How Will the FDA Impact the Laboratory Developed Test?

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How skilled are you at completing a Food and Drug Administration (FDA) pre-market approval or 510-K application? If your laboratory has developed tests in-house (also known as "home brew" and now termed laboratory developed tests or LDTs) and changes proposed in Washington actually occur, these terms may become part of our everyday vocabulary.

The FDA currently regulates most LDTs, through the reagents used, by the Analyte Specific Reagent (ASR) rule. This rule requires the laboratory using the reagent to perform its own method validation and include a comment in the test report that FDA approval is not required. However, given the rapid growth of gene and protein-based tests, some say additional regulation is needed to protect the public.

Last fall the FDA issued draft guidance stating it will require FDA premarket approval for *in vitro* diagnostic multivariate assays (IVDMIA). These assays pair a laboratory test with software or an algorithm that produces a result specific for the patient in question. Unfortunately, the performing laboratory cannot completely validate the test method, and the ordering physician cannot interpret results, without access to proprietary information. The FDA believes these test systems exceed ASRs and warrant further regulation because the novel technologies have a risk of lethal outcomes.

Two bills have also been introduced in Congress that mandate additional regulation of LDTs. First, the "Laboratory Test Improvement Act" (S.736) is sponsored by Edward Kennedy (D-MA) and Gordon Smith (R-OR). It would classify most LDTs as Class II medical devices and some as Class III. The FDA classifies all medical devices, including clinical laboratory tests, as Class I, II, or III. Class I devices are the least regulated and include such items as bandages, hand-held surgical instruments, and exam-gloves. Class II devices have greater requirements, such as specific labeling, mandatory performance standards, and post-market surveillance. Class III devices require FDA pre-market approval before a manufacturer can market a product. In the case of an LDT, submission to the FDA regarding the analytical and clinical validity would be required before patient testing is performed. If the FDA finds any deficiencies in the submission and FDA concerns are not satisfied, the laboratory would have to seek approval through a 510-K or pre-market approval (PMA) process. The appropriate process for approval would depend on whether a predicate device has already been approved for the test the laboratory is submitting. Test manufacturers are currently responsible for completing this very complex process.

In addition to requiring FDA approval, S.736 would require:

- an explanation of intended use,
- registration of the laboratories that manufacture LDTs, and
- the reporting of adverse reactions.

The paperwork alone for LDT FDA approval could easily overwhelm both laboratories and the FDA. While laboratories contend that analytical regulation occurs through CLIA, as all LDTs are classified as high-complexity tests, proponents say that clinical validity should also be regulated.

Secondly, Senator Barack Obama (D-IL) and Richard Burr (R-NC) are sponsoring the "Genomics and Personalized Medicine Act". S.976 is a broad initiative that seeks to "secure the promise of personalized medicine…, expanding and accelerating genomics research and improve the accuracy of disease diagnosis." The legislation would instruct the secretary of Health and Human Services (HHS) to form an interagency working group to facilitate and coordinate activities related to genomics and personalized medicine. The secretary would also contract with the Institute of Medicine (IOM) to perform an 18-month study and make recommendations regarding the regulation of genetic testing. Other provisions of S. 976 include initiatives for training more health professionals in the field of genomics and the creation of a new CLIA specialty area for molecular and genetics clinical tests.

Washington Beat is intended to provide a timely synopsis of activity in the nation's capitol of importance to clinical laboratory practitioners. This section is coordinated jointly by Judy Davis and Linda Comeaux, Co-chairs of the ASCLS Government Affairs Committee; and Don Lavanty, ASCLS Legislative Counsel. Direct all inquiries to ASCLS, (301) 657-2768 ext. 3022, (301) 657-2909 (fax); or mail to ASCLS, 6701 Democracy Boulevard, Suite 300, Bethesda MD 20817, attn: Washington Beat.

While most clinical laboratory groups oppose the direction taken by the Kennedy legislation, the approach in the Obama bill is more acceptable. Slower, well-conceived changes, developed by panels of experts and stakeholders, are prudent, considering the growth of the genomics / personalized medicine fields. Concerns remain that a sudden mandate to support the clinical validity of all laboratory-developed tests could force some laboratories to discontinue these tests and could stifle development of new assays. Balance is needed between an environment that encourages the innovation required to develop new and needed tests and protecting the public.

Both bills have been referred to the Senate Health, Education, Labor and Pension Committee (HELP), chaired by Senator Kennedy. At press time, neither bill had moved significantly. A possible attempt to attach the Kennedy bill to FDA user fee reauthorization legislation, which must pass, did not occur. However, an amendment by Mr. Obama has been attached to the final Senate FDA reauthorization bill. The amendment requires an IOM study of the safety and quality of genetic testing and recommendations to improve the regulation of genetic testing. While the outcomes of these regulatory and legislative efforts are unknown at this point, clearly LDTs will be facing increased scrutiny in the near future and some sort of FDA approval process may be required.