

## **The Regulatory Paradox of Laboratory Developed Tests**

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### **1. INTRODUCTION AND OVERVIEW**

FDA's statutory jurisdiction, hence the regulatory obligations governing the design, characterization, production, and commercialization of laboratory developed tests (LDT), is defined in part by two central elements—(a) the degree of risk associated with the use of the device, and (b) the device's intended use.

The development of increasingly more complex and sophisticated in vitro diagnostic (IVD) devices by clinical laboratories has precipitated FDA concern regarding a lack of product controls. These tests are often produced using available marketed kits, may include components purchased from a commercial supplier, and are offered for use as a diagnostic service. FDA contends that test ingredients or components used in the production of LDTs are essentially unregulated, therefore, of unpredictable quality. Although FDA has regulated the safety and effectiveness of IVD devices that are commercially distributed and marketed to end-users as finished products, LDTs, also known as “in-house” or “home brew” tests, have been produced and offered as clinical laboratory specialty services governed by federal regulations codified in the Clinical Laboratory Improvement Amendments of 1988 (CLIA) for compliance with general laboratory standards.<sup>1</sup>

Innovative technologies continue to emerge, providing clinical laboratories with the diagnostic tools to peer earlier and deeper into relevant molecular manifestations of disease and infection. The implications of this increasingly complex information toward clinical diagnosis and disease management decisions may well justify the approaching shadows of FDA regulation.

### **2. BACKGROUND**

Actions undertaken by FDA over the last 2 decades suggest that the regulatory landscape governing the production and use of LDTs is changing. On August 3, 1992, the Center for Devices and Radiological Health (CDRH) released a draft compliance policy guide (CPG) that declared that LDTs are considered unapproved medical devices and, therefore, subject to compliance with medical device regulations.<sup>2</sup> This prompted the submission of a citizen petition to FDA on October 22, 1992, requesting that FDA not regulate as medical devices LDTs developed by clinical laboratories strictly for in-house use. The basis for that petition was that (a) FDA regulation of LDTs would be inconsistent with CLIA regulations, (b) FDA does not have statutory authority to regulate LDTs, and (c) FDA regulation of LDTs would have a negative impact on the quality of health care in the United States. FDA would not respond to this petition for nearly 6 years, in part to consider comments on the draft CPG document and to allow for notification and comment to the Analyte Specific Reagent (ASR) final rule in November 1997.<sup>3</sup>

ASRs are typically molecules that serve as the core element of capture/detection in LDTs and are considered to be the active ingredient of a diagnostic test. ASRs include polyclonal and monoclonal antibodies, receptor proteins, molecular ligands, nucleic acid sequences, and other molecules/chemical moieties with specific affinity for a substance or ligand in a biological specimen, thus mediating its detection and/or quantitation. All ASRs are considered restricted medical devices by FDA and are, therefore, subject to restricted sale, distribution, and use and compliance with medical device regulations. The final rule further classifies/reclassifies ASRs into three classes: Class I (general controls, exempt from premarket notification), Class II (special controls, premarket notification), and Class III (special controls, premarket approval). The aim of these regulations was, in part, to ensure that ASR manufacturers provide quality materials, compliant with the medical device Quality System Regulation (QSR), to qualified laboratories for use in the development and production of LDTs. Although FDA stated in the preamble to the final rule that clinical laboratories that develop LDTs are acting as medical device manufacturers that are subject to medical device regulations, FDA has elected to not extend the rule to such tests and has exercised enforcement discretion over laboratory-developed ASRs and LDTs that employ commercially available and laboratory-developed ASRs. The exclusion of LDTs from the ASR rule was based on confidence in the ability of laboratories certified by CLIA for high-complexity testing to use ASRs.

FDA's August 1998 response to the citizen petition was to deny the petition request and to conclude that, consistent with the ASR final rule and the CPG, (a) FDA may regulate LDTs developed by clinical laboratories strictly for in-house use as medical devices, (b) FDA has the authority to provide industry guidance and issue a final CPG regarding LDTs, (c) the CPG may assert that FDA has the authority to regulate LDTs, and (d) any CPG issued by FDA regarding the distribution of IVD devices labeled for research or investigation may address assays developed by clinical laboratories for in-house use.

On September 7, 2006, FDA released a draft guidance document that defined in vitro diagnostic multivariate index assays (IVDMIA) as "a test system that employs data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software, to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease".<sup>4</sup> This guidance, therefore, provides that IVDMIA are medical devices and that they fall outside the scope of LDTs, which are entitled to exemption from the ASR rule.

A second citizen petition regarding FDA regulation of LDTs was submitted on September 28, 2006, based on concerns consistent with the previous citizen petition of 1992 and with subsequent material changes to the law. The new petition expressed concern that although FDA elected to not exert its jurisdiction over LDTs and chose to extend exemption from the ASR rule to LDTs, FDA had, in fact, begun taking action against various clinical laboratories offering LDTs in an effort to regulate them as medical devices. Although the formal Agency response to the 2006 citizen petition remains forthcoming, it is clear that IVD manufacturers remain at odds with the Agency over the once conspicuous regulatory boundaries that now seemingly blur with time.

### **3. IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS**

In the draft guidance on IVDMIAs released in September 2006, FDA acknowledged the existence of confusion regarding the regulation of these devices, which are developed and used by clinical laboratories. This confusion was attributed, in part, to the ASR rule that classifies and regulates ASRs that move in commerce. FDA reiterated that clinical laboratories that develop tests employing commercially available ASRs and use such tests exclusively in-house are considered medical device manufacturers and are subject to FDA jurisdiction. FDA further extended exemption from the ASR rule to these tests, electing instead to apply discretionary enforcement. This approach relied on the fact that FDA was now regulating ASRs and that clinical laboratories certified as high-complexity under CLIA regulations had the expertise and capability to use ASRs appropriately in these tests.

The defining characteristics of an IVDMIA are that:

- A. It uses clinical data, including data from one or more in vitro assays and, in some cases, demographic data, to empirically identify variables and to derive weights or coefficients employed in an algorithm.
- B. It employs the algorithm to integrate these variables in order to calculate a patient-specific result (e.g., a classification, score, or index). This result cannot be independently derived and confirmed by another laboratory without access to the proprietary information used in the development and derivation of the test.
- C. It reports this result, which cannot be interpreted by the well-trained healthcare practitioner using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness.

IVDMIAAs are classified on the basis of intended use and the requisite level of control needed to ensure safety and effectiveness. Accordingly, Class I IVDMIAs are exempt from premarket notification, Class II IVDMIAs are subject to premarket notification in the form of a 510(k) submission, and Class III IVDMIAs require the submission of an application for premarket approval (PMA). Along with Class III designation comes the likelihood that IDE regulations apply, along with postmarket compliance requirements. FDA believes that most IVDMIAs will be either Class II or Class III devices.

If an LDT meets these IVDMIA criteria, then commercialization requirements could include conduct of clinical studies to establish safety and effectiveness, compliance with the QSR, medical device reporting, other relevant medical device regulations, and a premarket application for approval.<sup>4</sup> This guidance, therefore, provides that IVDMIAs are medical devices and that they fall outside the scope of LDTs, which are entitled to exemption from the ASR rule.

### **4. PATHWAYS TO LABORATORY DEVELOPED TEST COMMERCIALIZATION**

Clinical laboratories with the vision, R&D resources, and innovation to develop their own proprietary in-house LDTs face two regulatory pathways by which these tests may be

commercialized. Because the ASR rule establishes that all ASRs are medical devices, any LDT that incorporates an ASR now falls within the definition of a device as described in the Federal Food, Drug, and Cosmetic Act and its regulations. Further regulatory obligations will be contingent upon discretionary enforcement actions undertaken by FDA regarding whether or not the LDT meets the criteria of an IVDMIA.

The first pathway is based on the intent to sell and distribute the LDT as a finished commercial product to other laboratories who then use them according to the instructions and labeling provided. This commercialization strategy renders the clinical laboratory that developed the LDT a device manufacturer and puts into effect a clearly defined regulatory pathway that requires establishment registration, medical device listing, premarket submission to FDA, adherence to the medical device QSR, good manufacturing practices (GMPs), labeling compliance, medical device reporting, and various other medical device regulatory obligations.<sup>5</sup> Furthermore, depending on the significance of risk associated with the LDT, nonclinical studies, clinical studies conducted under an investigational device exemption (IDE), and postapproval studies may be required to adequately characterize and confirm the device's performance, clinical utility, clinical validity, and the outcomes impact on the target patient population.

The second pathway is based on the intent of the clinical laboratory to solely use its LDT as an in-house test and offer it as a commercial specialty service to various health care providers and other laboratories. In the past, this commercialization strategy has largely rendered LDTs outside of FDA's statutory jurisdiction of medical devices, placing them instead under the regulations of CLIA. CLIA regulations, which are jointly administered by the Centers for Medicare and Medicaid Services (CMS), FDA, and Centers for Disease Control and Prevention ensure that clinical laboratories are registered, accredited, proficient, and compliant with numerous federal requirements toward the accuracy, reliability, and timeliness of patient test results. Historically, the clinical laboratory that developed the LDT would not be recognized as a medical device manufacturer in this regulatory pathway; therefore, there would be no requirement for establishment registration, medical device listing, premarket submission to FDA, adherence to the medical device QSR, GMPs, labeling compliance, medical device reporting,<sup>5</sup> and other medical device regulatory obligations as defined in the medical device regulations.<sup>5</sup> However, the ASR rule now recognizes these LDTs as medical devices, regards the clinical laboratory as a medical device manufacturer, and mandates compliance with the medical device regulations. Widespread and urgent enforcement of this abrupt regulatory transformation would logically stand to impact the availability of many current and important diagnostic tests. The long-term implications would suggest that the considerable investment, time, and regulatory uncertainty that comes with the development and launch of novel and innovative diagnostics may temper the willingness and incentive of clinical laboratories to remain stakeholders in this field. Amidst these concerns, FDA has instead elected to exempt LDTs from the ASR rule and apply discretionary enforcement of these regulations.

Although CLIA regulations establish requirements toward laboratory personnel qualifications, quality control, proficiency testing, patient test management, and quality assessment, these conditions and standards provide considerably more degrees of regulatory freedom than the QSR and its affiliated regulations in the commercialization process. Furthermore, irrespective of the

significance of risk associated with the LDT, CLIA requires that laboratories establish the analytical validity of the LDT (e.g., accuracy, precision, sensitivity, specificity with and without interfering substances, reportable range of results, normal values, etc.). CLIA has no statutory authority, nor is it required, to establish the clinical validity and/or clinical utility of the test. Consequently, there is no definitive requirement that clinical studies be conducted in an effort to characterize and confirm the device's performance and outcome's impact on the targeted patient population.

The current exemption of LDTs from, and discretionary enforcement of, the ASR rule by FDA notwithstanding, the regulatory paradox presented by these divergent commercialization paths allows that an LDT representing a significant-risk medical device may be authorized for use in the medical community as an instrument of diagnosis and treatment via the considerably less stringent CMS regulatory pathway, provided that the test is conducted by a single corporate end-user. Authorization for the sale, distribution, and use of the same LDT by multiple corporate end-users, however, would require a substantially more complex and costly development and regulatory approval process through FDA. Conceivably, the FDA commercialization pathway comes at a higher compliance and commercialization price yet stands to better characterize the benefits and risks associated with the use of the LDT than the CMS pathway. However, the medical community perceives no conspicuous difference in the value or validity of the test outcome delivered by either commercialization method. Although each regulatory pathway has an intended purpose, it is clear that the development and commercialization of IVD devices cannot simultaneously comply with both.

## **5. ROLE OF CLIA IN REGULATION OF LABORATORY DEVELOPED TESTS**

CLIA regulations establish conditions and standards that clinical laboratories must meet in order to be certified to conduct testing on human specimens. The requirements for CLIA certification are based on the complexity of tests performed by the laboratory. This includes waived tests, moderate-complexity tests, and high-complexity tests. To be compliant with CLIA regulations, clinical laboratories must be registered, certified, and/or accredited. They must undergo periodic proficiency testing on the tests they perform, their facilities must be adequate, and personnel must be qualified for the level of test-complexity conducted. Clinical laboratories are subject to CLIA inspection at 2 year intervals.

CLIA also requires that quality systems be in place for nonwaived testing and that a quality assessment component be enacted to ensure continuous improvement in its services. The quality system includes, but is not limited to, general laboratory systems that address confidentiality of patient information, specimen integrity, communications, personnel competency, evaluation of proficiency testing performance, complaint investigations (§493.1230, §493.1231, §493.1232, §493.1233, §493.1234, §493.1235, §493.1236, §493.1239), pre-analytic systems regarding test requests, specimen submission, handling and referral (§493.1240, §493.1241, §493.1242, §493.1249), analytic systems that include development and use of a procedure manual, requirements for instruments, equipment, test systems, reagents, supplies, verification or establishment of performance specifications, maintenance and function checks, calibration and control procedures (§493.1250, §493.1251, §493.1252, §493.1253, §493.1254, §493.1255, §493.1256), and postanalytic systems regarding test reports (§493.1290, §493.1291, §493.1299).

The most significant and relevant CLIA standards regarding the regulation of LDTs are found among the analytic systems requirements. When a clinical laboratory uses an unmodified, FDA-cleared, commercially available test, it must verify the performance specifications and reference intervals provided by the test manufacturer. However, if a clinical laboratory develops an in-house test, it must establish the performance specifications of the LDT (§493.1253). CLIA-required performance specifications include accuracy, precision, sensitivity, specificity (with and without the presence of interfering substances), identity of the reportable range of test results, reference intervals (normal values), and any other performance characteristic required for test performance. In addition, calibration and control procedures for the LDT, based on the performance specifications, must be determined and documented. The evaluation of LDT performance by CLIA occurs through proficiency testing, which requires that LDTs undergo an evaluation of accuracy twice each year. In the event the LDT does not meet the accuracy performance specification, corrective actions must be implemented after careful evaluation of the test results. CLIA does not, nor is it authorized to, assess or regulate the clinical validity or the clinical utility of an LDT.

Furthermore, although CLIA regulations establish requirements for identification of the proper storage conditions for reagents, proper labeling of reagents, use of expiration dates, and interchange of kit components or individual lot numbers, these basic standards allow considerable flexibility of compliance interpretation when a clinical laboratory prepares its own proprietary reagents, such as an ASR for which there is no interstate commerce. ASR manufacturers that commercially sell and distribute these reagents must comply with GMP regulations established in the QSR. In the absence of discretionary enforcement actions, it is not clear whether or not a clinical laboratory manufacturing its own proprietary ASR must accordingly comply with the QSR. The CLIA requirements for acceptable documentation of batch records, the determination of stability conditions and expiration dating, the establishment of batch acceptance criteria, and release specifications are not as stringently defined, regimented, or controlled as in the QSR. As a device undergoes modifications in design and components, these changes are explicitly chronicled in the device design history file and assessed in change control measures as mandated by the QSR. The extent to which CLIA regulations require comparable documentation and assessment of such design modifications is less conspicuous.

It is important to remember that CLIA certifies clinical laboratories and clinical laboratory practices. It does not certify tests or the individuals performing these tests. As new and innovative diagnostic technologies emerge and find their way to the healthcare field, we must consider whether the present bandwidth of CLIA regulations can maintain a quality assurance pace commensurate with the higher healthcare stakes.

## **6. CONCLUSION**

The regulatory boundary between FDA-regulated medical devices LDTs exempt from FDA jurisdiction remains somewhat blurred; however, the looming finalization of the CPG and IDVMIA guidance documents stand to better clarify this borderline. Concerns that FDA regulation of LDTs would stifle or hinder technical innovation, negatively impact patient care, or impose insurmountable work burdens on clinical laboratories in order to comply with the QSR because clinical laboratories simply do not operate that way, seem somewhat peripheral to the

quality issues lying at the core of this paradox. Although it seems inevitable that FDA regulatory changes may be on the horizon for medical devices, perhaps the extent of FDA's regulatory reach can be tempered through CLIA initiatives to fortify its statutory standards for significant-risk LDTs.

## 7. REFERENCES

1. Code of Federal Regulations, Volume 42, Part 493
2. Draft Compliance Policy Guide: Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation, Center for Devices and Radiological Health
3. Federal Register 62 (225):62243 1997
4. 63 Federal Register 62243, November 21, 1997
5. Code of Federal Regulations, Volume 21, Parts 800-899
6. Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays, September 7, 2006

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