ASM LDT Town Hall

June 3, 2024

AMERICAN SOCIETY FOR MICROBIOLOGY

Agenda

Topic	Presenter	Time
Introductions	**Linoj Samuel, PhD. D(ABMM)** Division Head, Clinical Microbiology, Pathology and Laboratory Medicine Henry Ford Health Chair, ASM Clinical and Public Health Microbiology Committee	5 Minutes
Policymaking and Legal developments	**Allen Segal, Esq.** Chief Strategy and Public Affairs Officer, ASM	5 Minutes
What does the FDA's Final LDT Rule Mean for You?	**Danielle H. Tangorre, Esq.** Partner, Robinson & Cole LLP	40 Minutes
Q&A	**Erin H. Graf, Ph.D., D(ABMM)** Associate Professor of Laboratory Medicine and Pathology | Co-Director, Microbiology Laboratory Mayo Clinic Arizona Vice Chair, ASM Clinical and Public Health Microbiology Committee	10 Minutes

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Thanks to those who helped craft ASM's Response

Volunteers	ASM Staff
Erin Graf	Nancy Wamburu, CPHM
Esther Babady	Paige Larkin, CPHM
Jim Dunn	Amalia Corby, Public Policy and Advocacy
Laura Filkins	Allen Segal, Public Policy and Advocacy
Melissa Miller	
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Policymaking and Legal Developments

Allen D. Segal
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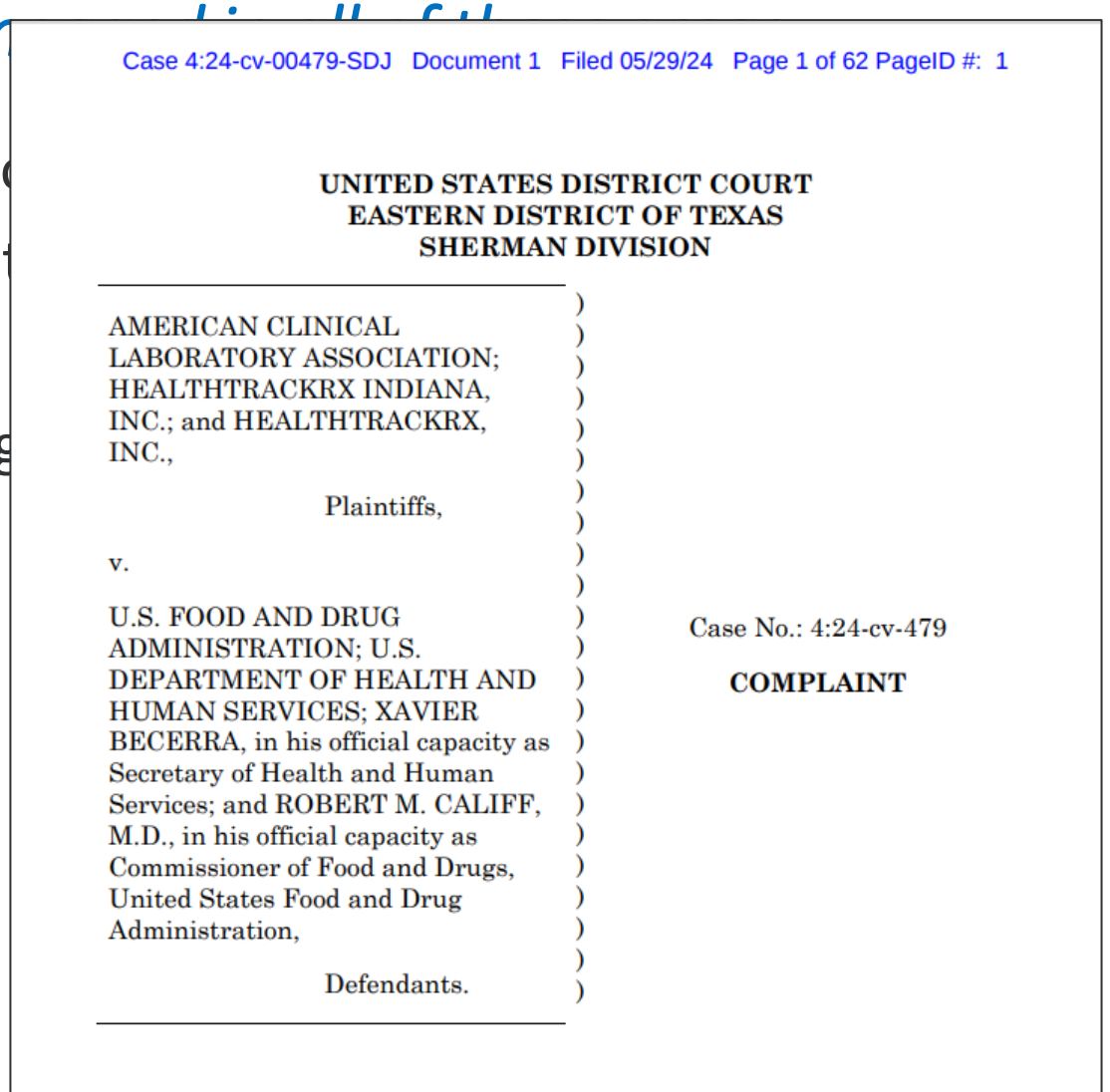
What are the possible outcomes?

ASM is actively en

- The rule goes int
- A lawsuit is filed
- A legislative fix
- FDA makes chang



Case 4:24-cv-00479-SDJ Document 1 Filed 05/29/24 Page 1 of 62 PageID #: 1

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
SHERMAN DIVISION

AMERICAN CLINICAL LABORATORY ASSOCIATION; HEALTHTRACKRX INDIANA, INC.; and HEALTHTRACKRX, INC.,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services; and ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, United States Food and Drug Administration,

Defendants.

Case No.: 4:24-cv-479

COMPLAINT

AMERICAN SOCIETY FOR MICROBIOLOGY

Robinson+Cole

What does the FDA's Final LDT Rule Mean for You?

Danielle H. Tangorre, Esq.

June 3, 2024

Of Note

We note that in this presentation we are only providing general information; the information contained in this presentation does not constitute legal advice. No attorney-client relationship has been created. If legal advice or other assistance is required, please contact us directly.

Amended Regulation

In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act, **including when the manufacturer of these products is a laboratory.**

Putting it into Context

- FDA asserts that it has exercised enforcement discretion and chosen not to enforce applicable legal requirements
  - Proceeded because "LDTs were mostly manufactured in small volumes by laboratories that served their local communities….rare diseases or for other uses to meet the needs of a local patient population"
  - Employed manual techniques and performed by personnel with specialized expertise
- LDT landscape has evolved
  - "Often used in laboratories outside of the patient's healthcare setting"
  - "Often run in high volume for large and diverse populations"
  - "more commonly manufactured with instruments or other components not legally marketed for clinical use"
  - "risks associated with most LDTs today are therefore much greater"
  - "the potential for cybersecurity vulnerabilities is growing"

Putting it into Context

"FDA's memorandum to file describing submissions for IVDs offered as LDTs detailed the many defects FDA has seen with laboratory validation, among other things, and described the submissions as raising "significant concerns" in some cases (Ref. 16). During the COVID–19 emergency, FDA's conversations with laboratory manufacturers revealed that many were unfamiliar with what constitutes appropriate analytical and clinical validation for an IVD generally (see comment response 37 and Ref. 18). FDA's experience is corroborated by new information in the record from New York State. New York State submitted data indicating that more than half of original applications from laboratories could not be approved by the New York State Department of Health Clinical Laboratory Evaluation Program (NYS CLEP) based on deficiencies such as 'design flaws, inadequate validation data, and process problems that call into question the reliability of the results'".
37292-3

Putting Into Context

"Some comments expressed concern regarding the use of IVDs offered as LDTs that are not clinically validated, and regarding scientifically dubious claims made about such IVDs, especially in areas like cancer prognosis and genetic screening."

"today LDTs are commonly used to diagnose infectious diseases, screen for various diseases and conditions, and identify the best treatment for patients with cancer, among other uses. The consequences of false results in these contexts can include spread of disease, missed diagnoses, misdiagnoses, use of ineffective treatments with toxic side effects, and lack of use of life-saving treatments"

"FDA is aware of IVDs offered as LDTs, particularly genetic IVDs offered as LDTs, that are offered for uses that lack sufficient scientific support. The availability of new technologies and increasing reliance on them for clinical decision-making has increased the risk of IVDs offered as LDTs. "

Putting it into Context

*FDA also 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 this way, FDA can work to assure the safety and effectiveness of currently marketed IVDs offered as LDTs without creating the risk of widespread market exit (*37305)*

Timeline for Implementation

Stage 1

May 6, 2025

- Corrections and Removals
- Medical Device Reporting
- Complaint Handling

Stage 2

May 6, 2026

- Registration and Listing
- Compliance with labeling
- Investigational Use Requirements

Stage 3

May 6, 2027

- QS Requirements
- Design Controls
- Purchasing Controls
- Acceptance Activities
- Corrective Action/Preventative Action
- Records

Stage 4

November 6, 2027

- High-Risk (Class III) LDTs require PMA applications, HDE or BLA

Stage 5

May 6, 2028

- Submit All Non-Exempt Tests for PMA or de novo submission

Phase 1

Corrections and Removals (21 CFR Part 806)

- Modify or remove a defective tests, must report to FDA
- Guidance: https://www.fda.gov/medical-devices/postmarket-requirements-devices/recalls-corrections-and-removals-devices

Medical Device Reporting (21 CFR Part 803)

- Identify, investigate, address and report adverse events
- Documentation is key


GUIDANCE DOCUMENT

Medical Device Reporting for Manufacturers

Guidance for Industry and Food and Drug Administration Staff

NOVEMBER 2016

Download the Final Guidance Document

Final

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Complaint Handling (21 CFR 820.198)

Guidance: https://www.fda.gov/media/109411/download

Phase 2

Registration and Listing (21 CFR Part 807)

- Register your facility
- List information on your LDTS in a public database
- Guidance: https://www.fda.gov/medical-devices/device-registration-and-listing/how-register-and-list

Labeling (21 CFR Parts 801, 809.10, 830)

- Performance Information & Summary of Supporting Validation
- Guidance:
  - https://www.fda.gov/medical-devices/overview-device-regulation/device-labeling
  - https://www.fda.gov/medical-devices/device-labeling/in-vitro-diagnostic-device-labeling-requirements

Investigational Use (21 CFR Part 812)

- LDTS not approved by FDA used in the context of a clinical trial

Phase 3

Compliance with QS Requirements

- https://www.fda.gov/medical-devices/postmarket-requirements-devices/quality-system-qs-regulationmedical-device-current-good-manufacturing-practices-cgmp

CLIA will account for some but not all QS. Still must comply with:

- Design Controls (21 CFR Part 820.30)
  - intended to ensure that the IVD has appropriate assurance of safety and effectiveness for its intended use.
  - Guidance: https://www.fda.gov/media/116573/download
- Purchasing Controls (21 CFR 820.50)
  - Selection of quality vendors
- Acceptance Activities (21 CFR Part 820 Subpart H)
- Corrective Action/Preventative Action (21 CFR Part 820.100)
- Records (21 CFR Part 820 Subpart M)

Enforcement Discretion

- FDA states that all LDTs are not permissible if they do not comply with its requirements
- FDA is choosing not to prosecute
- FDA can change its mind – fluid situation
  - And without prior notice

Enforcement Discretion

Category of IVD	Stage 1	Stage 2	Stage 3	Stage 4/5
1976-Type LDTs	Exempt	Exempt	Exempt	Exempt
HLA LDTs for Transplantation	Exempt	Exempt	Exempt	Exempt
Forensic Use LDTS	Exempt	Exempt	Exempt	Exempt
LDTs Approved by NYS CLEP	Required	Required – submit labeling	Required – exception design controls	Exempt
LDTS for Unmet Needs in integrated health system	Required	Required – submit labeling	Required – exception design controls	Exempt
Currently Marketed LDTs and not modified	Required	Required	Exempt – except design controls	Exempt
Direct to Consumer				
Non-molecular antisera LDTS for rare blood	Required	Required	Exempt – except design controls	Exempt
Modified version of another manufacturer's 510(k) cleared or De Novo authorized test within the scope described in the preamble	Required	Required	Required	Exempt

Enforcement Discretion

Currently marketed IVDs prior to the Rule unless there is

- change the indications for use of the IVD;
- alter the operating principle of the IVD (for example, changes in critical reaction components);
- include significantly different technology in the IVD (e.g., addition of artificial intelligence or 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 change the performance or safety specifications of the IVD.

1976-Type Tests – What is It?

- 1976-type characteristics
  - 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.
- Examples of 1976-type tests include: “various tests that use staining antibodies and general-purpose reagents for cytology, hematology, and bacterial infections; cystic fibrosis sweat tests; certain colorimetric newborn screening tests; certain immunohistochemistry tests; karyotyping tests; and fluorescence in situ hybridization (FISH) tests” (p.37408)

Unmet Need – What is it?

- Current Guidance
  - No available FDA-authorized IVD (rare disease or condition)
  - FDA authorized IVD but not indicated for use on a particular patient
  - FDA authorized IVD but unique attribute needs to be added
  - FDA-authorized IVD but not available to the patient
  - No FDA-authorized IVD

- FDA indicates that additional guidance to be forthcoming in accordance with good guidance practices

Modification

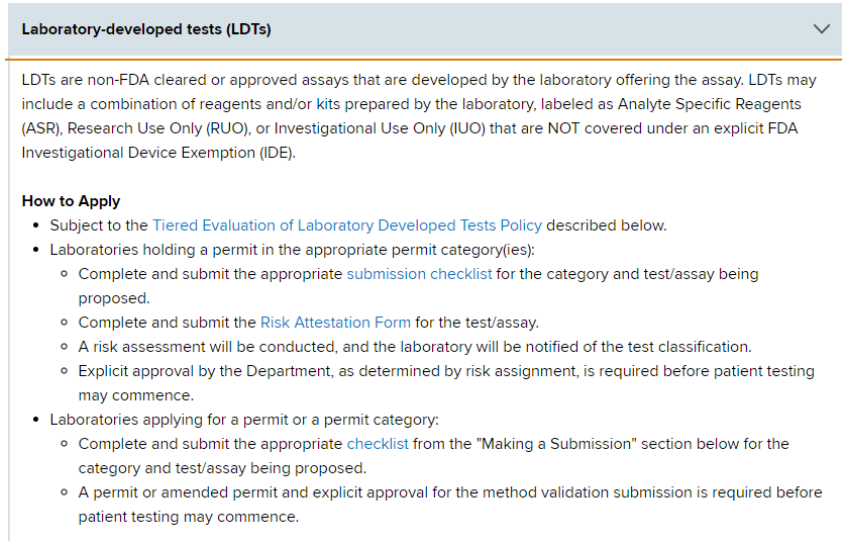
- Applies to currently marketed LDTs and FDA authorized test kits
- Enforcement discretion ends if there are modifications including:
  - Change in intended use
  - Alter the operating principle
  - Include significantly different technology
  - Include significantly different methodology
  - Adversely change the performance or safety specifications
- "FDA also intends to develop appropriately targeted enforcement discretion policies for certain common changes, such as extension of specimen stability and certain alternative specimen types, following good guidance practices"

NYS CLEP Approved Tests

‘LDTs approved by NYS CLEP’’ refer to LDTs that are approved, conditionally approved, or within an approved exemption from full technical documentation, under NYS CLEP.

“NYS CLEP evaluates analytical and clinical validity for high risk and moderate risk LDTs”

Policy: https://www.wadsworth.org/sites/default/files/WebDoc/Tiered-LDT_Review_Policy_Nov%202023.pdf



Laboratory-developed tests (LDTs)

LDTs are non-FDA cleared or approved assays that are developed by the laboratory offering the assay. LDTs may include a combination of reagents and/or kits prepared by the laboratory, labeled as Analyte Specific Reagents (ASR), Research Use Only (RUO), or Investigational Use Only (IUO) that are NOT covered under an explicit FDA Investigational Device Exemption (IDE).

How to Apply

- Subject to the Tiered Evaluation of Laboratory Developed Tests Policy described below.
- Laboratories holding a permit in the appropriate permit category(ies):
  - Complete and submit the appropriate submission checklist for the category and test/assay being proposed.
  - Complete and submit the Risk Attestation Form for the test/assay.
  - A risk assessment will be conducted, and the laboratory will be notified of the test classification.
  - Explicit approval by the Department, as determined by risk assignment, is required before patient testing may commence.
- Laboratories applying for a permit or a permit category:
  - Complete and submit the appropriate checklist from the "Making a Submission" section below for the category and test/assay being proposed.
  - A permit or amended permit and explicit approval for the method validation submission is required before patient testing may commence.

AST Breakpoints

- FDA recently issued a final guidance entitled "Antimicrobial Susceptibility Test (AST) System Devices—Updating Breakpoints in Device Labeling
  - This discusses when modifications are needed
  - "generally, updating the STIC of an AST system device could significantly affect the safety and effectiveness of the device, and therefore, such modifications, if not included in a PCCP or breakpoint change protocol, would likely require submission of a 510(k) prior to updating device labeling"
- For a modification to the breakpoint to an IVD currently offered as an LDT to be considered clinically validated, FDA expects the updated breakpoint to reflect that identified on the STIC website.
- More guidance should be forthcoming

Questions?

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Nancy Wamburu

Thank You!

Questions? Contact Us.

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