THE NEW YORK STATE CLINICAL LABORATORY ASSOCIATION

FDA's Final Rule Regulating LDTs

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On May 6, 2024, the Food and Drug Administration ("FDA") issued its long-anticipated final rule regulating laboratory developed tests ("LDTs"). In the May 6, 2024 final rule, the FDA outlined several categories of full and partial enforcement discretion, as described in more detail below.

The FDA's final rule subjects substantially all LDTs to FDA regulation. However, the FDA, in the commentary to the final rule, outline its intent to exercise enforcement discretion over a four-year phase-out period, and not subject certain categories of enforcement discretion to the entire set of FDA regulatory requirements that would otherwise be applicable to medical devices.

It is critical for laboratories to understand that the FDA's use of enforcement discretion is not the same as an "exception" or "grandfathering" under the final rule. Rather, the FDA's enforcement discretion can be altered or withdrawn at any time unilaterally by the FDA. In addition, the three most significant categories of partial enforcement discretion (currently marketed LDTs, certain LDTs performed by health systems, and LDTs with New York State's Clinical Laboratory Evaluation Program ("NYS CLEP") approval remain subject to significant FDA regulation, as explained below.

Litigation

The American Clinical Laboratory Association ("ACLA") and the Association for Molecular Pathology ("AMP") have both filed litigation challenging the final rule. The legal challenges of both organizations are primarily focused upon an argument that the FDA lacks the legal authority to regulate LDTs as medical devices under the Food, Drug and Cosmetics Act (the "Act"). Importantly, both legal challenges point out that Congress never explicitly stated that laboratory tests, and LDTs in particular, are subject to FDA regulation under the Act, even in the 50 years that have passed since the original passage of the Act. Moreover, the FDA itself remained silent on the issue for the first 20+ years after the enactment of the Act. It was only in the 1990s that the FDA first broached the subject of LDTs being subject to FDA regulation as medical devices. In the 30 years since, the FDA failed to enact any final regulation that would have subjected LDTs to FDA regulation under the Act, until the May 6, 2024 final rule. The FDA's explanation for its failure to take any definitive action with respect to the regulation of LDTs as medical devices is that it was exercising its enforcement discretion.

The ACLA and AMP litigation likely will take many months if not years to work through the legal system. At the same time, interested parties are pursuing lobbying with Congress, including an updated iteration of the VALID Act. The prospect of success for the ACLA and AMP litigation has improved with the Supreme Court's decision in *Loper Bright Enterprises*, which overturned the Chevron Doctrine. The overturning of the Chevron Doctrine means that the courts that will rule upon the ACLA and AMP litigation will not be required to give deference to the FDA's position that

it has the authority to regulate LDTs as medical devices. Rather, the courts can make this determination *de novo* based upon the words of the Act itself.

Even though the likelihood of success for the ACLA and AMP litigation has improved with the *Loper Bright* decision, it is unlikely that there will be a complete resolution of the issues prior to at least the first or second stage of the FDA's phase out of its enforcement discretion (discussed in more detail below). This means that laboratories still need to take action now to consider how they will approach compliance with the FDA's final rule, particularly if certain aspects of FDA regulation survive legal challenge.

Phase-out Process

Pursuant to the new rule, the FDA will phase out its historic enforcement discretion over a four-year period. All LDTs (with the exception of four very limited categories of LDTs that are eligible for full enforcement discretion) will be subject to the first three transition deadlines in the table below: (a) medical device reporting system requirements, (b) registration, class-based listing, labeling and investigational use standards, and (c) at least some of the quality systems requirements. Those LDTs that are not eligible for any enforcement discretion will be subject to premarket review requirements, which include premarket application submissions for high-risk LDTs and premarket review for low and moderate-risk LDTs, as outlined in the fourth and fifth transition deadlines in the table.

FDA's Final Timeline for LDT to IVD Transition				
May 6, 2025	**May 6, 2026**	**May 6, 2027**	**Nov. 6, 2027**	**May 6, 2028**
• Medical device reporting system (adverse event reporting, correction, and removal standards) • 21 CFR Part 803 • 21 CFR Part 806 • 21 CFR §820.198	• Registration and class-based listing, labeling (includes summary of performance data) and investigational use • 21 CFR Part 801 • 21 CFR Part 807 • 21 CFR §809.10 • 21 CFR Part 812	• All remaining quality systems requirements not covered in the first two phase-outs (applicable to each laboratory and each LDT) • 21 CFR Part 820	• PMA submissions for "high-risk" LDTs (includes mandatory on-site inspections)	• FDA submissions for "moderate risk" LDTs

LDTs Subject to Full Enforcement Discretion

The FDA indicated in the final rule that four categories of tests will be subject to full enforcement discretion, meaning that they will not be subject to any of the FDA's regulatory controls (at least for so long as the FDA deems it appropriate to continue its full enforcement discretion). These four tests are:

1. 1976-type LDTs, which are assays that use manual techniques performed by laboratory technicians with specialized expertise and only use components that are legally marketed for clinical purposes. These tests must also otherwise meet the FDA's LDT definition.

2. Human leukocyte antigen tests that meet the FDA's LDT definition.

3. Tests intended solely for forensic purposes in law enforcement.

4. LDTs manufactured and performed in laboratories within the Veterans Health Administration or the Department of Defense.

Rare Blood Cell Antigen Testing

The FDA also intends to exercise partial enforcement discretion with respect to rare blood cell antigen testing performed by blood establishments such as transfusion centers and immunohematology laboratories, and when there is no available FDA-authorized test to meet the patient's needs. These LDTs will be exempt from premarket approval requirements (fourth and fifth boxes in the table) and most of the quality systems requirements.

Enforcement Discretion

For most laboratories, the three categories of enforcement discretion that are likely to be applicable are the following: (1) LDTs marketed prior to May 6, 2024, (2) LDTs offered by integrated health care systems to meet unmet needs, and (3) LDTs that have NYS CLEP approval. Importantly, the FDA states multiple times in the commentary to the final rule that each of these categories of enforcement discretion may be modified at any time at the FDA's discretion. This means that these categories are not grandfathered exceptions, but rather are more transitory safe harbors upon which laboratories cannot place absolute reliance. Furthermore, as discussed in more detail below, each of these categories of enforcement discretion has significant limitations with respect to their applicability, particularly for any new LDTs.

Currently Marketed LDTs

Perhaps the most important new category of partial enforcement discretion announced by the FDA is for tests that are currently marketed as LDTs. The FDA announced that it intends to exercise enforcement discretion and not enforce the premarket review (the fourth and fifth boxes in the table above) and most of the quality system requirements (except for records requirements) (the third box in the table) for tests that were first marketed prior to the issuance of the rule (May

6, 2024), and currently are marketed as LDTs. These tests remain subject to all other FDA requirements under the phase-out policy (the first and second boxes in the table). As explained in more detail below, these remaining requirements under the phase-out policy are still significant for many laboratories, and could present a significant burden.

It is critical to note that these LDTs will only remain eligible for enforcement discretion from premarket review and most of the quality systems requirements as long as they are not modified, individually or in the aggregate, to (a) change the indications for use, (b) alter the operating principle of the test, (c) include significantly different technology in the test, or (d) adversely change the performance or safety specifications of the test. If a currently marketed LDT is modified in such a way, it would then be subject to full FDA controls, including the premarket review and all quality systems requirements.

There is also a question as to who will have the responsibility to determine that changes to an existing LDT do not constitute such a substantial modification as to exclude the test from enforcement discretion. Presumably the laboratory director would be responsible for this determination. Does this mean that the FDA could impose penalties upon the laboratory director if the FDA disagrees with the director's professional judgment? At a time when the country is facing an extreme shortage of pathologists and laboratory professionals, imposing uncertainty with the threat of penalty only exacerbates the staffing crisis.

The FDA's position also means that currently marketed LDTs will be substantially frozen in time. Routine modifications to LDTs to improve the performance of the LDTs, react to reagent shortages, adjust to changes in laboratory equipment and other systems, etc. may kick the LDTs out of this category of enforcement discretion. The new incentive for laboratories will be to maintain the status quo, rather than make improvements for the benefit of patient diagnosis and treatment – this is exactly the opposite of the FDA's purported intent for the final rule. Accordingly, before there are any modifications to existing LDTs, laboratories must consider the ramifications of the changes and whether they would preclude the LDT from further enforcement discretion as an existing LDT that was marketed prior to May 6, 2024.

Certain Health System LDTs

A second category for which the FDA has indicated its intent to exercise partial enforcement discretion covers LDTs manufactured and performed by a laboratory that is integrated within a health system and that are designed to address an unmet medical need of a patient receiving care within such system. The FDA will continue to exercise enforcement discretion with respect to the premarket review requirements (the fourth and fifth boxes in the table) as well as the medical records standards of the quality systems requirements (the third box in the table). In addition, the testing must be for an unmet need, which the FDA considers to be a situation where there is no available FDA authorized test that meets the patient's needs. Importantly, the FDA stated that potential improvements and performance or lower cost in comparison to an FDA authorized test that meets the patient's needs would not fall within the exemption.

Furthermore, the FDA indicated that its enforcement discretion is only applicable when the laboratory is owned by the health system (it does not include testing performed by a laboratory that is under different corporate ownership), the patient is a patient of the health system, and the ordering physician must be on staff at the health system. This means that LDTs performed by health system laboratories for "outreach" patients would be subject to the full phase out of the FDA's enforcement discretion, unless the LDTs fall within another enforcement discretion exception.

In the commentary to the Final Rule, the FDA concedes that "laboratories integrated within a healthcare system may be more likely to stop developing many of these LDTs for unmet needs if the proposed phaseout policy were finalized." (Page 37302) The FDA continues with the following insight, many aspects of which are applicable to all LDTs, and not just those performed by laboratories in integrated healthcare systems: "The cost of compliance with premarket review and QS requirements may be deemed too high given the limited market for many of these LDTs … (for example, FDA's primary estimates anticipate the cost per premarket submission to range from approximately $250,000 to $4.5 million … in addition to costs associated with QS requirements, annual reporting requirements (for PMAs) and applicable user fees. … [W]e are concerned that many laboratories would stop manufacturing LDTs for unmet needs altogether if they are expected to comply with premarket review and QS requirements." (Page 37302)

The FDA's proposed exercise of enforcement discretion for LDTs performed by integrated healthcare system laboratories for unmet needs has the practical effect of replacing the medical judgment of experienced physicians with the FDA's administrative determinations of what might or might not fall within an unmet need. Some of these physicians and PhD laboratory directors have expressed concerns about certifying that a proposed LDT would address an unmet need given the risk that the FDA could disagree with their determinations, and the professional and personal risk that they would incur.

It is uncertain what obligation laboratories in integrated healthcare systems will have to constantly monitor the industry to determine whether comparable FDA-approved tests are available, who is responsible for the decision as to whether or not an FDA-approved test is "comparable" to an LDT that is offered to address an unmet need, and whether they need to immediately cease offering in LDT if an FDA-approved test appears in the marketplace (regardless of cost).

New York CLEP Approved Tests

The FDA indicated that it will exercise partial enforcement discretion for LDTs that have been approved under NYS CLEP

Given the FDA's determination of the rigor of the NYS CLEP and the similarities between NYS CLEP and the FDA's premarket review process. LDTs that are approved under the NYS CLEP will be exempt from the premarket review processes of the FDA (the fourth and fifth boxes in the table above), but will still be subject to the phase-out of the FDA's enforcement discretion for the medical device reporting requirements, registration class based listing and labeling, and quality system requirements (the first three boxes in the table above).

In the commentary to the final rule, as well as in public statements since the issuance of the final rule, the FDA has indicated that it considers NYS CLEP approval to be a viable alternative for many laboratories. However, this is not the case for several reasons. Historically, not only does NYS CLEP impose very high standards for approval, the process can be quite lengthy, often 12 months or more. In addition, an out of state laboratory that wishes to pursue NYS CLEP approval likely will need to implement more rigorous (and expensive) criteria than would typically be required for CLIA approval.

It is expected that the NYS Department of Health's existing thorough and lengthy process for approval likely will extend even further with an anticipated influx of applications, particularly from out of state laboratories, as a result of the final rule. It would not be surprising if the NYS Department of Health prioritizes the applications, with the highest priority from laboratories situated in the State of New York, the second priority from out of state laboratories that already have tests with CLEP approval, and the very lowest priority from out of state laboratories that never have sought CLEP approval in the past. It is conceivable that for this last category of laboratory, seeking FDA Class II device clearance might be a faster alternative.

The FDA has warned that its enforcement discretion for NYS CLEP approval is only available for the laboratory location that actually received the approval. If a laboratory has CLEP approval for a test in its Syracuse facility but not for the same test performed in its Cleveland facility, the enforcement discretion for NYS CLEP approval will apply only to the test performed in the Syracuse facility.

The FDA also has advised that the NYS CLEP enforcement discretion will be lost if the labeling of the LDT under the FDA's May 2026 registration and labeling requirements differs from the description of the LDT submitted to the NYS Department of Health. Therefore, laboratories should be very careful to ensure that any LDTs that qualify for NYS CLEP enforcement discretion are identified and the labeling of the LDTs matches the NYS CLEP submissions.

Areas of Concern for Laboratories

Although the final May 6, 2024 rule is not as onerous as the proposed October 3, 2023 rule, most laboratories that perform LDTs will still face significant challenges and burdens in complying with the final rule because the systems and protocols that they have in place for compliance with federal and state laboratory regulations, such as the Clinical Laboratory Improvement Amendments of 1988, are not adequate for compliance with the FDA's controls.

<u>MDR Reporting</u>

All laboratories covered under the partial enforcement discretion will need to comply with the requirements for medical device reporting ("MDR") (first box in the table). This means that laboratories must develop and/or refine policies and protocols to identify, track, and report defects or errors in their LDTs and, as applicable, correct or withdraw the LDTs and submit MDRs to the FDA. One or more responsible parties will need to be designated (and trained) to oversee compliance with these requirements. In many laboratories, the sales representatives are often

the first to hear of complaints from ordering physicians, and therefore will need to be trained to immediately report such complaints to the responsible parties.

More specifically, laboratories will need to establish protocols for receiving, reviewing and evaluating complaints by a designated unit. A compliant is any written, electronic or oral communication that alleges deficiencies with the test after it is performed and the test results are released. The protocols must document complaints, reviewing complaints to determine if an MDR reportable event has occurred, investigate device failures and MDR reportable events, and maintain records of all complaints and investigations.

An MDR reportable event is one that reasonably suggests that a test (a) may have "caused or contributed" to a death or "serious injury" or (b) has "malfunctioned" and the test, or a similar test performed by the laboratory, would be likely to "cause or contribute" to a death or "serious injury" if the "malfunction" were to recur. "Serious injury" includes an injury or illness that is life-threatening, permanent, or that necessitates medical or surgical intervention to preclude permanent impairment or damage. This includes event occurring as a result of test failure, malfunction, improper or inadequate design, manufacture, labeling or user error. No death or injury need occur, but an MDR reportable event includes one where the test failed to meet its performance specifications or otherwise perform as intended, and if the same failure/malfunction were to recur with the same or a similar test, there is a likely (not remote) chance that a death or serious injury could occur.

Standard MDRs must be reported to the FDA within 30 calendar days of the time that the laboratory becomes aware of the event, which includes when any employee becomes aware of the event. Becoming aware of the event means when an employee has acquired information that reasonably suggest that a reportable event has occurred. MDR reportable events that require remedial action to prevent an unreasonable risk of substantial harm, or events for which the FDA requests that an MDR be submitted, must be reported within 5 working days. Supplemental reports are due within 30 days.

Registration and Labeling

As part of the registration requirements (second box in the table), laboratories will need to submit the following information: (a) name and address if the laboratory, (b) name, address, phone number, fax number and email address of the owner or operator of the laboratory, (c) name, address, phone number, fax number, and email address of the official correspondent, (d) all trade names of the laboratory, (e) the registration number of the laboratory, (f) the brand name of the test, (g) the PMA number, 510(k) number or product code, and (h) each activity or process (manufacturing, development, etc.) that is conducted at the location. If the LDT is subject to enforcement discretion, the category of enforcement discretion will need to be indicated. The FDA intends to publish additional guidance for LDTs that are subject to enforcement discretion.

As part of the labeling requirements, laboratories will need to determine the class into which their LDTs fall, and prepare the labeling to reflect the characteristics and performance data related to their LDTs. The labeling will be available to the public on the FDA's website. In the commentary

to the final rule, the FDA alluded to the review of this publicly available labeling data by laboratory competitors as a way to ensure compliance with the labeling standards.

The labeling requirements will require strict adherence to FDA guidelines by all sales and marketing functions in the laboratory. Sales representatives will need to be trained to stay "on script" with the laboratory's labeling in all conversations with ordering clinicians regarding the ordering and use of the LDT. Going "off script" could be viewed as promoting off label use of the LDT. Similarly, all of the laboratory's marketing materials, whether digital or hard copy, must align completely with the laboratory's labeling of the LDT. Protocols must be developed and monitored to ensure that the sales and marketing personnel comply with these requirements and the laboratory must maintain documentation of the same.

Quality Systems

Depending upon which quality systems requirements are applicable (the third box in the table), a laboratory may discover that its existing laboratory information system or document control system is inadequate to meet the quality systems requirements. Laboratories will need to make this determination and, if necessary, budget for, acquire, and install adequate systems to meet the FDA requirements.

Steps to Take Now

As noted above, the enforcement discretion for currently marketed LDTs will be lost if the LDT is modified in a manner that individually or in the aggregate, (a) changes the indications for use, (b) alters the operating principle of the test, (c) includes significantly different technology in the test, or (d) adversely changes the performance or safety specifications of the test. Laboratories frequently "tweak" their LDTs to improve performance, address vendor modifications to reagents, deal with vendor shortages, etc. Prior to making such modifications in the future, laboratories will need to determine if the modifications are such that the LDT would no longer be eligible for enforcement discretion.

Laboratories should assemble an internal team (with outside consultant assistance if needed) and map out a timeline for compliance with the FDA's four year phase-out process. After this team is assembled, the laboratory should assess whether any of the categories of enforcement discretion are applicable to its LDTs. If so, the next step will be to determine the FDA standards to which each LDT will be subject, along with the deadlines for compliance with the applicable standards.

Following these determinations, it is advisable for the laboratory's team to estimate the costs of compliance with the FDA standards for each LDT, including not only actual dollars invested, but also personnel time and effort. Most laboratories do not have extra personnel sitting around with time on their hands, so personnel who already are busy with other tasks may need to be partially or fully redirected to the FDA project, or new personnel hired to work on the project.

Once the laboratory has estimated the costs of compliance for each LDT, the laboratory should consider a "make vs. buy" analysis. In other words, does it make financial business sense for the

laboratory to continue to perform the LDT at issue? Or can a similar test be performed with an existing FDA approved test kit, or purchased from a reference laboratory?

Finally, the FDA will be issuing additional guidance in the coming months and years with respect to compliance with the final rule. In addition, given that much of final rule rests upon "enforcement discretion", the FDA can modify this enforcement discretion at any time. Therefore, the laboratory's internal team should regularly monitor the FDA's website and other applicable publications and resources for important developments.