

## Laboratory-developed Tests: A Legislative and Regulatory Review

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**BACKGROUND:** Twenty-five years ago, the Food and Drug Administration (FDA) asserted in a draft document that “home brew” tests—now commonly referred to as laboratory-developed tests (LDTs)—are subject to the same regulatory oversight as other in vitro diagnostics (IVDs)<sup>4</sup>. In 2010, the FDA began work on developing a proposed framework for future LDT oversight. Released in 2014, the draft guidance sparked an intense debate over potential LDT regulation. While the proposed guidance has not been implemented, many questions regarding LDT oversight remain unresolved.

**CONTENT:** This review provides an overview of federal statutes and regulations related to IVDs and clinical laboratory operations, with a focus on those potentially applicable to LDTs and proposed regulatory efforts. Sources reviewed include the Code of Federal Regulations, the Federal Register, congressional hearings, guidance and policy documents, position statements, published literature, and websites.

**SUMMARY:** Federal statutes regarding IVDs were passed without substantive evidence of congressional consideration toward the concept of LDTs. The FDA has clear oversight authority over IVD reagents introduced into interstate commerce. A 16-year delay in publicly asserting FDA authority over LDTs, the pursuit of a draft guidance approach toward oversight, and establishment of regulations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88) applicable to LDTs contributed to community uncertainty toward

LDT oversight. Future regulatory and/or legislative efforts may be required to resolve this uncertainty.

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Advances in in vitro diagnostics (IVDs)<sup>4</sup> over the past century have transformed the practice of medicine. To help ensure public safety in the context of this innovation, federal laws regarding medical device regulatory authority and clinical laboratory oversight were established and strengthened. While considerable attention was placed on oversight of commercially manufactured IVDs and clinical laboratory operations, less focus was directed toward tests created by and performed within individual laboratories.

“Home brew” tests, now commonly referred to as laboratory-developed tests (LDTs), have long been a component of clinical laboratory operations. LDTs have been defined as “an IVD that is intended for clinical use and designed, manufactured, and used within a single laboratory” (1). While federal regulations under the authority of the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88; “CLIA”) were implemented to ensure the analytical validity of LDTs, the Food and Drug Administration (FDA) asserted in a 1992 draft document that LDTs were subject to the same regulatory oversight as other IVDs (2). While FDA plans for LDT oversight have not been implemented, dialogue between regulatory agencies, Congress, and the clinical laboratory and IVD communities has offered diverse and at times conflicting perspectives on how LDTs should be regulated. The purpose of this report is to provide a legislative and regulatory history of IVDs to provide a foundational basis for future LDT discussions.

### MEDICAL DEVICE REGULATION

Federal regulation of “foods, drugs, medicines, and liquors” was established in the *Pure Food and Drug Act* of 1906 (3). The Act prohibited the misbranding and adulteration of products sold in interstate commerce, with oversight administered by the US Department of Agriculture (USDA) Bureau of Chemistry (4). While it was an important milestone in consumer safety legislation, the Act did not place responsibility on manufacturers to prove safety and legitimacy before or after commercial distribution. The burden was on the government to

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<sup>4</sup> Nonstandard abbreviations: IVDs, in vitro diagnostics; CLIA, Clinical Laboratory Improvement Amendments; CMS, Centers for Medicare and Medicaid Services; CPG, Compliance Policy Guide; FDA, Food and Drug Administration; FFDC, Federal Food Drug and Cosmetic Act; HEW, Department of Health, Education, and Welfare; HHS, Department of Health and Human Services; IVDMA, in vitro diagnostic multivariate index assays; LDT, laboratory-developed test; MDA, Medical Device Amendments; SACGT, Secretary’s Advisory Committee on Genetic Testing.

prove misbranding and adulteration (5). Without adequate resources and with limited authority, the Bureau of Chemistry did not have the capacity to provide sufficient oversight to fully ensure safety. The Bureau of Chemistry was subsequently renamed the Food, Drug, and Insecticide Administration in 1927 before being renamed the Food and Drug Administration (FDA) in 1930 (6).

In 1937, a medicinal sulfanilamide formulation (dissolved in poisonous diethylene glycol) was released into commercial distribution and resulted in >100 fatalities (7). In the wake of public concern, the *Federal Food, Drug, and Cosmetic Act (FFDCA)* of 1938 was passed (8). The FFDCA included language prohibiting misbranding and adulteration of devices, defining “devices” in Sec. 201 (h) as:

“instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals” (8).

The FFDCA, however, did not create a comprehensive regulatory system for medical device safety, efficacy, and evaluation.

The FDA was transferred from the US Department of Agriculture to the Federal Security Agency in 1940 (6). It was subsequently moved in the 1950s into the newly established Department of Health, Education, and Welfare (HEW) (6, 9) and then integrated into the Public Health Service under HEW in the late 1960s (10, 11). HEW was eventually renamed the Department of Health and Human Services (HHS), and the FDA has remained part of HHS and the Public Health Service since that time (6, 12).

In the decades following the passage of the FFDCA, an increase in the number, complexity, and use of medical devices has led to concerns over their safety and effectiveness. Out of concern for public safety and interpretation of congressional intent, in 1969, the Supreme Court ruled that the Secretary of HEW had the authority to regulate a device (an antimicrobial susceptibility disk) as a drug such that the “Secretary can subject it to pre-market clearance regulations” (13).

In a message to the Congress on consumer protection, President Richard Nixon commented on medical device safety, stating that “certain minimum standards should be established for such devices” and that “a thorough study of medical device regulation” would be undertaken (14). The Study Group on Medical Devices released its 1970 legislative plan (known as the “Cooper Committee Report”) outlining recommendations for review and categorization of medical devices and the establishment of performance standards (15). The report did not specifically highlight laboratory diagnostic tests.

In 1972, the FDA released a notice announcing that they would “in the near future propose regulations gov-

erning in vitro diagnostic products,” which include “reagents, instruments, and kits” (16). In a subsequent Notice of Proposed Rulemaking, the FDA asserted jurisdiction over in vitro diagnostic products, stating that they are medical drugs or devices under the FFDCA (17). Procedural regulations regarding in vitro diagnostic product labeling, standards, and general requirements were incorporated in the Code of Federal Regulations (18). Federal regulations describe “in vitro diagnostic products” as devices and define them as:

“reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, 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) of the Federal Food, Drug, and Cosmetic Act” (19).

Several bills were subsequently introduced in Congress proposing the creation of new regulatory structures for medical devices. In September 1973, a Senate subcommittee held hearings regarding proposed medical device legislation (20). The discussion was primarily directed toward conventional physical devices (e.g., intrauterine devices). Custom devices were discussed in the testimony of multiple participants, particularly in the context of allowing the practice in fields where products must be customized (e.g., dental implants), while preventing loopholes that might allow manufacturers to market products without regulation.

Several participants in these hearings did discuss in vitro reagents. For example, testimony in support of medical device legislation regarding the IVD industry was provided by the Scientific Apparatus Makers Association ((20); p. 558). While the concept of home brew testing was not specifically discussed in these hearings, an article submitted as supplementary material did discuss the regulatory aspects of reagents in relation to the FDA and FFDCA (21). The College of American Pathologists submitted a letter in support of the need for medical device legislation and suggested that diagnostic kits be included in the definition of in vitro reagents ((20); p. 928).

Hearings on medical devices were then held in 1975 by the Subcommittee on Health and the Environment of the House Committee on Interstate and Foreign Commerce (22). While the issues discussed were similar to those discussed in 1973, a prepared statement by Dr. Theodore Cooper (Assistant Secretary for Health, HEW) clarified the FDA’s position on device customization. He noted that “it should also be made clear that FDA would be able to take necessary action to curb a practitioner’s use of a custom device as a course of conduct on a number of patients, where this use is repeated to such an extent that the practitioner is in effect conducting unsupervised

experiments, or allowing the marketing of a product that would otherwise be unlawful” (22); p. 217).

The *Medical Device Amendments (MDA) of 1976* was ultimately passed to amend the FFDCa to “provide for the safety and effectiveness of medical devices” (23). The MDA provided a risk-based classification system for medical devices under the authority of the FDA (23). The MDA includes an amendment to the FFDCa and the Federal Trade Commission Act to specifically define a “device” as any

“instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . [among other qualifiers] . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease . . .” (23).

Thus, in vitro reagents, as well as in vitro diagnostic products, when used for the diagnosis of disease are considered as medical devices under current federal regulations.

The MDA specifically applies to devices introduced into “interstate commerce for commercial distribution” (23). In practice, there is very little that does not fall under the jurisdiction of the federal government through the interstate commerce clause. Article I Section 8 of the United States Constitution provides Congress the “power . . . [t]o regulate Commerce with foreign Nations, and among the several States” (24). Examples of where the commerce clause has been exercised include channels of interstate commerce (e.g., roads, canals, rivers, etc.) (25). Also regulated under the commerce clause are articles or things and the instrumentalities (e.g., machines) used to carry out commerce (26). Less apparent, but more frequently exercised, is Congress’ dormant commerce clause authority. The dormant commerce clause refers to the concept that state and local laws are unconstitutional if they place an undue burden on interstate commerce. Congress has asserted its interstate commerce authority to regulate articles covered under the FFDCa and the Supreme Court has affirmed this (27).

The MDA statute itself does not include language that differentiates the concept of LDTs. For the first few decades after MDA implementation, the FDA focused primarily on regulation of commercially distributed tests from diagnostic manufacturers. This has been described by FDA officials as the “commercially distributed test pathway” (28). The MDA statute does, however, include several requirements to be considered in the context of possible LDT regulation.

MDA requirements regarding *records and reports on devices* stipulate that prescribed regulations “shall not impose requirements unduly burdensome to a device manufacturer, importer, or distributor, taking into account his cost of complying with such requirements and the need for the protection of the public health and the implementation of this Act” [Sec. 519 (a) (1)] (23). The

MDA exempts certain licensed practitioners from reporting requirements, specifically “any practitioner who is licensed by law to prescribe or administer devices intended for use in humans and who manufactures or imports devices solely for use in the course of his professional practice” [Sec. 519 (b) (1)] (23). The scope of professional practice related to clinical pathology and laboratory medicine should therefore be considered in the context of interpreting MDA requirements for IVD records and reporting.

MDA requirements for performance standards and premarket approval do not apply to certain categories of *custom devices*. The language is quite restrictive but may be pertinent to LDTs in limited circumstances. The scenario of exempt custom devices only occurs if [Sec. 520 (b); capitalization added]:

“to comply with the order of a physician or dentist” [or other specially qualified person designated under regulations] “necessarily deviates from an otherwise applicable performance standard . . . if:

- (1) The device is not generally available in finished form for purchase or for dispensing upon prescription AND is not offered through labeling or advertising by the manufacturer, importer, or distributor thereof for commercial distribution, AND
- (2) Such device—
  - (A)(i) is intended for use by an individual patient named in such order of such physician or dentist (or other specially qualified person so designated) AND is to be made in a specific form for such patient, OR
  - (ii) is intended to meet the special needs of such physician or dentist (or other specially qualified person so designated) in the course of the professional practice of such physician or dentist (or other specially qualified person so designated), AND
  - (B) is NOT generally available to or generally used by other physicians or dentists (or other specially qualified persons so designated)” (23).

In a 1977 Final Rule regarding establishment registration in accordance with the MDA, the FDA defined classes of persons *exempt from registration*, including “persons who dispense devices to the ultimate consumer or whose major responsibility is to render a service necessary to provide the consumer (i.e., patient, physician, laymen, etc.) with a device or the benefits to be derived from the use of a device; for example, a . . . clinical laboratory” (29). Clinical laboratories are therefore exempt from device registration, although this exemption is only specified in regulations and not the original statute.

#### CLIA REGULATIONS

The Partnership for Health Amendments passed by Congress in 1967 contained a section dedicated to clinical laboratories. Known as CLIA’67, this law established a licensing program for clinical laboratories that were involved in interstate commerce (30). CLIA’67 contained

**Table 1. FDA and CMS oversight of laboratory testing.**

FDA	CMS
Authority: FFDCa and MDA	Authority: CLIA'88
Safety and Effectiveness of Devices/Reagents	Quality of Clinical Testing Process
Quality of Design and Manufacture	Quality of the Laboratory
Analytical and Clinical Validity	Analytical Validity
Adverse Event Reporting	Requirements to Assess Performance

Adapted from (77).

language suggesting that interstate commerce applied to the acts of soliciting or accepting specimens, including in the statute “no person may solicit or accept in interstate commerce, directly or indirectly, any specimen for laboratory examination or other laboratory procedures, unless there is in effect a license” [Sec. 353 (b) (1)] (30). While CLIA'67 provided a regulatory foundation for clinical laboratory licensure, it left a fragmented system of different requirements for different types of laboratories.

A growing national concern regarding the quality of laboratory testing, including particular attention toward Papanicolaou “Pap” test interpretation, led to multiple Congressional subcommittee hearings in 1988. Hearings before the Subcommittee on Regulation and Business Opportunities of the House Committee on Small Business were poignantly titled *Deadly Mistakes: Are Laboratory Results Reliable?* (31). While prominent organizations and leaders from the clinical laboratory community provided testimony, the concept of LDTs was not specifically highlighted. LDTs were also not discussed at hearings on clinical laboratories held before a separate House subcommittee (32).

Additional hearings in 1988 were held by the Subcommittee on Oversight of Government Management of the Senate Committee on Governmental Affairs (33). A perspective regarding LDTs was included in a testimony provided by the Director of the New York State Wadsworth Center for Laboratories and Research. In the written testimony, when describing the existing federal program for laboratory regulation, the director noted that “while FDA requirements must be met if a kit or reagent is to be commercially marketed, laboratories that use their own techniques and reagents need no approval” (34).

CLIA'88 was ultimately passed to revise and improve the oversight and certification of clinical laboratories (35). The clinical laboratory testing program under CLIA is now primarily regulated by the Centers for Medicare and Medicaid Services (CMS). General differences in the current roles and responsibilities of FDA vs CMS with regard to laboratory test regulation are summarized in Table 1.

CLIA is frequently discussed as providing an existing regulatory mechanism for LDTs. Current federal regulations under CLIA delineate a standard by which clinical laboratories can offer testing by use of modified FDA-cleared or approved assays or test systems that are “not subject” to FDA clearance or approval [42 C.F.R. § 493.1253 (2)]:

“Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable . . .” (36).

Given the focus on this standard in the context of the proposed LDT regulation, it is important to note that the language above was *not* present in the original CLIA'88 statute (35). It was introduced in promulgated regulations over time (Table 2). Specifically, mention of methods “not cleared by the FDA” was introduced in 1992, whereas the verbiage “not subject to FDA clearance or approval” was incorporated in 2003.

#### FDA AND LDT ENFORCEMENT DISCRETION

Since passage of the MDA and CLIA'88, scientific advances have led to a greater technical complexity of reagents and testing processes. In response to these advances, the FDA prepared and released several draft documents and rules to clarify regulatory requirements.

In 1992, the FDA released a draft Compliance Policy Guide (CPG) titled *Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation* (2). In the draft CPG, they wrote:

“it has come to the attention of the FDA that laboratories have been manufacturing, ‘home brew’ products, either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes. These products are subject to the same regulatory requirements as any unapproved medical device . . .” (2).

**Table 2. Evolution of CLIA regulations applicable to LDTs.**

Time	Source	Verbiage <sup>a</sup>
1988	"Clinical Laboratory Improvement Amendments of 1988." (PL 100-578, Oct. 31, 1988) United States Statutes at Large, 102 (1988) pp. 2903-2915.	<i>Authorization:</i> "(f) Standards; (1) In General—The Secretary shall issue standards to assure consistent performance by laboratories . . . of valid and reliable laboratory examinations . . . (A) to maintain a quality assurance and quality control program adequate and appropriate for the <u>validity and reliability of the laboratory examinations</u> and other procedures of the laboratory . . ."
1990	<i>Final rule with comment period:</i> Medicare, Medicaid and CLIA Programs; Revision of the Laboratory Regulations for the Medicare, Medicaid, and Clinical Laboratories Improvement Act of 1967 Programs. 55 Fed. Reg. 9538 (March 14, 1990); Codified at 42 C.F.R. § 493.1215 (1990)	"The laboratory must have a written protocol and documentation for the validation of each method that verifies that the method produces test results within the laboratory's stated performance characteristics. <u>Method validation must be performed before a test procedure is placed into routine use . . .</u> "
1992	<i>Final rule with comment period:</i> Medicare, Medicaid and CLIA Programs; Regulations Implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 57 Fed. Reg. 7002 (February 28, 1992); Codified at 42 C.F.R. § 493.1213 (1992)	"After September 1, 1992, a laboratory that introduces a new procedure for patient testing using: <u>a method developed in-house; a modification of the manufacturer's test procedure; or a method (instrument, kit, or test system) that has not been cleared by the FDA</u> as meeting the CLIA requirements for general quality control, must, prior to reporting patient test results . . ."
2003 <sup>b</sup>	<i>Final rule:</i> Medicare, Medicaid and CLIA Programs; Laboratory Requirements Relating to Quality Systems and Certain Personnel Qualifications. 68 Fed. Reg. 3640 (January 24, 2003); Codified at 42 C.F.R. § 493.1253 (b)(2) (2003)	"Each laboratory that <u>modifies an FDA-cleared or -approved test system, or introduces a test system not subject to FDA clearance or approval (included methods developed in-house and standardized methods such as text book procedures, Gram stain, or potassium hydroxide preparations)</u> , or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics . . ."

<sup>a</sup> Underlines added for clarity.

<sup>b</sup> "Gram stain, or potassium hydroxide preparations" deleted in subsequent 2003 correction; see 68 Fed. Reg. 50722 (August 22, 2003); Codified at 42 C.F.R. § 493.1253 (b)(2) (2003).

A citizen petition from the law firm of Hyman, Phelps & McNamara representing "clinical laboratories that would be affected by FDA regulation of assays developed or modified by clinical laboratories" was subsequently filed in 1992 in response to the draft CPG (37). The petition requested "that the Commissioner of Food and Drugs not regulate as medical devices assays developed by clinical reference laboratories strictly for in-house use," objecting to the FDA's assertion on the following four grounds: (a) that the proposal was inconsistent with CLIA, (b) that the FDA lacked statutory authority to regulate in-house assays, (c) that the proposal would violate the Administrative Procedure Act, and (d) that it would diminish the quality of healthcare (37).

In the 1997 *Final Rule on Analyte Specific Reagents*, the FDA included responses to public comments in relation to the new *Analyte Specific Reagents* rules (38). In response to a comment on risk classification, the FDA stated (with regard to development of in-house tests) their position on manufacturing, stating that the "FDA

believes that clinical laboratories that develop such tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act" (38).

The FDA formally denied the Hyman, Phelps & McNamara citizen petition in 1998 (39). Of note, in relation to the statutory authority argument, the FDA asserted that if an "ingredient" crosses state lines, then the interstate commerce requirements are met (39). While the FDA was declaring that it had authority to regulate LDTs, since it had thus far not chosen to exercise that authority, external parties "did not challenge FDA's assertion of jurisdiction in court" (40).

It should also be noted that while the MDA specifically discusses the "safety and effectiveness" of medical devices, this has subsequently been described by the FDA and the clinical laboratory community in the context of "analytical and clinical validity." *Analytical validity* has been described as "the ability of a test to detect or measure the analyte it is intended to detect or measure," whereas *clinical validity* has been described as "its ability to accu-

rately diagnose or predict the risk of a particular clinical outcome" (41). This shift in terminology likely reflects a practical consideration of how "safety and effectiveness" could be interpreted in the context of IVDs, although it is not strictly defined as such within the MDA.

For example, product labeling requirements for *in vitro* diagnostic products (proposed by the FDA in 1972) specify performance characteristics, including "accuracy, precision, specificity, and sensitivity," whereas performance standards also require data regarding the "support of claims" (16). In describing "reasonable assurance of the safety and effectiveness" of devices, the MDA statute includes "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," noting how effectiveness may be determined through the use of well-controlled studies, review by experts, and valid scientific evidence (23). In the 1997 Final Rule regarding *Analyte Specific Reagents* published in the Federal Register, the FDA itself used the specific terms *analytical validity* and *clinical validity* to respond to comments from the public (42).

## GENETIC AND MULTIVARIATE TESTING

Attention in the 1990s and 2000s was largely focused on genetic and multivariate testing. The Task Force on Genetic Testing was convened in 1994 by the Working Group on Ethical, Legal and Social Implications of Human Genome Research, National Institutes of Health (43). Among other recommendations, the Task Force called on the Secretary of HHS to establish an advisory committee on genetic testing. In 1998, the Secretary's Advisory Committee on Genetic Testing (SACGT) was chartered (44). SACGT gathered background information and developed principles and recommendations regarding genetic testing. One such recommendation was that the "FDA should be the federal agency responsible for the review, approval, and labeling of all new genetic tests that have moved beyond the basic research phase" and that the "level of review applied by FDA should correlate with the level of scrutiny warranted by the test" (44).

HHS initially intended to implement these recommendations, including new CLIA regulations for "expanded oversight of genetic testing" and implementation of numerous FDA regulatory controls (45). In 2001, SACGT decided to curtail their efforts related to risk classification of genetic tests as "irresolvable questions had been raised about the feasibility of categorizing tests for oversight purposes based on a limited set of elements in a simple, linear fashion" (46). They also noted "significant progress made by the FDA to develop an innovative regulatory process for genetic tests" (46). SACGT was ultimately restructured into the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) in 2003 (47). Secretary's Advisory Committee on Genetics, Health, and Society focused more on social, clinical, ed-

ucational, and ethical issues surrounding molecular testing, whereas the FDA continued to promote their regulatory stance regarding LDTs (48).

For example, in a 2004 letter to Correlologic Systems (regarding the OvaCheck<sup>®</sup> multiparameter proteomic assay for ovarian cancer), the FDA expressed their position that this test had not gone through required premarket approval as a medical device (49). The FDA subsequently released a draft guidance in 2007 on *In Vitro Diagnostic Multivariate Index Assays* (IVDMIA), defining them as a category of complex, frequently "high-risk" tests "developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratorians, and clinicians who order these tests" (50). Although the IVDMIA draft guidance was never finalized, it reiterated the FDA's stance on regulatory authority over LDTs. Examples of IVDMIA cleared or approved by the FDA include MammaPrint (2007; Agendia), Tissue of Origin Test [2008; Pathwork Diagnostics (now from Cancer Genetics)], AlloMap Molecular Expression Testing [2008; xDx (now CareDx)], OVA1 [2009; Vermillion (ASPiRA) with Quest Diagnostics], and Prostate Health Index ( $\phi$ ) (2012; Beckman Coulter).

Studies through the Government Accountability Office between 2006 and 2010 noted misleading, deceptive, and/or inaccurate results from numerous "direct-to-consumer" (DTC) genetic testing services. These findings were highlighted in several congressional hearings (51, 52). The FDA sent letters to numerous companies that were involved with producing such direct-to-consumer tests and services, emphasizing the FDA's position that these tests are medical devices subject to regulatory oversight (53).

Many parties in the pharmaceutical and IVD industries supported the idea of FDA regulatory oversight over LDTs. For example, in 2008, Genentech sent a Citizen Petition to the FDA requesting that the Commissioner "require all *in vitro* diagnostic tests intended for use in drug or biologic therapeutic decision-making be held to the same scientific and regulatory standards . . . regardless of whether the *in vitro* diagnostic tests are developed and sold by device manufacturers as diagnostic test 'kits' or are developed in-house by laboratory-based companies for in-house testing" (54). The Genentech Citizen Petition noted that "the use of such high-risk tests, if based on scientific claims made but not adequately validated, could place patients at risk" (54). The Advanced Medical Technology Association (AdvaMed) sent a proposal to the FDA in 2009 as a comment on the Citizen Petition, advocating for a risk-based regulation of all diagnostic tests "regardless of where they are produced" (55).

**ADMINISTRATIVE PROCEDURE ACT**

Before describing the FDA's 2010 announcement regarding a proposed approach to LDT oversight, it is important to outline the rulemaking process for federal agencies. The *Administrative Procedure Act* of 1946 was enacted to specify how federal agencies must establish new rules (56). The Office of the Federal Register has summarized the required steps in *A Guide to the Rulemaking Process* (57), which is summarized briefly below. In response to a law or based on agency priorities, a potential rule may be developed through internal deliberation and/or by soliciting preliminary public opinion. Before advancing a proposed rule, the agency must publish a "Notice of Proposed Rulemaking" in the Federal Register allowing for public comment. After closure of the comment period, feedback is considered and the proposed rule is revised. If advanced, a Final Rule is then published in the Federal Register, including responses to categories of public comments received. Information on additional review requirements by the Office of Management and Budget can be found online (58).

An agency may also release guidance documents (also known as interpretations or general policy statements) that "explain how it interprets an existing regulation or statute, how a rule may apply in a given instance, and what things a person or corporation must do to comply" (57). It is critical to note that guidance documents cannot be used to establish new rules. Whether a proposal should follow a rulemaking vs guidance approach is not always straightforward, and a 2006 US Court of Appeals ruling has addressed distinguishing factors between promulgated rules and policy statements (59, 60). In 1997, the FDA published the document *Good Guidance Practices* in the Federal Register, which outlined how they would consistently develop and use such guidance documents (61). An unresolved issue between the FDA and many in the clinical laboratory community, however, is whether LDT oversight would create new rules and therefore would be subject to notice and comment rulemaking. Choosing a guidance approach (if rulemaking is ultimately required) risks the possibility of nullification in subsequent judicial review (60).

**FDA PROPOSAL FOR LDT OVERSIGHT**

In June 2010, the FDA announced that it would hold a public meeting to discuss "how the agency will oversee" LDTs (62). The public meeting included statements from the FDA on the concept of enforcement discretion and how it related to their choice of why they intended to follow a guidance process instead of formal notice and comment rulemaking. When asked at the public meeting why notice and comment rulemaking were not being proposed "as a potential way forward," an FDA official stated "the reason why not for notice and comment rulemaking is because the requirements actually already ap-

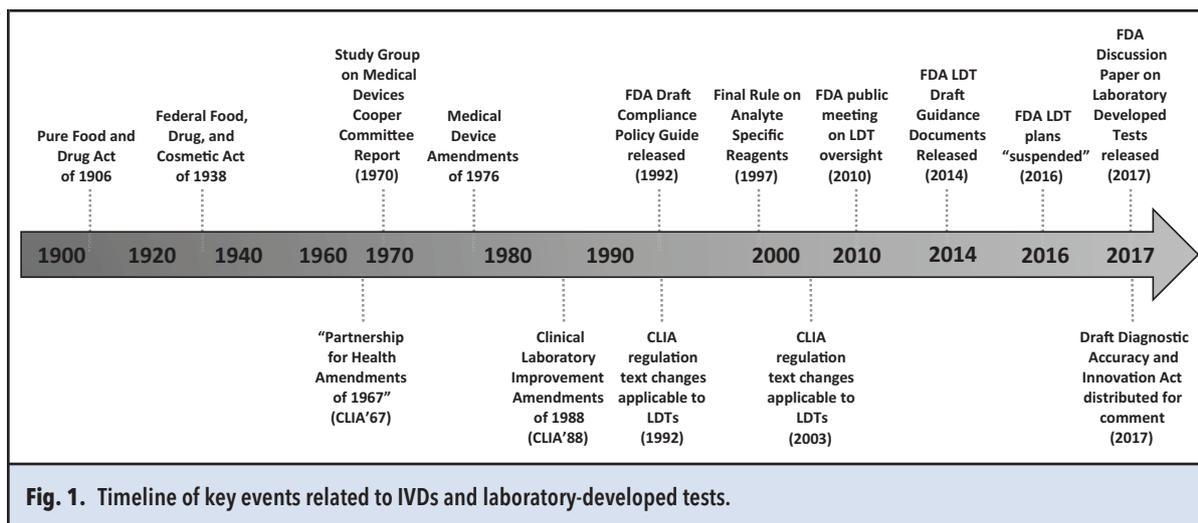
ply now. The law is in effect. We have simply, as a matter of policy, determined not to exercise or not to enforce that authority as of right now" (63). The FDA has also written that "enforcement discretion for LDTs developed as a matter of general practice" (1).

After the 2010 public meeting, the FDA began developing draft guidelines related to LDT oversight. On July 31, 2014, the FDA notified Congress of its intent to release the draft guidance documents (64). At a September 2014 hearing before the Subcommittee on Health of the House Committee on Energy and Commerce, an FDA official was asked how "implementing this new regulatory framework via guidance [would] comply with the Administrative Procedures Act" ((65); p. 20). The official responded that "[t]hose kinds of general policy statements where we are not imposing a new requirement . . . are not subject to Administrative Procedures Act . . . rulemaking" (65).

The FDA's draft guidance documents were released on October 3, 2014 (1, 66). The *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* described processes and requirements for notification, reporting, categories of continued enforcement discretion, a risk-based approach to premarket review for high- and medium-risk LDTs, and a proposed approach to quality system regulation (1). The second document, *FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)*, described the proposed processes and requirements for notification to the FDA of LDTs, as well as medical device reporting requirements for adverse events (66). This draft guidance document specifically states that "notification" is not "registration", as "completion of this notification does not constitute compliance with registration and listing requirements" ((66); p. 6).

Release of the draft guidance documents initiated strong responses from the clinical laboratory, IVD, and healthcare communities both for and against the FDA proposal. The diversity of perspectives and lack of community consensus were evident in the comments provided at a January 2015 public workshop on LDTs (67). These positions reflected deeply held personal and organizational viewpoints on how to ensure public safety through adequate safeguards while not creating an undue regulatory burden that might stifle innovation or hinder laboratories from providing valuable testing services for patients. In support of their proposal, the FDA subsequently released a report from their Office of Public Health Strategy and Analysis describing 20 cases provided as examples of LDTs that "may have caused or have caused actual harm to patients" (68).

Since the draft guidance release, legal white-papers on behalf of laboratory and professional organizations have argued that laboratory testing services "are" or "are not" the practice of medicine (69, 70). This is a particularly challenging component of the LDT debate, as it



points to uncertainties about what constitutes the practices of laboratory medicine (also known as clinical pathology) and/or PhD clinical laboratory directorship. These doctoral-level career pathways include daily activities that are profoundly impacted by federal regulations.

The proposed LDT regulations also prompted the attention of Congress. Hearings on LDTs were held by the Subcommittee on Health of the House Energy and Commerce Committee in 2014 and 2015 (65, 71). Draft proposals on an alternative LDT regulatory structure for “in vitro clinical tests”—reportedly developed with input from the Diagnostic Test Working Group—were also circulated (72). In April 2016, a nonbinding report (included as an explanation of an accompanying appropriations bill) from the House Committee on Appropriations asked the FDA to suspend “further efforts to finalize” the LDT proposal, stating that “the FDA’s guidance circumvents the normal rulemaking process and changes expectations for patients, doctors, and laboratories” (73).

Shortly after the 2016 Presidential election, the FDA communicated to stakeholder organizations that it intended to suspend plans to move forward with its current LDT proposal, noting that they would “continue to work with stakeholders, our new administration, and Congress to get our approach right” (74). In January 2017, the FDA released its *Discussion Paper on Laboratory Developed Tests (LDTs)*, which shared a “synthesis of feedback” received during the public comment period and stakeholder engagement (75). More recently, a draft discussion of the potential *Diagnostic Accuracy and Innovation Act (DAIA)* was made available for public comment from two members of the Subcommittee on Health of the House Energy and Commerce Committee (76). The DAIA draft attempted to more clearly delineate regulatory authority over all in vitro clinical tests, with

“FDA jurisdiction over test development and manufacturing” and updated CLIA regulations overseeing laboratory operations (76). A summary of key events related to IVDs and LDTs presented throughout this manuscript is presented in Fig. 1.

## SUMMARY

A quarter of a century after the FDA first asserted regulatory authority over LDTs in a draft guidance document, rules and/or guidance regarding LDT oversight have not been implemented. As such, legal questions regarding MDA authority over LDTs and the FDA draft guidance approach have neither been escalated to nor resolved by the judiciary. In addition, many questions central to this debate have not been answered. Are clinical laboratories manufacturers? Should laboratory devices and procedures be regulated similarly? Are there always clear limits between laboratory operations and the practice of laboratory medicine? Any future LDT regulatory or legislative efforts will need to balance and address these concerns if they are to be successful. It is unlikely that interpretation of current statutes and regulations can fully resolve these issues.

It is interesting that in public testimony before implementation of the MDA and CLIA’88, the concept of LDTs was simply not adequately considered or discussed by Congress; therefore, it is difficult to definitively attribute congressional intent. CMS chose to address validation of non-FDA cleared tests through notice and comment rulemaking—likely out of a practical need to decide what to do with this category of tests as CLIA regulations were being finalized. The FDA’s draft guidance approach has faced resistance from many in the clinical laboratory community who believe that the logistical “requirements” of the draft guidance should be considered new “rules” and therefore subject to notice and

comment rulemaking. Notice and comment rulemaking may have also fostered a more open assessment of whether the proposed framework would have placed an undue burden on the laboratory community.

A lack of consensus within the clinical laboratory community has also likely contributed to the uncertainty present in the LDT regulatory debate. Differences between professional society positions on LDT oversight may foster an environment in which federal agencies or Congress ultimately decide the future of LDT regulation on behalf of the clinical laboratory and IVD communities because consensus is not present. While legitimate justification underlies the diversity of opinions, it would behoove the affected parties to find common ground where possible and then advocate for these shared concerns in future proposals and/or legislative efforts.

With the current suspension of FDA efforts to advance regulatory oversight, it is unclear whether and/or how LDTs will be addressed going forward. Discrete and immediate concerns for public safety were strong motivators for prior legislative efforts regarding medical device and clinical laboratory regulation. Given the ongoing controversies and lack of consensus, progress toward achieving clarity in the LDT regulatory arena may be difficult to achieve in the absence of a clear, collaborative effort or a legislative mandate.

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