

Regulation of Laboratory-Developed Tests: Decades of Debates Bring the Industry Full-Circle

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As our scientific understanding of diseases has increased dramatically in recent years, the industry has been presented with a number of opportunities for advanced applications within the realm of clinical diagnostics. Traditional laboratory-developed tests have become more advanced in order to keep up with this ever changing environment and show significant promise to continue to improve patient care both quickly and efficiently. However, their rapidly increasing complexity and extensive commercial applications well beyond the clinical space have caused many to question if they should continue to be exempted from rigorous premarket review processes that are already in place for *in vitro* diagnostics. As a result, the FDA has attempted to assert their authority over laboratory-developed tests to tighten regulations, further sparking debates among stakeholders on what regulatory frameworks may look like.

An *in vitro* diagnostic (IVD) is defined as a type of medical device that uses samples from the human body, such as blood or saliva, in order to detect diseases or monitor health conditions. The FDA has historically regulated all medical devices since the passage of the Medical Device Amendments of 1976 (MDA) and have evaluated their safety and efficacy through rigorous premarket review processes. The stringency of the premarket review process increases based on the risk associated with use of the IVD and includes both premarket approvals (PMA) and 510(k) pathways ¹.

In contrast, a laboratory-developed test (LDT) is a diagnostic test that is developed and validated for use within a single laboratory setting, also for disease detection or monitoring of health conditions using samples from the human body. These LDTs, or “home-brew”, tests are only intended to be used by the laboratory in which they were developed in and are not valid for use in other laboratories ². Although LDTs are currently regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) program within the Centers for Medicare and Medicaid Services (CMS), the FDA has previously defined LDTs as a subset of IVDs according to their interpretation of the MDA and therefore subject to oversight. However, historically they

have exercised enforcement discretion as a general practice and have not required premarket submissions for LDTs prior to laboratories marketing for patient testing ³.

Despite the fact that many stakeholders have argued that IVDs and LDTs have the same basic function, there are a number of factors that distinguish the two and have contributed to their sharply contrasting regulatory schemes to date. LDTs are typically performed in clinical settings, such as hospitals or reference laboratories, by trained personnel following detailed protocols and procedures under the supervision of a qualified laboratory director. These detailed protocols and procedures consist of proprietary methods⁴ that often require technical expertise and utilization of various instrumentation to complete testing. These traditional LDTs that are performed in hospital or academic medical centers are ordered by physicians in order to diagnose or aid in medical treatment decisions ⁵. IVDs on the other hand, are a finished physical product that includes labeling with detailed instructions for use by others outside of the facility they were manufactured² and subsequently introduced into interstate commerce ⁴. Additionally, as sequencing applications have become more cost effective and informative, direct to consumer (DTC) testing has become an additional consideration impacting discussions for enhanced regulatory scrutiny of LDTs ⁶.

Development of LDTs allows innovation on a rapid and continual basis⁴ and also provides an unmet need where FDA-cleared IVD platforms may not exist for certain diagnostic screenings. Additionally, commercial manufacturers do not always consider development of FDA-cleared assays due to the limitations on potential economic returns and ever evolving scientific advancements that would be quickly outdated, potentially even before premarket review can be completed. In cases where such platforms do exist, it may be cost prohibitive for a laboratory to maintain a wide array of platforms⁷ and the current framework allows them to develop similar LDT methods that are comparable and more cost-effective ⁵. Regardless of the circumstance, LDTs provide more accessible, efficient and affordable solutions⁴ that are no less reliable than FDA-cleared counterparts when validated appropriately ⁵.

According to the current regulatory frameworks of LDTs, laboratories who perform testing of human specimens must register with CLIA and establish defined performance characteristics of the LDT prior to the release of any patient results. These performance characteristics are intended to support analytical validity of the assay and can include metrics such as accuracy, specificity, reportable range and reference intervals. Additionally, validation of the LDT must be performed under controlled conditions by qualified and adequately trained staff, using calibrated equipment and known patient populations. This is one of the primary reasons that LDTs are only considered validated within the CLIA-certified laboratory that has defined the performance characteristics, making tests insignificant outside of the lab ². Although currently CLIA validation requirements do not assess the clinical validity of the assay, they do assess the clinical utility. This can determine if the assay may be useful in clinical practices⁸ and if it is responsible for the improvement or worsening of patient outcomes. CMS relies on the clinical utility in order to determine reimbursement potentials which are not accounted for within FDA premarket submissions.

In addition to detailed validation requirements, laboratories subject to CLIA regulations are also part of a continuous certification process which includes routine biennial surveys⁵ well beyond initial marketing of a test ⁷. CLIA laboratories are required to be overseen by a qualified medical director, who is typically a Doctor of Medicine (MD), and often have pathologists on staff for certain specialties, such as anatomic pathology. This allows for constructive conversations with practicing medical professionals who can also review test results and provide clinical consultations where needed ⁶. Some argue that this process classifies LDTs as a medical practice, further distinguishing them from IVDs and not subject to FDA authority ⁴.

Although there is an existing regulatory framework in place for LDTs, there are some limitations and pitfalls that are of concern to stakeholders. Current CLIA regulations do not require that any validation data be reviewed prior to marketing tests commercially and only states the release of patient results is prohibited prior to completion of the analytical validation.

Furthermore, CMS does not conduct an initial accreditation inspection of the laboratory in order to assess its suitability for testing or compliance with other CLIA regulations beyond those for validation ². Alarming, this current practice does not provide for the identification of potential issues patients may be exposed to prior to the use of the LDT on the market and is considered to be the most significant of gaps within the existing regulatory framework. This gap has become more apparent following the very public demise of companies such as Theranos who marketed their tests as LDTs under the CLIA program ⁶. A number of patients underwent additional, more invasive testing that was unnecessary as a result of the inaccurate test results they were provided. If CMS had a framework which supported fulfillment of initial accreditation requirements, this situation could have been avoided altogether ⁵.

As LDTs have continued to become increasingly complex over time, largely due to significant scientific advances and cost reductions of whole genome sequencing applications, the FDA has proposed implementation of a risk-based classification system in order to begin exercising their existing authority over LDTs ⁹. In July 2014, they announced their intent to execute such regulations through publication of the draft guidance document *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* ¹⁰. In addition to the guidance document, the Agency had already begun to execute their authority over LDTs, particularly in the DTC testing space, even going as far as to issue warning letters ¹¹. These actions have sparked a number of responses, both in support and opposition, and revealed questionable flaws in their enforcement entitlement as well as proposed framework ⁶.

Strong supporters of more stringent FDA oversight of all LDTs include larger corporations that typically fall under IVD classifications requiring extensive PMAs. Companies such as Genentech and AdvaMedDx have argued that the existing discretionary approaches of LDTs undermine the regulatory rigor they bear in order to comply with premarket review requirements. As a result, traditional manufacturers can be discouraged from investing both the time and funds required in order to fully evaluate the safety and efficacy of their IVD ⁶.

Aside from concerns clinical laboratories escape significant economic impacts, critics also argue there are huge risks to patient safety as the analytical validity of tests are not reviewed prior to commercial use of the assay ³. Imposing tighter regulations would provide stronger reliability of test results and could also evaluate its clinical validity prior to marketing as well ⁵. Inaccurate test results, or even tests that are not determined to be clinically relevant, can lead patients to undergo invasive and unnecessary medical procedures or make incorrect treatment decisions that can be detrimental to the patient ⁶.

Legislators have also chimed in on the debate, and in recent years even drafted several bills intended to address these disparities. In 2017, the Diagnostic Accuracy and Innovation (DAIA) Act was introduced which would grant the authority to regulate *in vitro* clinical tests (IVCT) within a new center of the FDA – the Center for In Vitro Clinical Tests ⁶. The DAIA was ultimately modified based on feedback from the FDA and led to drafting of the Verifying, Accurate, Leading-edge, IVCT Development (VALID) Act in 2018. The VALID Act incorporates elements from the DAIA Act and further enhances a novel classification scheme and framework for the regulation of IVCTs ¹¹. To date however, the VALID Act has not been passed into law ¹².

In stark contrast, opposers of FDA oversight have also voiced a number of concerns regarding these regulations and their overall impact to the industry. Critics argue that LDTs are clinical services which fall outside the scope of FDA enforcement according to the statutory definition of a device within the MDA and therefore should not be subject to the same regulatory rigor as IVDs. Timelines to complete such premarket requirements sufficient for an LDT to obtain premarket approval would be drastically longer than those required to complete a CLIA compliant analytical validation. Additionally, LDTs would now potentially be faced with supplemental premarket requirements for any assay modifications⁴ which can deter laboratories from implementing improvements for fear of being subjected to additional regulatory scrutiny ⁷. As a majority of clinical labs are in hospital or academic settings, they typically do not have the resources or capital on hand to comply with these extensive premarket requirements which can

stifle the industry. This can prevent development of new LDT technologies⁶ and also significantly decrease the availability of current testing abilities that are only available in laboratories with the specialized technical staff who are capable of performing these assays. In turn, this can also adversely affect patient care by limiting the availability of critical diagnostic tests that are needed to support a multitude of specialties⁷ which include RNA/DNA expression, chromosomal and newborn screening tests⁴.

Opposers have also pointed out that Congress enacted CLIA regulations in order to ensure quality performance of LDTs and for over 30 years, CMS has enforced these regulations. Adding FDA oversight on top of this would be redundant and, based off of initial guidance documents published, ultimately conflicting. Furthermore, there are approximately 260,000 laboratories currently participating within the CLIA program¹³ and as of 2015, the FDA estimated approximately 11,000 of these entities within the United States were permitted to use and develop LDTs⁴. Over five years later, one can only expect that this number has gone up significantly although it should be noted that there is currently no comprehensive listing of LDTs being used by laboratories¹⁴. Even based on the previous estimates however, adding LDTs to FDA purview would pose a significant burden and risk not only delaying the availability of LDTs, but also drugs and IVDs that are already experiencing significantly delayed review periods. In addition to the burden imposed, FDA oversight would conflict with the regulatory path Congress had already defined when the CLIA program was initiated altogether. If Congress had the intent for LDTs to be regulated by the FDA, they would have expressly granted them the authority to do so in 1988 and not given oversight to CMS⁴.

The most critical argument presented by opposers stems from exactly how the FDA has gone about attempting to impose their enforcement to date and ultimately questioned the sheer legality of these actions. The Agency has received significant backlash from a number of clinical organizations, including the American Clinical Laboratory Association (ACLA), that their intent to enforce LDT regulation through draft guidance violates notice and comment rulemaking

procedures that are outlined within the Administrative Procedure Act (APA). As a result, this has deprived stakeholders of their right to comment and challenge the substantive changes proposed, to which the FDA is required to consider. In addition to bypassing Congress in the process, the FDA also failed to consider economic impacts that are likely to result from such an extensive framework ⁴.

The ongoing COVID-19 pandemic has only further intensified this debate when the FDA mandated that any LDTs intending to screen for or diagnose COVID-19 would need to file an Emergency Use Authorization (EUA) prior to offering such test on the market ¹⁵. This was considered an unprecedented move as LDTs were never held to this standard previously and it was quickly challenged by the Department of Health and Human Services (HHS). Following announcement of their position on the matter, they removed all guidance documents describing premarket review of LDTs stating the FDA cannot enforce these requirements without following proper notice and comment rulemaking ¹⁶.

As conversations regarding LDTs have dragged on for years now, it seems as though stakeholders have lost focus on the existing regulatory gaps that pose the greatest risks to patient safety. Despite decades of debate on the topic, which has even included publication of numerous guidance documents and drafting of several legislative bills, the industry is no closer to implementing solutions to bridge these critical gaps now than it was when discussions began almost 30 years ago. For that reason, in the short-term, a modified approach should be considered. Currently, there are several other accrediting bodies following more robust frameworks that could provide guidance to improve the existing CLIA program. These examples include the New York State Department of Health (NYSDOH) through their Clinical Laboratory Evaluation Program (CLEP) ¹⁸ and the College of American Pathologists (CAP) Accreditation Program¹⁷.

The NYSDOH individually certifies CLIA laboratories who are intending to process specimens of New York state residents through CLEP. Prior to issuance of a NYSDOH permit,

laboratories are required to submit validation documents for all test systems offered and undergo an on-site survey. Although this process currently only operates on the state level, it does exemplify an existing, more successful model that could be adjusted and applied on a federal level ¹⁸.

The CAP accreditation program also builds on existing CLIA regulations in order to further ensure laboratory quality. It is a peer-based program in which participating laboratories inspect one another for initial accreditation and biennially thereafter ¹⁷. As many labs ultimately apply for CAP accreditation following CLIA certification, CAP already has delegated authority to inspect on behalf of CMS in order to satisfy routine CLIA inspection requirements ⁶.

Based on these frameworks, the existing CLIA program could potentially be altered to require an initial on-site inspection, which would include a review of analytical validation documents, prior to laboratories achieving CLIA certification and performing patient testing. As CMS already has oversight over the CLIA program, this modification would utilize existing resources for initial accreditation surveys who also have an understanding of clinical LDT applications. This would avoid placing undue burden on the FDA and further stretching their already limited resources. However, if CMS is unable to fully support this effort, CAP could provide additional support as they have already been approved for routine inspection of CLIA laboratories ⁶.

This modified process could be implemented in the short term as a more reasonable solution to address the most critical of patient safety concerns. However, as LDTs continue to increase in complexity and have DTC applications beyond the clinical space, additional conversations should continue among stakeholders to determine when more robust premarket review processes may be warranted. Any proposed classification schemes and regulatory frameworks that stem from this should undergo traditional notice and comment rulemaking following the APA to ensure the most sufficient approach is implemented and considers all potential impacts to stakeholders and patients alike.

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