



Science Policy News



American Society for Investigative Pathology
Investigating the Pathogenesis of Disease

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

The American Society for Investigative Pathology (ASIP) appreciates the opportunity to engage in dialogue with the Food and Drug Administration (FDA) concerning its Proposed Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) [Docket N. FDA-2011-D-0360], which we refer to here as the “**FDA Draft LDT Guidance**.” ASIP is a nonprofit educational organization of approximately 1,350 scientists who primarily work in academic medical centers in the United States. Our members investigate disease, linking the presentation of disease in the whole organism to its fundamental cellular and molecular mechanisms using a variety of structural, functional, and genetic techniques. As investigative pathologists, we partner with other physicians to determine the most appropriate ways to diagnose and treat patients.

LDTs are the product of basic and clinical research and represent the power of translational research to advance modern precision medicine. The regulation of LDTs presents challenges in both the scope and the intrinsic complexity associated with the way they are performed in the clinical laboratory and ultimately how they affect patient care. It is vital that any regulatory framework for LDTs strike the right balance so that patients are best served by having access to cutting-edge and innovative laboratory tests that are safe, precise, and appropriate to guide treatment decisions.

For many years, academic departments of pathology and their associated clinical laboratories have been intimately involved in the non-commercial development and implementation of LDTs. Many of the scientific and clinical discoveries and other innovations that underlie the development of LDTs were first made in academic departments of pathology, and their



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associated clinical laboratories are often first to make such LDTs available to patients and their caregivers. LDTs are typically developed and implemented by clinical laboratories in academic departments at the request of and in close collaboration with clinical caregivers in the same health care system in response to the rapid advance of new diagnostic and prognostic criteria and new therapeutic opportunities. As such, these tests fill important gaps in the ability to effectively diagnose and/or characterize significant disease states and guide treatment. With regard to LDTs, ASIP's goals are to:

- Ensure patient access to cutting edge but safe and reliable tests to improve patient care and treatment options;
- Ensure that the quality and reliability of LDTs be maintained at the highest levels possible; and
- Avoid unnecessary, costly, and burdensome regulatory restrictions that would limit or deny patient access to life-saving and life-enhancing laboratory diagnostics.

Recommendations

ASIP makes the following observations and recommendations:

1. LDTs are already highly regulated under a three-part framework that consists of CLIA, state and local laws, and accreditation by deemed authorities, all of which require extensive validation of the quality of diagnostic services. The FDA Draft LDT Guidance would impose an additional regulatory framework that would be largely duplicative, costly, and potentially have significant unintended negative consequences by denying patients safe, reliable, cutting edge tests. Patients may be denied potentially life-saving treatments or may be treated unnecessarily and/or ineffectively (for example, mutational analysis of *RAS* genes by LDTs can render unnecessary costly tyrosine kinase inhibitor treatments of certain cancers).
2. One of the major drivers of the proposed FDA Draft LDT Guidance is that CLIA does not require that all LDTs undergo clinical validation (although CLIA does require both test and analytical validation). Although technically correct, there appears to be a central misunderstanding on the part of the FDA in this regard. Virtually all clinical laboratories in academic medical centers achieve their CLIA certification through inspection and accreditation by the College of American Pathologists (CAP), which includes review of clinical validation of LDTs. Therefore, in practice, academic departments offering LDTs within their healthcare system are engaged not only in test validation and analytical validation but also in clinical validation. ASIP urges the FDA to perform a detailed review of CAP inspection and accreditation practices to verify that test, analytical, AND clinical validation are currently required in order to achieve CAP accreditation.
3. FDA may not fully understand the LDT landscape and the implications of its proposed oversight mechanisms. We estimate that there are tens of thousands of LDTs currently provided across academic medical centers, to say nothing of those in other



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environments. **It is essential that FDA fully and completely evaluate the use of LDTs within the current healthcare system before proceeding with any guidance or rule-making efforts and that the economic impact of new regulations be fully considered before implementation of new enforcement.** ASIP is concerned that thousands of LDTs may no longer be available to patients because of the increased cost and time associated with unnecessary and burdensome regulations. **Before proceeding to increase oversight of LDTs, FDA should proceed with its Notification Guidance to collect essential facts about the LDTs currently offered.**

- a. The notification process should focus on providing basic information and should utilize previously utilized data fields, such as those in use in the Genetic Test Registry, so as to streamline the data-gathering process by the affected laboratories.
 - b. After collection of the data, FDA should consider the scope of the LDT landscape and provide a framework that would be practical and consistent with its workforce and budget. It is critical that patients not be harmed by unnecessarily delayed or denied access to these tests.
4. FDA should work with other Federal agencies, such as the Centers for Medicare and Medicaid Services (CMS) and the National Institutes of Health (NIH), to modernize and harmonize existing regulatory frameworks, and to recommend new legislation to streamline the statutory authorities of the various Federal agencies.
- a. FDA should consult with certified laboratory professionals (pathologists, geneticists, chemists, microbiologists), clinicians, patients, researchers, and payer organizations to clarify and better define proposed regulations and a timeline for enforcement.
 - b. FDA should consider lessons from the National Science Board's recently released report [<http://www.nsf.gov/pubs/2014/nsb1418/nsb1418.pdf>]: "Reducing Investigators' Administrative Workload for Federally Funded Research." Although primarily addressing the need to harmonize and streamline administrative burden on researchers, the NSB report has important recommendations concerning the lack of consistency and standardization of regulatory requirements across Federal agencies.
5. FDA should take a more nuanced approach to oversight of LDTs.
- a. FDA should cease trying to retrofit regulation of LDTs as medical devices. The nature of LDTs is not consistent with the design and manufacture of devices that are intended for sale and physical distribution; therefore, many manufacturer reporting requirements are inappropriate for LDTs.



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- b. FDA has artificially separated the provision of laboratory developed procedures into manufacturing and testing components, but these two processes are inextricably linked in the clinical laboratory.
 - c. FDA should recognize that academic medical center laboratories are not manufacturers.
 - d. FDA's priority should be oversight of mass marketed, complex tests that rely on non-validated, computer-generated algorithms ("black box").
 - e. FDA should recognize that reference laboratories serve a vital role in providing innovative and cost-effective tests to patients outside their healthcare system.
6. FDA is considering exercising enforcement discretion by exempting LDTs for forensic purposes, for transplantation when used in a CLIA-certified high-complexity histocompatibility laboratory, and for unmet needs such as rare diseases. ASIP notes that the FDA definition of rare diseases is too restrictive, especially since some LDTs are used for screening purposes applied to a broad population (significantly more than 4,000), expecting only a very small percentage to test positive.
7. If FDA proceeds with its Draft LDT Guidance, ASIP strongly urges the expansion of enforcement discretion to exempt LDTs that meet all of the following criteria:
 - a. The LDT is performed in laboratories whose directors are certified pathologists, geneticists, clinical chemists, or microbiologists (American Board of Pathology, American Board of Medical Genetics and Genomics, American Society for Microbiology, American Board of Clinical Chemistry, AABB, etc);
 - b. LDTs are performed in CLIA-certified laboratories that are accredited by deemed authorities requiring test, analytical and clinical validation;
 - c. The LDT is not marketed directly to the public but instead is developed at the request of and in consultation with treating physicians to provide appropriate tests to patients within the same healthcare system or patients who are referred for testing by their caregivers in another healthcare system (qualified reference laboratory); AND
 - d. The LDT is not a highly complex test that utilizes "blackbox" computer algorithms that cannot be easily validated.
8. Any additional guidance or rule-making should foster innovation and accommodate the dynamic nature of LDTs, which are frequently modified to improve their performance and enhance patient care as new data become available.

Sincerely,



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A handwritten signature in black ink that reads 'Mark E. Sobel'.

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Executive Officer

Cc:

Margaret A. Hamburg, MD, Commissioner, Food and Drug Administration

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