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Client Alert

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LDT Final Rule: Shifting the LDT Battlefield

On April 29, 2024, the Food and Drug Administration ("FDA" or "the Agency") released a pre-publication version of the highly anticipated laboratory developed test final rule ("LDT Final Rule"). The LDT Final Rule is scheduled to be published in the Federal Register on May 6, 2024 and will take effect 60 days after publication.

The proposed rule was published on September 29, 2023, and was open for public comment through December 2, 2023 (see our Client Alert on the proposed rule).

SUMMARY OF THE FINAL RULE

The pre-publication version of the LDT Final Rule is a hefty 528-page document, despite the LDT Final Rule consisting of only one change to the codified regulation. Specifically, the LDT Final Rule revises the definition of "in vitro diagnostic products" at 21 C.F.R. § 809.3(a) to mean "devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act . . . including when the manufacturer of these products is a laboratory" (new language underlined).

This language, added to 21 C.F.R. § 809.3(a), was implemented exactly as initially proposed in the laboratory developed test ("LDT") proposed rule. According to FDA, adding these few words to the definition of "in vitro diagnostic products" has the effect of clarifying that all LDTs meet the definition of "device" in Section 201(h) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), and therefore, are subject to FDA's regulatory authority.

FDA received over 6,500 comments from stakeholders on the proposed rule.[1] Not surprisingly, the bulk of the preamble to the LDT Final Rule is dedicated to responding to the issues raised in these comments and attempting to justify this highly controversial assertion of sweeping regulatory authority.

When Congress enacted the Medical Device Amendments to the FDCA in 1976, it did not explicitly exclude laboratories from the legislation. The LDT Final Rule is premised on FDA's apparent view that Congress, therefore, did not intend to preclude FDA from subjecting professional laboratory developed testing services to the same regulatory requirements as manufactured medical devices. According to FDA, before the LDT Final Rule, the testing services that laboratories provided were fully subject to FDA regulation as in vitro diagnostic ("IVD") tests, except that the Agency had maintained a policy opting not to apply the FDCA and associated device regulations against laboratories as a matter of "enforcement discretion." That policy was formally outlined in a 2014 draft guidance titled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" ("2014 Draft Guidance").

The 2014 Draft Guidance defined an LDT as "an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory." Although the LDT Final Rule applies to LDTs within this traditional definition, the final rule is intended to apply to all tests developed by laboratories, "even if those IVDs do not fall within FDA's traditional understanding of an LDT because they are not designed, manufactured, and used within a single laboratory." In other words, the LDT Final Rule applies to tests that meet FDA's definition, as well as to tests that are offered as LDTs, even if they do not meet FDA's definition.

ENFORCEMENT DISCRETION PHASE-OUT

As outlined in our prior Client Alert, the proposed rule included a proposed "phase-out" policy, in which the Agency would gradually apply the statutory and regulatory device premarket and postmarket requirements to LDTs over a period of four years, thereby phasing out its enforcement discretion policy (and phasing in its new exercise of regulatory authority).

As with the proposed rule, the "phase-out" is scheduled to occur in five stages. Although the final policy is largely the same as the proposed policy, as described below, FDA has made some adjustments in response to comments on the proposed rule:

- **Stage 1:** Beginning 1 year after LDT Final Rule publication, FDA will expect compliance with Medical Device Reporting ("MDR") requirements under 21 C.F.R. Part 803, correction and removal reporting requirements under 21 C.F.R. Part 806, and complaint handling requirements under 21 C.F.R. § 820.198.
    - *Change compared to the proposed rule:* FDA added to this stage complaint handling requirements under 21 C.F.R. § 820.198. Under the proposed rule, complaint handling was included with general Quality System Regulation ("QSR") compliance in Stage 3. Because complaint handling is necessary for adequate MDR compliance, FDA moved complaint handling to Stage 1.
- **Stage 2:** Beginning 2 years after LDT Final Rule publication, FDA will expect compliance with requirements not covered during other stages of the phase-out policy, including registration and listing requirements under 21 C.F.R. Parts 607 and 807, labeling requirements under 21 C.F.R. Parts 801 and 809, and investigational use requirements under 21 C.F.R. Part 812.
    - *Change compared to the proposed rule:* In the final version of the policy, FDA provided registration and listing and labeling as examples of the requirements included in this stage. FDA also included investigational use requirements under this stage, stating that this addition was "in recognition that there has been some confusion about [FDA's] enforcement approach in this area" and "laboratories often are not complying with investigational use requirements currently."
- **Stage 3:** Beginning 3 years after LDT Final Rule publication, FDA will expect compliance with 21 C.F.R. Part 820, except that complaint handling requirements under 21 C.F.R. § 820.198 will be required in Stage 1. At the time

Stage 3 is effective, the QSR will instead be the revised "Quality Management System Regulation," or "QMSR," which has an effective date of February 2, 2026.

  - *Change compared to the proposed rule:* As described above, complaint handling was moved from this stage to Stage 1. The preamble to the LDT Final Rule also notes that FDA expects "laboratories to retain manufacturing records they may already have or may create for certain IVDs prior to stage 3 of the enforcement policy," and in particular, records "that are relevant to validation and the other topics covered" under the recordkeeping requirements in 21 C.F.R. Part 820, Subpart M (Records).

- **Stage 4:** Beginning 3.5 years after LDT Final Rule publication, FDA will expect compliance with premarket review requirements for high-risk IVDs offered as LDTs (i.e., Class III devices). If a premarket submission is received by FDA by the beginning of this stage, FDA intends to continue to exercise enforcement discretion for the test subject to the submission during the pendency of its review.
  - *No change compared to the proposed rule.*
- **Stage 5:** Beginning 4 years after LDT Final Rule publication, FDA will expect compliance with premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs that require premarket submissions (i.e., non-510(k)-exempt Class I and II devices). If a premarket submission is received by FDA by the beginning of this stage, FDA intends to continue to exercise enforcement discretion for the test subject to the submission during the pendency of its review.
  - *No change compared to the proposed rule.*

CARVE-OUTS FROM DEVICE REGULATION

FDA has added some significant carve-outs in its enforcement discretion phase-out policy in the preamble to the LDT Final Rule, compared to the policy in the preamble to the proposed rule. For these carve-outs, FDA asserts that it intends to continue to exercise enforcement discretion, and not to enforce some or all applicable statutory requirements. But, significantly, the preamble also suggests that FDA could change these carve-outs at any time, as a matter of agency discretion. This illustrates the substantial regulatory uncertainty created by FDA's policy change bringing all LDTs within its regulatory oversight.

A common critique of the LDT proposed rule was that FDA does not have the resources necessary to perform premarket reviews and exercise postmarket oversight of all LDTs. The Final LDT Rule effectively concedes the point, implicitly acknowledging that FDA currently lacks the resources and personnel necessary to review premarket submissions for all LDTs. One purpose of these carve-outs is likely to soften the immediate budgetary impact of the final rule, reduce the immediate harm to patients that would result if LDTs were no longer available, and reduce the administrative burdens on the Agency itself. FDA also indicates its intent to enhance the Third Party 510(k) review program to enable greater review (approximately 50 percent) of low- and moderate-risk tests offered as LDTs by third party review organizations, as well as to use the next reauthorization of the Medical Device User Fee Amendments ("MDUFA"), which will align with the phase out of enforcement discretion for premarket review, to negotiate with industry the user fees and Agency performance goals as applicable to IVD and LDT premarket submissions.

Most significantly, FDA intends to exercise enforcement discretion, and not enforce premarket review and QSR compliance (except for recordkeeping requirements under 21 C.F.R. Part 820, Subpart M), for currently marketed LDTs that were first marketed prior to issuance of the LDT Final Rule. This carve-out effectively exempts all tests currently on the market from the most onerous and costly requirements that apply to medical devices. That said, these LDTs will still

be required to comply with MDR requirements, reports of corrections and removals, registration and listing requirements, and labeling requirements.

The Agency's enforcement discretion policy will apply unless or until certain significant modifications are made to any existing LDT. Specifically, if the modification changes the indications for use, alters the operating principle, includes significantly different technology, or adversely changes the performance or safety specifications, then FDA has indicated that it will require premarket review and QSR compliance for the modified test.

It appears the rationale for this approach is that currently marketed testing services will eventually come under FDA's purview as they evolve in the future. However, carving out all currently marketed tests from the final rule arguably undercuts FDA's only public health rationale for the final rule—namely, that FDA oversight of LDTs is necessary to ensure their safety and effectiveness.

As part of its policy, FDA plans to request submission of labeling information and to use this information to "identify and address" currently marketed LDTs "that specifically raise concerns." In conducting this labeling review, FDA intends to focus its review on performance summaries and superiority claims. According to FDA, it intends to "take action" where the labeling of an LDT is false or misleading or lacks appropriate assurance of safety or effectiveness.

The following new categories of tests will also be carved out from both premarket review and compliance with the QSR, except for records requirements under 21 C.F.R. Part 820, Subpart M:

- Tests 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. This carve-out was seemingly included in response to over 100 comments received by FDA raising concerns that the burden of premarket review and QSR compliance would lead to laboratories, including academic medical centers, ceasing to offer tests for individual patients or patient populations with unmet needs (e.g., tests for rare diseases). It is unclear how FDA intends to apply these requirements. The Final LDT Rule suggests that a test is intended for an "unmet need where there is no available FDA-authorized IVD that meets the patient's needs," and provides some examples, but the rule does not fully explain this category, stating instead that "FDA intends to provide additional guidance on this enforcement discretion policy" at an unspecified time point.
- Non-molecular antisera LDTs for rare red blood cell antigens, when such tests are manufactured and performed by blood establishments, including transfusion services and immunohematology laboratories, and when there is no alternative IVD available to meet the patient's need for a compatible blood transfusion.

FDA also stated that it will not enforce premarket review requirements for LDTs that have been approved by New York State's ("NYS") Clinical Laboratory Evaluation Program ("CLEP"). Under the NYS CLEP program, moderate-risk and high-risk tests offered in NYS are evaluated by CLEP for both analytical and clinical validity. FDA believes that the CLEP approval process adequately mitigates the risk of inaccurate and unreliable tests that it can substitute for FDA's premarket review requirements. Tests reviewed by CLEP that are not otherwise carved out from FDA regulation would still be subject to postmarket requirements, including QSR compliance.

In addition, similar to the proposed LDT rule, FDA has pledged to continue its current general enforcement discretion policy, and will not enforce both premarket and postmarket requirements, for the following categories of LDTs:

- "1976-Type LDTs," which are tests that share characteristics with the tests offered in 1976 (at the time of enactment of the Medical Device Amendments of 1976): (1) use of manual techniques, without automation, performed by laboratory personnel with specialized expertise; (2) use of components legally marketed for clinical use; and (3)

design, manufacture, and use within a single laboratory certified in accordance with the Clinical Laboratory Improvement Amendments ("CLIA") for high-complexity testing.

- Human leukocyte antigen tests for organ, stem cell, and tissue transplantation that are designed, manufactured, and used within a single CLIA-certified laboratory that meets requirements to perform high-complexity histocompatibility testing.
- Tests intended solely for forensic (i.e., law enforcement) purposes.
- Tests manufactured and performed within the Department of Defense or Veterans Health Administration.

NEXT MOVES

Significantly, FDA makes the same legal argument as it made in the proposed rule—namely, that LDTs fall within the statutory "device" definition. This legal argument remains vulnerable to challenge. The notion that Congress intended to subject the entire industry of professional laboratory developed testing services to FDA medical device jurisdiction in 1976, but that this was not known publicly until FDA announced its enforcement discretion policy more than 20 years later, is open to challenge. The laboratory community has long asserted that the statutory definition of a manufactured "device" does not apply to professional "services," such as the clinical testing services conducted by laboratories.

FDA's release of the LDT Final Rule does not change the nature of the battle over whether Congress granted FDA jurisdiction to regulate laboratory services as if they are equivalent to manufactured medical devices; it just shifts the battlefield from FDA to the courts. Given the controversial and far-reaching nature of the LDT Final Rule, we expect multiple legal challenges.

Regardless of how the courts evaluate the legality of FDA's final rule, it is likely that these issues will ultimately shift back to Congress. Congress previously attempted to regulate LDTs through the proposed legislation, the Verifying Accurate, Leading-edge IVCT Development ("VALID") Act, which failed to pass in the December 2022 omnibus spending bill. The many concessions made by FDA in the LDT Final Rule—in particular, the significant carve-outs that were required as a practical matter for FDA to be able to assert regulatory authority over laboratories—are likely to be table stakes (i.e., a starting point) for new legislation.

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[1] It seems that the Agency was able to quickly complete its review of such an exceptionally large number of comments because many of the comments were duplicative, containing the same position statements in favor or against the LDT proposed rule.