Expectations for the LDT Final Rule: Focus on Software Interaction

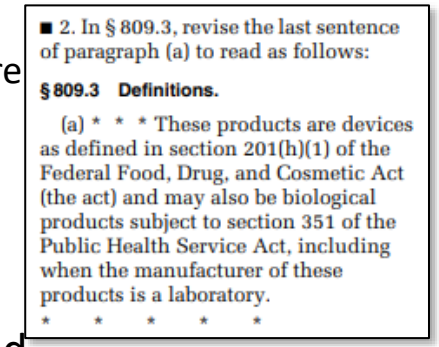
Lisa M. Dwyer, Partner, King & Spalding LLP
Jeremiah J. Kelly, Partner, Venable LLP
Joshua M. Oyster, Partner, Ropes & Gray LLP
Moderated by **Bethany Hills**, Vice Chair, FDA Regulatory Practice, DLA Piper (US)

Laboratory Developed Tests (LDTs) – Overview

- FDA has historically considered LDTs to be a subset of in vitro diagnostics (IVDs) designed, manufactured, and used within a single clinical laboratory.
- Primarily regulated under Clinical Laboratory Improvement Amendments of 1988 (CLIA).
- FDA has historically exercised enforcement discretion for compliance with FDA requirements (e.g., premarket review, QSR, and labeling).
  - Nonetheless, FDA has generally always asserted that it has the authority to regulate such tests.
  - The precise framework for regulating LDTs has been the subject of much controversy, as well as shifting policies and legal interpretations.

September 2023 LDT Proposed Rule

- FDA released a **proposed rule** that would affirm FDA's position that LDTs are IVDs regulated as medical devices under the FDCA.
  - "FDA is proposing to amend FDA's regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer is a laboratory."
- In conjunction with the proposed rule, FDA plans to phase out the enforcement discretion policy it has historically applied to most LDTs.
- Certain categories would not be subject to the phaseout and would continue to be subject to enforcement discretion (1976-Type LDTs, Human Leukocyte Antigen tests, tests solely for forensic (law enforcement) purposes, and tests exclusively for public health surveillance that meet certain criteria).



■ 2. In § 809.3, revise the last sentence of paragraph (a) to read as follows:

§ 809.3 Definitions.

(a) * * * 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.

* * * * *

Proposed Phaseout of Enforcement Discretion for LDTs

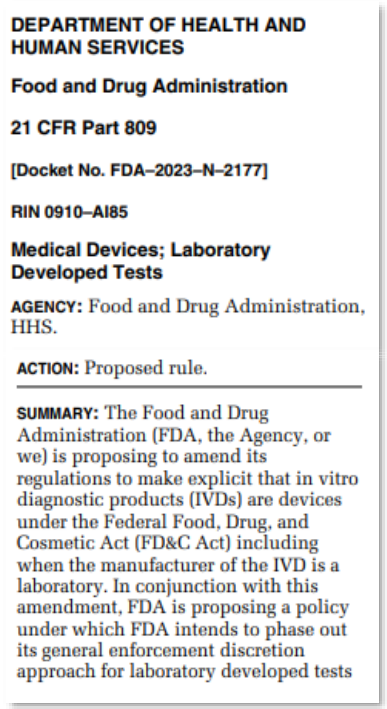
Stage 1	• MDR requirements and correction and removal reporting requirements: **1 year** after FDA publishes a final policy
Stage 2	• Registration and listing, labeling requirements, and investigational use requirements: **2 years** after FDA publishes a final policy
Stage 3	• Quality System Regulation (QSR) requirements: **3 years** after FDA publishes a final policy
Stage 4	• Premarket review requirements for high-risk IVDs (i.e., Class III): **3.5 years** after FDA publishes a final policy, but not before **October 1, 2027**
Stage 5	• Premarket review requirements for moderate- and low-risk IVDs (i.e., Class I or II): **4 years** after FDA publishes a final policy, but not before **April 1, 2028**

September 2023 LDTs Proposed Rule

- FDA is phasing out enforcement discretion because it asserts LDTs are now higher risk – i.e., more complex, performed in higher volume, and performed outside the immediate patient care setting

"[T]he LDT landscape has evolved significantly since 1976. Today, **many LDTs rely on high-tech or complex instrumentation and software** to generate results and clinical interpretations."

"[Today's test] systems generally consist of highly specialized components with complex functionality working in combination... For example, a modern-day next generation sequencing (NGS) test system for genetic testing typically consists of (among other things) a DNA extraction kit to extract nucleic acids from a human sample; an NGS instrument that analyzes the nucleic-acid output and (after days) generates gigabytes of sequencing raw data; and **multiple pieces of computer software that translate that raw data into a test report**."



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 809

[Docket No. FDA–2023–N–2177]

RIN 0910–AI85

Medical Devices; Laboratory Developed Tests

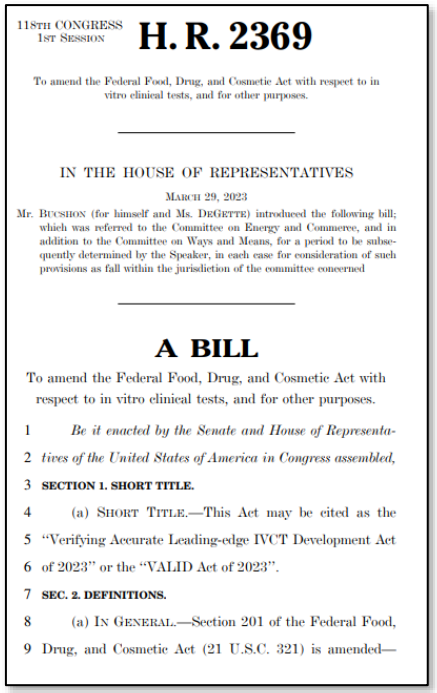
AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act) including when the manufacturer of the IVD is a laboratory. In conjunction with this amendment, FDA is proposing a policy under which FDA intends to phase out its general enforcement discretion approach for laboratory developed tests

Proposed LDT Legislation

- Verifying Accurate Leading-edge IVCT Development (VALID) Act has been introduced in Congress multiple times over the last few years.
- **VALID Act** most recently introduced in March 2023.
  - Seeks to create a framework for new product type "in vitro clinical tests" (IVCTs) that would include any test intended by its developer to be used in the collection, preparation, analysis or in vitro clinical examination of human specimens for diagnosis, screening, monitoring, or informing therapy or treatment.
  - All IVCTs would be required to undergo premarket review unless exempt (e.g., due to being a "low-risk" IVCT or an IVCT subject to a Technology Certification Order) or meet grandfathering criteria.



118TH CONGRESS
1ST SESSION

H. R. 2369

To amend the Federal Food, Drug, and Cosmetic Act with respect to in vitro clinical tests, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

MARCH 29, 2023

Mr. BUCSHON (for himself and Ms. DEGETTE) introduced the following bill; which was referred to the Committee on Energy and Commerce, and in addition to the Committee on Ways and Means, for a period to be subsequently determined by the Speaker, in each case for consideration of such provisions as fall within the jurisdiction of the committee concerned

A BILL

To amend the Federal Food, Drug, and Cosmetic Act with respect to in vitro clinical tests, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

(a) SHORT TITLE.—This Act may be cited as the "Verifying Accurate Leading-edge IVCT Development Act of 2023" or the "VALID Act of 2023".

SEC. 2. DEFINITIONS.

(a) IN GENERAL.—Section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321) is amended—

Current Exception to FDA's LDT Enforcement Discretion Policy: Draft In Vitro Diagnostic Multivariate Index Assay Guidance (2007)

Definition of IVDMIA

Device that:

(1) Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a "classification," "score," "index," etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and

(2) Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.

Example 1: Example of an IVDMIA

independently analyze the input variables to arrive at the same interpretation. In general, an IVDMIA might use measured or observed values of multiple variables, such as a patient's age, weight, metabolite level, and gene expression levels. A unique interpretation function specific to the IVDMIA would then combine and analyze these variables to yield a score. The intended use of the IVDMIA would, for example, be to diagnose disease or predict risk of disease based upon this score. The following are more specific examples of IVDMIAs:

A device that integrates a patient's age, sex, and genotype of multiple genes to predict risk of or diagnose a disease or condition.

FDA's Draft IVDMIA Guidance (2007)

- "Some IVDMIAs are Laboratory Developed Tests (LDTs)….Laboratory developed IVDMIAs are a specific subset of LDTs." (IVD MIA Guidance, at 4).

- "[FDA] has generally exercised enforcement discretion over standard LDTs." However, due to their complexity, intended use and the risks associated with reliance upon IVDMIAs, "there is a need for FDA to regulate these devices to ensure that the IVDMIA is safe and effective for its intended use." (*Id.*).

"…[E]ven when offered as LDTs, IVDMIAs must meet pre- and post-market device requirements under the [FD&C Act], including premarket review requirements for most class II and III devices."

21st Century Cures Act – "Device" Exclusion for Clinical Decision Support ("CDS")

(1) <u>Not</u> intended to acquire, process, or analyze a medical image, a signal from an IVD, or a pattern or signal from a signal acquisition system;

(2) Displays, analyzes, or prints medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);

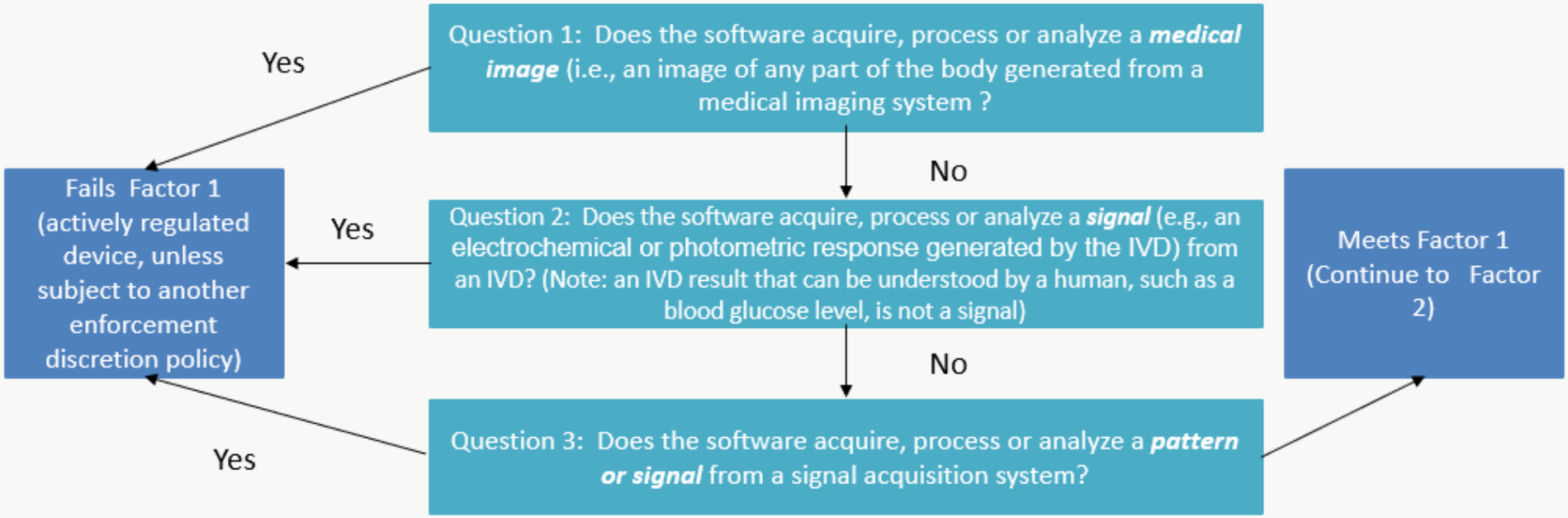
(3) Supports or provides recommendations to an HCP about prevention, diagnosis, or treatment of a disease or condition; and

(4) Enables such HCP to independently review the basis for the recommendations so that it is not the intent that the HCP rely primarily on the recommendations to make a clinical diagnosis or treatment decision

Factor 1: Does Not Acquire, Process, or Analyze a Medical Image, a Signal from an IVD, or a Pattern or Signal from a Signal Acquisition System

Question	Yes/No
Are results from an IVD or multiple IVDs (e.g., HDL level, magnesium level, HDL level, BRCA1 status) inputs that meet Factor 1?	• Yes • Data/results from IVD tests can meet Factor 1 (p. 9) • Example - Software that analyzes family history, prior mammogram results, and BRCA status from the medical record meets Factor 1 (p.18) • Software function that analyzes blood glucose laboratory test results and pre-diabetes diagnosis from a patient's medical record meets factor 1 (p. 18) (Note: to FDA a lab test is an IVD).
Are electrochemical signals generated by an IVD data inputs that meet factor 1?	No (p.7)

Factor 1: Does Not Acquire, Process, or Analyze a Medical Image, a Signal from an IVD, or a Pattern or Signal from a Signal Acquisition System



Discussion Topics

- How different is the VALID Act from the proposed LDT rule?
- Public comments and timing of FDA final rule
- Expectations for the LDT final rule and what's next in Congress and the courts; How serious is FDA?
- Impact of FDA/CMS joint statement Jan 2024
- Labs' outsourcing of bioinformatics processes and FDA regulation of bioinformatics software; How to deal with uncertainty in counseling clients