an estimated 17,318 of 79,114 IVDs or 22% offered as LDTs are from small businesses.

## 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 51, 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 \$2,294 to \$3,351,459 per laboratory, depending on its size classification.<sup>85</sup> As shown in Table 51, the annualized costs per small entity averages \$953,002 represent 2.8 percent of receipts for the small laboratories (with annual receipts of less than \$41,500,000), making it unlikely that some small entities in this size category will exit the market or reduce operations. We also estimate that small laboratories hold a 24 percent share of receipts while producing 22 percent of all IVDs offered as LDTs.

For large laboratories (with annual receipts of \$41,500,000 or greater), the average annualized costs per entity is estimated as 6.4 percent of average annual receipts whereas for small firms the average costs over average receipt is 2.8% per small firm. Small laboratories have a lower estimated percentage of costs over revenues than large laboratories because we apply our total low cost estimate for small laboratories and our total primary estimate for large laboratories. The reason is because our lower bound costs in our cost model are estimated with assumption that lower costs applied to small firms.<sup>86</sup> If we estimate percent of costs over receipts

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<sup>85</sup> The average annualized cost per small entity ranges from \$5,871 per laboratory with annual receipts that are less than \$150,000 and to \$3,767,503 per laboratory with annual receipts between \$40 and \$45 million.

<sup>86</sup> Throughout our costs estimates for each individual stage (1-5) we estimate low, primary and high costs. The low estimates are more reflective of the type of costs that would be incurred by small businesses.

using our primary cost estimate evenly across all size categories, then the average cost over average receipt per lab would be 5.6%.<sup>87</sup>

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.<sup>88</sup> The estimated average recurring transfer for small businesses is \$4,838. As seen in Table 51, the percent transfers over receipts associated with the phaseout policy are estimated to be 0.12 percent for 154 laboratories (14 percent of the small entities) with their annual receipts less than \$150,000.

Table 51. 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                 | 154  | \$81,816         | \$2,294             | 2.8%                     | \$97                    | 0.12%                        |
| \$151 - \$999           | 327  | \$430,532        | \$12,071            | 2.8%                     | \$510                   | 0.12%                        |
| \$1000 - \$1,999        | 145  | \$1,172,533      | \$32,875            | 2.8%                     | \$1,388                 | 0.12%                        |
| \$2,000 - \$3,999       | 169  | \$2,601,807      | \$72,949            | 2.8%                     | \$3,081                 | 0.12%                        |
| \$4,000 - \$5,999       | 120  | \$5,733,410      | \$160,752           | 2.8%                     | \$6,789                 | 0.12%                        |
| \$6,000 - \$9,999       | 51   | \$9,459,407      | \$265,221           | 2.8%                     | \$11,201                | 0.12%                        |
| \$10,000 - \$14,999     | 27   | \$12,425,958     | \$348,396           | 2.8%                     | \$14,713                | 0.12%                        |
| \$15,000 - \$19,999     | 40   | \$17,395,652     | \$487,736           | 2.8%                     | \$20,598                | 0.12%                        |
| \$20,000 - \$24,999     | 28   | \$23,750,766     | \$665,919           | 2.8%                     | \$28,123                | 0.12%                        |
| \$25,000 - \$29,999     | 7    | \$29,082,108     | \$815,398           | 2.8%                     | \$34,436                | 0.12%                        |
| \$30,000 - \$39,999     | 15   | \$33,924,383     | \$951,165           | 2.8%                     | \$40,169                | 0.12%                        |
| \$40,000 - \$49,999     | 5    | \$49,317,674     | \$2,883,526         | 5.9%                     | \$108,296               | 0.22%                        |
| \$50,000 - \$99,999     | 24   | \$52,498,495     | \$3,351,459         | 6.4%                     | \$124,656               | 0.24%                        |

<sup>87</sup> For example, dividing our low estimate of total annualized costs of 1.28 billion dollars (or \$1,282,779,740) by 154 labs in receipt category of < 150 (first row of Table 51), we estimate total average costs per lab as \$2,294 which represents 2.8 percent of costs over average receipts of \$81,816.

<sup>88</sup> 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 \$97 divided by \$81,816 of the low estimate of total annualized fees of \$23.79 million.

|               |       |               |              |      |           |       |
|---------------|-------|---------------|--------------|------|-----------|-------|
| \$100,000 +   | 68    | \$209,184,656 | \$13,354,171 | 6.4% | \$496,702 | 0.24% |
| Total         | 1,181 | \$17,017,221  | \$953,002    | 5.6% | \$35,973  | 0.21% |
| <\$41.5 M     | 1,085 | \$4,054,973   | \$113,692    | 2.8% | \$4,838   | 0.12% |
| Percent small | 92%   | 24%           | 12%          | 50%  | 13%       | 56%   |

### C. Alternatives to Minimize the Burden on Small Entities

Regulatory alternative 3, described in section II.J, would reduce costs for all laboratories. Below we show how the reduction in cost under the alternative would reduce the cost on small laboratories.

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 \$877 to \$525,536 per small entity.<sup>89</sup> For small laboratories (with annual receipts of less than \$41,500,000) total recurring costs are estimated to be 1.7 percent of their average receipts. This alternative would also reduce transfers

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<sup>89</sup> 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 52 from costs per lab column in Table 50 For example \$2,294 from Table 51 minus \$1,417 in Table 52 equals \$877.



for all laboratories offering IVDs as LDTs from an average of \$4,838 to \$2,409 per entity for laboratories with their annual receipts below \$41.5 million, which is \$2,429 less than the estimated transfers of the phaseout policy. For the smallest laboratories (with annual receipts lower than \$150,000), total transfers would be 0.06 percent of receipts. See Table 52.

Table 52. 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                 | 154  | \$81,816         | \$1,417            | 1.7%                     | \$48                   | 0.06%                        |
| \$151 - \$999           | 327  | \$430,532        | \$7,457            | 1.7%                     | \$252                  | 0.06%                        |
| \$1000 - \$1,999        | 145  | \$1,172,533      | \$20,308           | 1.7%                     | \$685                  | 0.06%                        |
| \$2,000 - \$3,999       | 169  | \$2,601,807      | \$45,063           | 1.7%                     | \$1,520                | 0.06%                        |
| \$4,000 - \$5,999       | 120  | \$5,733,410      | \$99,302           | 1.7%                     | \$3,350                | 0.06%                        |
| \$6,000 - \$9,999       | 51   | \$9,459,407      | \$163,835          | 1.7%                     | \$5,526                | 0.06%                        |
| \$10,000 - \$14,999     | 27   | \$12,425,958     | \$215,215          | 1.7%                     | \$7,259                | 0.06%                        |
| \$15,000 - \$19,999     | 40   | \$17,395,652     | \$301,289          | 1.7%                     | \$10,163               | 0.06%                        |
| \$20,000 - \$24,999     | 28   | \$23,750,766     | \$411,359          | 1.7%                     | \$13,875               | 0.06%                        |
| \$25,000 - \$29,999     | 7    | \$29,082,108     | \$503,696          | 1.7%                     | \$16,990               | 0.06%                        |
| \$30,000 - \$39,999     | 15   | \$33,924,383     | \$587,564          | 1.7%                     | \$19,819               | 0.06%                        |
| \$40,000 - \$49,999     | 5    | \$49,317,674     | \$2,384,597        | 4.8%                     | \$83,937               | 0.17%                        |
| \$50,000 - \$99,999     | 24   | \$52,498,495     | \$2,825,923        | 5.4%                     | \$99,707               | 0.19%                        |
| \$100,000 +             | 68   | \$209,184,656    | \$11,260,129       | 5.4%                     | \$397,290              | 0.19%                        |
| Total                   | 1181 | \$17,017,221     | \$780,015          | 4.6%                     | \$27,421               | 0.16%                        |
| <\$41.5 M               | 1085 | \$4,054,973      | \$70,231           | 1.7%                     | \$2,409                | 0.06%                        |

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## 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)<sup>90</sup>. 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 labs 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 Trust (Ref. [12]) that

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<sup>90</sup> [https://qcor.cms.gov/advanced\\_find\\_provider.jsp?which=4&backReport=active\\_CLIA.jsp](https://qcor.cms.gov/advanced_find_provider.jsp?which=4&backReport=active_CLIA.jsp)

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 labs 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)<br>Total | (B)<br>Waiver and<br>Microscopy | (C)<br>Difference<br>(A) - (B) | (D)<br>High<br>Complexity<br>Rate | (E)<br>No. HC<br>Labs<br>(C) x (D) | (F)<br>Integrated<br>Healthcare<br>System Rate | (G)<br>No. HC Labs<br>within<br>Healthcare<br>System<br>(E) x (F) |
|------------------------|--------------|---------------------------------|--------------------------------|-----------------------------------|------------------------------------|--|---|
| Physician Office<br>** | 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    | -             |      | -            |
| <b>Total</b>                      | <b>349,207</b> | <b>313,815</b> | <b>35,392</b> |      | <b>11,808</b> |      | <b>4,586</b> |

### 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 tests expected 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 IVDs would range 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 per lab 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.<sup>91</sup> We also estimate new IVDs from new laboratories entering the market every year (8 percent of affected laboratories). The total number of new IVDs 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

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<sup>91</sup> 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**

| <b>Number of affected labs and tests</b>                                   | <b>Primary</b> | <b>Low</b> | <b>High</b> | <b>Calculation</b>    |
|--|----------------|------------|-------------|-----------------------|
| 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 LDTs excluding tests by submission type 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 ( $2,362 = 1,181 \text{ affected labs} * 2$ ). 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 2,552 LDTs for unmet needs ( $2,139 = 459 * 2 * 55\% + 1,635$ )<sup>92</sup>, 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 (column A of Table A.3) to calculate the number of new IVDs excluding LDTs for unmet needs.

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

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<sup>92</sup> 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.

|         | No. IVDs, total<br>(A) | No. LDTs for unmet<br>needs<br>(B) | No. IVDs excluding<br>LDTs for unmet needs<br>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 individual IVDs to determine the appropriate level of regulatory controls and whether a new test may be classified into Class II through de novo classification (and special controls established), rather than being class III and subject to the PMA pathway. Based on our experience, we believe that special controls could be developed, along with general controls, that could provide a reasonable assurance of safety and effectiveness for most future 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 downclassified 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)**

| <b>Review Track</b>                | <b>(A)</b><br>Average Historical IVD submissions per Year | <b>(B)</b><br># from column A that fall into procodes considered for reclassification | <b>(C)</b><br>Average FOAK used to estimate future # De Novo per Year | <b>(D)</b><br>Average non-FOAK used to estimate future # 510(k) per Year | <b>(E)</b><br>Estimated # Remaining PMA per year in future | <b>(F)</b><br><b>Remaining PMA Rate</b><br>=(E)/(A) | <b>(G)</b><br><b>De novo Rate</b><br>=(C)/(A) | <b>(H)</b><br><b>510(k) Rate</b><br>=(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 IVD Submissions Before and After Potential Reclassification**

| <b>Submission Type</b> | <b>Before Potential Reclassification</b> |            |             | <b>After Potential Reclassification</b> |            |             |
|------------------------|--|------------|-------------|---|------------|-------------|
|                        | <b>Primary</b>                           | <b>Low</b> | <b>High</b> | <b>Primary</b>                          | <b>Low</b> | <b>High</b> |
| PMA                    | 287                                      | 143        | 574         | 115                                     | 58         | 230         |
| 510(k)                 | 2,294                                    | 1,147      | 4,588       | 2,480                                   | 1,240      | 4,959       |
| De novo                | 287                                      | 143        | 574         | 304                                     | 152        | 608         |
| PMA supplements        | 67                                       | 33         | 133         | 35                                      | 17         | 70          |

As mentioned in section II.G, we estimate that 11.4 percent of the of IVDs offered as LDTs are expected to be reviewed by NYS CLEP each year and thus exclude them from the number of affected tests after potential reclassification (Table A.5). Table A.6 below shows the final number of premarket submissions, excluding tests for unmet needs and submissions

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 102 ( $=115 - 115*0.114$ ).

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

| <b>Submission Type</b> | <b>Primary</b> | <b>Low</b> | <b>High</b> |
|------------------------|----------------|------------|-------------|
| PMA                    | 102            | 51         | 204         |
| 510(k)                 | 2,197          | 1,098      | 4,394       |
| De novo                | 269            | 134        | 538         |
| PMA supplements        | 31             | 15         | 62          |

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 51 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.<sup>93</sup> We also re-classify enterprise size categories given our new estimated average receipts per lab (Table B.2).

| <b>Table B.1 Growth Adjusted Annual Receipts from IVDs Offered as LDTs by Enterprise Size (2022, U.S. Dollars)</b> |                                  |              |                             |  |                       |
|--|----------------------------------|--------------|-----------------------------|--|-----------------------|
| <b>Number of Firms and Receipts by Enterprise Receipt Size 2017</b>  |                                  |              |                             | <b>Receipts Only IVDs Offered as LDTs (\$1,000) in 2022 dollars adjusted for growth since 2017</b> | <b>Calculation</b>    |
| <b><i>I</i></b>  | <b>Enterprise Size (\$1,000)</b> | <b>Firms</b> | <b>Receipts (\$1,000) D</b> |  |                       |
| 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 |
|  | <b>Total</b>                     | <b>3,365</b> | <b>\$35,658,201</b>         | <b>\$20,093,935</b>  |                       |

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 1,181 (total LDT labs) to obtain 154 ( $438/3,365 * 1,181 = 154$ ). We repeat this calculation for the rest of the rows. We then estimate the average receipts per laboratory by receipt size category.

<sup>93</sup> This is also explained in detail in section II.D.3 Baseline Market Revenue.

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

| <i>i</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  | 154              | \$82                     |
| 2        | \$151 - \$499             | 933   | \$250,134          | \$140,954   | 327              | \$431                    |
| 3        | \$500 - \$999             | 413   | \$301,551          | \$169,929   | 145              | \$1,173                  |
| 4        | \$1,000 - \$2,999         | 481   | \$779,302          | \$439,148   | 169              | \$2,602                  |
| 5        | \$3,000 - \$5,999         | 343   | \$1,224,596        | \$690,078   | 120              | \$5,733                  |
| 6        | \$6,000 - \$7,999         | 146   | \$860,008          | \$484,627   | 51               | \$9,459                  |
| 7        | \$8,000 - \$9,999         | 77    | \$595,808          | \$335,747   | 27               | \$12,426                 |
| 8        | \$10,000 - \$14,999       | 115   | \$1,245,731        | \$701,988   | 40               | \$17,396                 |
| 9        | \$15,000 - \$19,999       | 79    | \$1,168,397        | \$658,409   | 28               | \$23,751                 |
| 10       | \$20,000 - \$23,999       | 21    | \$380,304          | \$214,307   | 7                | \$29,082                 |
| 11       | \$24,000 - \$29,999       | 43    | \$908,377          | \$511,884   | 15               | \$33,924                 |
| 12       | \$30,000 - \$35,999       | 15    | \$460,659          | \$259,588   | 5                | \$49,318                 |
| 13       | \$36,000 - \$99,999       | 67    | \$2,190,319        | \$1,234,278   | 24               | \$52,498                 |
| 14       | \$100,000 +               | 194   | \$25,270,700       | \$14,240,421  | 68               | \$209,185                |
|          | Total                     | 3,365 | \$35,658,201       | \$20,093,935  | 1,181            | \$17,017                 |

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>i</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%                             | 154                     | 0.06%                              | 50  |
| 2        | \$151 - \$999             | 28%                             | 327                     | 0.70%                              | 555   |
| 3        | \$1000 - \$1,999          | 12%                             | 145                     | 0.85%                              | 669   |
| 4        | \$2,000 - \$3,999         | 14%                             | 169                     | 2.19%                              | 1,729   |
| 5        | \$4,000 - \$5,999         | 10%                             | 120                     | 3.43%                              | 2,717   |
| 6        | \$6,000 - \$9,999         | 4%                              | 51                      | 2.41%                              | 1,908   |
| 7        | \$10,000 - \$14,999       | 2%                              | 27                      | 1.67%                              | 1,322   |

|    |                     |      |              |        |        |
|----|---------------------|------|--------------|--------|--------|
| 8  | \$15,000 - \$19,999 | 3%   | 40           | 3.49%  | 2,764  |
| 9  | \$20,000 - \$24,999 | 2%   | 28           | 3.28%  | 2,592  |
| 10 | \$25,000 - \$29,999 | 1%   | 7            | 1.07%  | 844    |
| 11 | \$30,000 - \$39,999 | 1%   | 15           | 2.55%  | 2,015  |
| 12 | \$40,000 - \$49,999 | 0%   | 5            | 1.29%  | 1,022  |
| 13 | \$50,000 - \$99,999 | 2%   | 24           | 6.14%  | 4,860  |
| 14 | \$100,000 +         | 6%   | 68           | 70.87% | 56,067 |
|    | Total               | 100% | <b>1,181</b> |        | 79,114 |

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