REGULATORY FOCUS

The changing regulatory landscape for laboratory developed tests

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The COVID-19 pandemic has highlighted the importance of reliable and accurate diagnostic tests. Laboratory developed tests (LDTs) do not typically require premarket review. The US Food and Drug Administration (FDA) has repeatedly proposed more rigorous regulatory frameworks for LDTs but has been unsuccessful owing to concerns about the impact on test availability and innovation. In this article, the authors describe the existing regulations and consider both sides of the debate, including protecting the public from erroneous test results and the ramifications of requiring premarket review.

Introduction

Laboratory developed tests are in vitro diagnostic (IVD) tests designed, manufactured, and used within a single laboratory.[1] They can range in complexity, for instance, they could be a simple test to measure sodium levels, or a complex DNA analytic for genetic disease diagnosis. The COVID-19 pandemic has highlighted the importance of reliable diagnostic tests and quick development of novel assays but has also led to increased discussion of LDT

regulation. Regulation of LDTs is an area in which the FDA has proposed numerous draft guidances and documents over the past 2 decades. LDTs are classified as medical devices but do not generally require FDA clearance or approval before use because they are subject to "enforcement discretion." IVDs that are not LDTs do not receive enforcement discretion and must comply fully with medical device regulations, requiring 510(k) clearance or an approved premarket approval (PMA) before they can be legally used. If a diagnostic test fails to meet the criteria for an LDT but is being marketed or used as one, the test is not compliant with the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the FDA will act accordingly. It is therefore essential to understand whether a product legitimately qualifies as an LDT and how it is regulated. Here, the authors will discuss the distinctions between LDTs and IVDs, the impact that the reagents used in the diagnostic test can have, and the current regulatory guidance of LDTs and how it might change in the future.

LDT components

The classification of an LDT is partly dependent on its components. LDTs must use only in-house materials, general purpose reagents (GPRs), and analyte specific reagents (ASRs).[2] GPRs are chemical reagents that might commonly be used in a laboratory, such as a pH buffer. ASRs are substances essential to the function of the diagnostic test and which act as the "active ingredient" in the test. ASRs might be "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reactions with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens" (21 CFR 864.4020). LDTs can use GPRs and ASRs manufactured by parties other than the laboratory developing the LDT – this does not affect the single laboratory requirement for the LDT.

Regulation of ASRs and ASR manufacturers

Manufacturers of ASRs must comply with more regulations than the manufacturers and users of LDTs because of the possible wider distribution of ASRs and their possible use in different tests. ASRs are medical devices regulated by the FDA and so must comply with current good manufacturing practices, medical device regulations (21 CFR Part 820) and the ASR regulations (21 CFR 809.10(e), 809.30, 864.4020)).[3] The ASR regulations include classifications of ASRs as Class I to III medical devices, sale and distribution restrictions, and labelling requirements. The class of a medical device refers to the level of risk posed to the patient, or user, by the device. For example, Class I medical devices are generally deemed a low safety risk, with Class III medical devices being the highest risk. Most ASRs are classified as Class I medical devices and so do not require 510(k) clearance or PMA premarket notification. If ASRs are used in tests in blood banking, donor screening, and certain infectious diseases they may be Class II or Class III, and such tests would require FDA clearance or approval due to regulations for human blood and blood components (21 CFR 864.4020). Manufacturers of ASRs must comply with the FDA's postmarket requirements, including establishment registration, device listing, and medical device reporting requirements. ASRs can be sold for clinical

diagnostics only to laboratories certified through the Clinical Laboratory Improvement Amendments (CLIA) program, or elsewhere for use in nonclinical or research testing. The CLIA program regulates clinical laboratory testing on human specimens in the US (see Regulation of LDTs). Laboratories that perform LDTs using an ASR must include a statement with the test report as follows: "This test was developed, and its performance characteristics determined by, [Laboratory Name]. It has not been cleared or approved by the US Food and Drug Administration" (21CFR809.30).

Impact of components on LDTs

If a component in an LDT is manufactured outside of the development laboratory and is not classified as an ASR, it may result in the LDT being classified as an IVD and therefore subject to regulation enforcement. This is because of the potential risk in using components not necessarily manufactured to the standards with which ASR manufacturers must legally comply. If a product does not qualify as an ASR it may be treated by the FDA as an IVD or IVD component and cannot be used in an LDT.

ASRs and GPRs cannot be labelled or marketed for a specific diagnostic test or clinical use, or include any validation claims beyond scientific information on what the component binds to (21 CFR 864.4010(a)). For example, any product that includes an ASR in a combination (e.g., a test kit) is no longer classed as an ASR because a laboratory buying the mixture cannot appropriately validate it. Similarly, any components designed for use in a specific assay or diagnostic test are not ASRs, because that would involve the manufacturer making a validation claim that the component works when used in a specific system. It is interesting to note that laboratories are able to use FDA-approved and non-FDA approved tests as their own LDTs, provided they are used in a way that was not intended or foreseen by the original manufacturer and are fully validated by the new laboratory for their new purpose.

As technology develops, there is discussion over whether more biologically complicated components, such as cells, could qualify as ASRs to be used in LDTs if they were produced by a manufacturer. One particular regulatory uncertainty for the medical device industry is around the classification of ASRs. Class I ASRs "do not operate using a different fundamental scientific technology than a legally marketed Class I ASR" (21 CFR § 864.9), so it is unclear whether more complex components could be categorised as a Class I device. The FDA has not specifically detailed whether a laboratory producing ASRs for internal-use only as a component of an LDT would be regulated as a medical device manufacturer. As such, production of cellular components would likely fall under the development of the LDT, so the laboratory would be subject only to CLIA requirements (see Regulation of LDTs) rather than to ASR regulations.

Regulation of LDTs

The FDA requirements for a diagnostic test to be classed as LDT, and therefore subject to regulatory discretion, include single laboratory development and use, authorized physician instruction, and CLIA certification and accreditation. First, the development and performance of the test must be conducted by a single

laboratory. The test can no longer be classified as an LDT if any aspect of the LDT extends beyond a single laboratory, such as the test having been developed in a separate laboratory, used in multiple laboratories, or relying on third party manufacturers for critical components not deemed ASRs, and will instead be classed as an IVD. Second, the LDT must be performed because of an instruction from an authorized physician or healthcare professional. An LDT cannot be offered direct-to-consumer, and a physician ordering the test must be independent from the laboratory offering the LDT. Third, the laboratory must be appropriately certified under the CLIA program[4] as able to "perform high-complexity testing." The single laboratory requirement for test development and use refers to a single CLIA certification.

The CLIA require laboratories that perform clinical testing (including IVDs and LDTs) to be certified by the Centers for Medicare and Medicaid Services (CMS) before accepting materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or the impairment of, or assessment of the health of human beings (42 CFR Part 493). CLIA requirements for certification depend on the complexity of tests conducted by the laboratory; LDTs are classed as high complexity and as such, the requirements include demonstration of the analytical validity of the test, quality assurance protocols, and presence of qualified personnel (42 CFR 493). The focus of the CLIA is to ensure accurate and reliable diagnostic test results. Laboratories must receive CLIA certification before releasing any test results and will be inspected by the CMS to ensure compliance with the requirements. All analytical validity assessments are conducted only within the laboratory because the test will be used only within the laboratory and therefore validation conducted outside the laboratory environment is not necessary or relevant. The validation is reviewed during its routine two-yearly survey.

There are no CLIA requirements for clinical validity, meaning there is no assessment of how well a test can diagnose or predict a clinical condition. Instead, the CMS evaluates whether the test successfully detects the substance it is designed to detect, for instance, assessing whether a test can accurately and reliably measure the presence of a biomarker associated with lung cancer rather than assessing whether the test can accurately diagnose lung cancer. Clinical validity requirements fall under FDA authority in the FD&C Act during the premarket review, something with which LDTs are not required to comply via enforcement discretion.[5] LDTs are also not required to comply with the FDA's quality system regulations. However, enforcement discretion toward LDTs does not equal exemption, and the FDA can chose to enforce full regulatory compliance of an LDT "when appropriate, such as when it is appropriate to address significant public health concerns."[6] In summary, the FDA focuses on ascertaining the safety and effectiveness of a diagnostic, and, if it is an IVD, the design and manufacture quality, whereas the CMS checks the scientific performance of the test.

Consequences of improper LDT usage and marketing

If a diagnostic test is being marketed incorrectly as an LDT, the FDA will communicate with the laboratory. This may take the form of an informal email

or letter to request further information about a test, or a warning letter identifying regulatory violations. A warning letter is the most significant of these and is made publicly available, requiring a company response within 15 days. A warning letter may require that the diagnostic test needs a premarket review by the FDA or it may require changes to labelling or marketing claims, unless perceived regulatory violations are suitably clarified by the laboratory.

Warning letters have previously been received by laboratories that have not complied with the LDT requirement for one-site development, for example, where a test has been developed by an academic or commercial laboratory but then sold or transferred to a different laboratory for use in the same capacity.[7,8] It is not possible for the design of an LDT to be transferred or contracted from one laboratory to another. The FDA has not given specific detail on how much information can be provided to an LDT developer by an external party; provided the laboratory has obtained any information as reference information only, and has conducted all design, development, and validation independently, it should not affect the LDT status. Letters from the FDA have also been received by companies relying on external manufacturers for key components that are not ASRs.[9]

The FDA has issued warning letters to several companies offering LDTs on a direct-to-consumer basis, instead of through the instruction of a physician as required.[3] There has been a significant rise in the number and range of direct-to-consumer genetic tests available, and subsequently in the potential risk to public health posed by incorrect or unreliable tests. It is essential that consumers correctly understand the test results provided to them and that they interpret them correctly, taking physician guidance before making any medical decisions. The FDA has issued a number of letters to such companies offering tests without valid clinical evidence, for example, tests claiming to predict a patient response to a named drug based on genetic variants.

A major concern with such a test is that a patient may alter the dosage of a drug they are taking in response to a test result, without having an appropriately informed understanding of the impact that could have. Companies offering genetics tests to predict patient response to a drug have generally taken action to remove specific medication names from their marketing to address concerns from the FDA. Inova Genomics Laboratory stopped performing some of their pharmacogenomic tests after receiving a warning letter from the FDA in 2019 advising that their LDT required a PMA, and to correct their company view that their test was “exempt” because it was an LDT. The FDA made it clear that an LDT would be subject to enforcement discretion and not exemption.[6]

Changes in FDA regulation and guidance of LDTs

Given the increasing number of LDTs and their growing complexity, the FDA has been keen to evolve the regulatory framework governing them in order to ensure public safety. The FDA has regulated medical devices, including diagnostic tests, since the Medical Device Amendments of 1976.[10] At that time, LDTs tended to be simple “in-house” tests for rare diseases and were deemed to be low risk, so the FDA chose to waive compliance with the medical device

regulations for such products. LDTs have since become well-used tools developed by large companies and used on many patients. This means large patient populations could be at risk if a test result is not clinically validated or is falsely labelled and where adverse events are not reported.

FDA changes in LDT regulation following the Medical Device Amendments have tended to involve guidance documents and regulation of subsets of LDTs or their components. In 1997, instead of updating the regulation on LDTs directly, the FDA declared the regulation of ASRs within LDTs.[1] As the use of software and automation in diagnostic testing increased, the FDA issued draft guidance for in vitro diagnostic multivariate index assays[11] requiring LDTs that use complex algorithms to diagnose high-risk diseases. For example, gene expression profiling assays for breast cancer prognosis must obtain 510(k) clearance or PMA authorization. In 2014, the FDA aimed to introduce premarket reviews of most LDTs and published a draft guidance for a risk-based framework for their assessment. In 2015, to highlight the importance of increased regulation, the FDA published a report on 20 case studies of LDTs that either caused or could have caused harm to patients.[12] With the change of presidential administration in 2016, the draft guidance for LDTs was not finalized and a discussion paper was instead published in 2017,[13] with a suggested scaled back regulatory approach based on comments received on the draft guidance.

As the COVID-19 pandemic began to have a greater global reach in 2020, the FDA required laboratories to obtain emergency use authorization (EUA) before use of molecular-based SARS-CoV-2 LDTs. However, following push back by the industry, the FDA then stated laboratories could conduct tests while their EUA was under review by the agency, provided the test had been validated. In August 2020, the Department of Health and Human Services (HHS), the recipient of the data for SARS-CoV-2 tests being conducted, announced that the FDA must introduce new official rules to require premarket review for LDTs, rather than guidance documents or website statements ("Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests"[14]). However, this HHS announcement is no longer available on its website. Legislation for the Verifying Accurate Leading-Edge In Vitro Clinical Tests Development Act of 2020 (VALID Act) has been reintroduced recently in July 2021, proposing separation of in vitro clinical tests from the existing medical device regulation and establishment of regulatory framework for LDTs and IVDs through a new FDA Center. This suggested legislation would require laboratories to comply with new requirements for registration with the FDA and, depending on the risk classification of their LDT, potentially with quality requirements, premarket review and approval and adverse event reporting.

Much of the discussion arguing against increased regulation of LDTs surrounds the increased costs, time and efforts surrounding premarket review, which may lead to fewer tests being developed and performed, and consequently impact patients. There are also concerns around the transparency of proposed risk classifications of LDTs, and whether the existing LDTs would be required to comply with any new regulations – which would be a significant undertaking.

Whilst some LDTs are being developed at the cutting-edge of genetic science, others are the same tests as IVDs currently on the market that have been approved or cleared by the FDA. However, the latter group of LDTs may be cheaper or have been adapted to be conducted in-house. The ramifications of increased regulation still require consultation and practical discussion.

Conclusion

Scientific technology has made very significant advances since the medical device regulations were first established. Many of the suggestions and proposals for increased regulation of diagnostic tests, particularly LDTs, have been met with backlash from those who feel such regulation would reduce patient access to clinical tests and hinder the development of novel diagnostics. This has been particularly apparent during the global pandemic where much of the spotlight has been on rapid access to testing. However, as diagnostic tests become more complex and their use becomes common place, the potential risk of harm to patients from unreliable and inaccurate tests is increasingly high in terms of both reach and individual consequences. Greater regulatory oversight through new legislation and FDA regulation such as the VALID Act, or through updates to the CLIA and involvement of the CMS, may need to be considered in order to protect public safety.

Abbreviations

ASR, analyte specific reagent; **CLIA,** Clinical Laboratory Improvement Amendments; **CMS,** Centers for Medicare and Medicaid Services; **DTC,** direct-to-consumer; **EUA,** emergency use authorization; **FD&C,** Federal Food, Drug, and Cosmetic Act [Act]; **FDA,** [US] Food and Drug Administration; **GPR,** general purpose reagent; **HHS,** Department of Health and Human Services; **IVD,** in vitro diagnostic; **LDT,** laboratory diagnostic test; **PMA,** premarket approval; **VALID,** Verifying Accurate Leading-edge In Vitro Clinical Tests Development [Act].

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References

All references accessed 26 August 2021.

1. Food and Drug Administration. Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) [draft guidance]. https://www.fda.gov/regulatory-

information/search-fda-guidance-documents/framework-regulatory-oversight-laboratory-developed-tests-ldts. Issued 2014, current as of 13 July 2018.
2. Food and Drug Administration. Medical devices; classification/reclassification; restricted devices; analyte specific reagents [21 CFR Parts 809 and 864]. https://www.govinfo.gov/content/pkg/FR-1997-11-21/pdf/97-30564.pdf. Federal Register, Rules and Regulations. 1997;62(225):62243.
3. Food and Drug Administration. Commercially distributed analyte specific reagents (ASRs): Frequently asked questions [draft guidance]. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/commercially-distributed-analyte-specific-reagents-asrs-frequently-asked-questions. Issued 2007, current as of 13 March 2018.
4. Food and Drug Administration. Clinical Laboratory Improvement Amendments. Subpart 2—Clinical laboratories §263a. Certification of laboratories (42 USC 263). 1988:371-8. https://www.govinfo.gov/content/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapII-partF-subpart2-sec263a.pdf.
5. Centers for Medicare and Medicaid Services. Clinical Laboratory Improvement Amendments – LDTs and CLIA FAQs. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf. Dated 22 October 2013.
6. Food and Drug Administration. Warning letter – Inova Genomics Laboratory. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/inova-genomics-laboratory-577422-04042019. Dated 4 April 2019.
7. Food and Drug Administration. Warning letter – Laboratory Corporation of America. https://www.fdalabelcompliance.com/letters/ucm1048114. Dated 29 September 2008.
8. Food and Drug Administration. Warning letter – Exact Sciences Corporation. https://www.fdalabelcompliance.com/letters/ucm076536. Dated 11 October 2007.
9. Food and Drug Administration. Warning letter – deCODE Genetics. https://www.fda.gov/media/79216/download. Dated 10 June 2010.
10. Food and Drug Administration. Medical Device Amendments of 1976. https://www.govinfo.gov/content/pkg/STATUTE-90/pdf/STATUTE-90-Pg539.pdf. Dated 28 May 1978.
11. Food and Drug Administration. In vitro diagnostic multivariate index assays [draft guidance]. https://www.fda.gov/media/71492/download. Issued July 2007.
12. Food and Drug Administration. The public health evidence for FDA oversight of laboratory developed tests: 20 case studies. http://wayback.archive-it.org/7993/20171115144712/https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf. Dated 16 November 2015.
13. Food and Drug Administration. Discussion paper on laboratory developed tests (LDTs). https://www.fda.gov/media/102367/download. Dated 13 January 2017.
14. Sarata AK. Congress Research Service. HHS announcement on FDA premarket review of laboratory-developed tests (LDTs) [prepared for members and committees of US Congress]. https://crsreports.congress.gov/product/pdf/IN/IN11548. Dated 30 December 2020.

Additional reading

— Spitzenberger, et al. Laboratory developed tests: Design of a regulatory strategy in compliance with the international state-of-the-art and the Regulation (EU) 2017/746 (EU IVDR [In Vitro Diagnostic Medical Device Regulation]). https://link.springer.com/article/10.1007/s43441-021-00323-7. 21 July 2021.
— Centers for Disease Control. Lab Alert: FDA suspends review of EUA requests for laboratory-developed tests for SARS-CoV-2. https://www.cdc.gov/csels/dls/locs/2020/fda_suspends_review_of_eua_requests_for_lab_developed_tests_for_SARS-CoV-2.html. Dated 9 October 2020.
— Association for Molecular Pathology. Regulation of laboratory developed testing procedures (LDPs). https://www.amp.org/advocacy/laboratory-developed-testing-procedures-ldps1/. Not dated.