



PPD clinical research business of Thermo Fisher Scientific

CRO Regulatory Landscape

Navigating the changing regulatory landscape for laboratory-developed tests: A CRO lab perspective.

Laboratory-developed tests (LDTs) often play a vital role in drug development and clinical trials. Recent regulatory proposals in the U.S. and regulatory changes in the EU must be considered when performing trials in these countries. This article describes the evolving regulatory landscape for LDTs and, in particular, the challenges for developing next-generation sequencing (NGS) assays for gene-based therapies and vaccines.

REGULATORY LANDSCAPE FOR LDTs

An LDT is a type of *in vitro* diagnostic test that is designed, developed, manufactured, validated, and used by a clinical laboratory. In the U.S., laboratories conducting LDTs are governed by Clinical Laboratory Improvement Amendments (CLIA) regulations, the federal program of the Center for Medicare and Medicaid Services (CMS). CLIA certification ensures that laboratories are performing tests accurately and reliably. Additionally, laboratories may choose to be accredited by the College of American Pathologists (CAP). The CAP guidelines aim to ensure quality of data and processes through regular proficiency testing and inspection of laboratories every two years.

The current system exercises enforcement discretion of LDTs to CLIA laboratory directors, so that the primary requirement is CLIA certification. The U.S. government is considering changing this system and requiring additional regulatory oversight of LDTs. A bill under discussion in Congress, called the Verifying Accurate Leading-edge IVCT (*In Vitro* Clinical Test) Development Act of 2021 (VALID Act), is currently in committee in both the House and Senate, and further changes are expected before the bill is moved forward for a vote. One of the likely changes is the addition of a “grandfathered”

provision for legacy tests so that LDTs currently in use would not be required to follow the new regulations. Because LDTs are always based on unmet needs, however, new LDTs are continually being developed and would need to be approved by the U.S. Food and Drug Administration (FDA). This proposed approval process is likely to slow the development of LDTs, which could hinder drug development. Proponents of an alternative plan suggest modernizing the CLIA regulations to provide more oversight but avoid slowing down development and clinical trials.

While changes in the U.S. are under debate, a new rule has come into effect in the European Union (EU). The EU’s *In Vitro* Diagnostics Medical Devices Regulation 2017/746 (IVDR) became applicable on May 26, 2022. EU laboratories must use commercial assays that: 1) have the CE marking, certifying that they have met EU health, safety, and environmental requirements; and 2) comply with the IVDR or, if a commercial test doesn’t meet patient needs, they can use an LDT (referred to as an in-house device) that complies with Article 5.5 of the IVDR. Although the LDT itself does not receive a CE mark, it may help facilitate the validation of the assay to use instruments and consumables that are CE-marked because the quality of these products is known. The IVDR uses a new risk-based classification system that specifies four risk classes ranging from low (class A) to high (class D) risk for individual and public health.

The IVDR can be seen as a road map for potential changes to U.S. regulations. It is expected that changes to the U.S. regulations will include some of the principles of the IVDR, particularly the concept of risk-based categories. In the U.S., however, stakeholders are working to further define risk subcategories to

provide clarification for how LDTs will be classified.

The UK's health authority is also working on regulations for LDTs. These are expected to be similar to the IVDR.

For all regulatory bodies, it is essential to ensure that the LDT has robust quality and is well validated. It is also essential to determine how data from the LDT will be used. If it is intended for research use only without any impact on the therapy of a specific patient, it is considered no risk and is exempted from the IVDR regulations. If data will affect patient treatment, it is considered higher risk. Therefore, a clinical research organization (CRO) lab should have the scientific and technical capabilities as well as the infrastructure to develop, validate and perform LDTs.

One category of LDTs that is rapidly advancing for both exploratory research and patient treatment is next-generation sequencing (NGS), which is used in the development of cell and gene therapies.

ADDRESSING CHALLENGES FOR NGS LDTs

NGS provides rapid identification of genetic changes for research and exploratory early drug development, as well as for diagnostic testing in clinical trials and clinical practice. These NGS-based LDTs increasingly are being used for the diagnosis of cancer, hereditary disorders, and infectious diseases.

Due to the complexity of genetic diseases, however, NGS-based LDTs may, in some cases, result in conflicting results on a given variant's penetrance and pathogenicity. To mitigate this challenge, LDTs should be carefully designed to cover the mutation region with targeted sequencing. In certain cases, error correction is crucial to prevent high error rates with NGS LDTs. This can be achieved either at library construction or by optimizing the analytical pipeline.

Selecting the optimal platform for an NGS assay is crucial. A CRO lab should communicate with the client to first determine what they are trying to achieve and then propose the best solution. NGS platforms continue to evolve, as suppliers develop new platforms, improved flow cells and chemistries. A lab must validate assays and analytical pipelines while maintaining version control with these new tools as they are introduced.

For EU laboratories qualifying as health institutions to gain approval for NGS LDTs under the IVDR, both sample preparation and data analysis must be well validated. Standardized processes aid in obtaining the reproducibility necessary for approval.

BEST PRACTICES FOR LDTs

Efficient development of validated LDTs is crucial for the progress of clinical trials. The first step for any trial protocol is to determine what tests are needed. Is an FDA-approved or CE-marked test commercially available? If not, an LDT is needed. The second step is to determine what geographic areas will be involved in the trial. In global clinical trials, it is important to understand and comply with the regulations of each of the specific countries in which the trial and the associated laboratory

testing will occur. If these locations are determined, the sponsor can then apply for any required LDT approvals along with the submission of the clinical trial protocol approvals. If conducting trials in the EU, obtaining LDT approvals in this manner can save time in conducting the trial.

Once an LDT is validated, a clinical lab could use it for multiple clients, if applicable. The sponsor, however, is responsible for applying for approval for use of the LDT for their particular protocol for each relevant country.

The quality of data generated by LDTs is very important. A lab must ensure that the test method is accurate and reproducible. Any limitations to the test should be identified and disclosed prior to use in a clinical trial. In addition to the method, another component of test quality is the performance of the lab and its instruments. Certifications, such as the CAP program, are beneficial for ensuring that lab processes are high quality. In CAP's proficiency testing program, a lab is required to regularly test a standard sample and submit the results to be compared to the expected result. If the result is not accurate, corrective action can be taken. We recommend using a CAP-accredited lab that monitors the quality of its data.

KEY TAKEAWAYS

It is crucial that test data from LDTs are of a high quality. A lab that is certified and regularly evaluated by regulatory authorities helps ensure quality of data globally. With the new requirements for LDTs in the EU under the IVDR, it is important to both have quality data and to submit applications for the necessary LDT approvals in a timely manner. A CRO laboratory with understanding of global regulatory requirements can help its clients navigate the current and evolving regulatory landscape to avoid delays to clinical trials and to speed the drug development process. **CP**



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