FDA and LDTs—What’s Next?

The Administration is Claiming Power Over Laboratory-Developed Tests. However, the Lab Industry Disagrees.

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Laboratory-developed tests (LDTs) continue to proliferate. Companies are regularly announcing the introduction of new LDTs, and these tests are playing a more important role in diagnosis and patient management. Laboratories offering LDTs continue to file initial public offerings (IPOs). Given the pace of technological change and innovation, this trend towards rapid introduction and commercialization of new LDTs should continue.

One large question for the industry, though, is whether the FDA will regulate LDTs and, if so, how. For over twenty years, FDA has asserted that it has the authority to regulate LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (FDCA), and also that LDTs are subject to applicable device requirements. Over that same period, FDA has stated that it will exercise enforcement discretion and does not invoke that power. Industry watches warily for a change in policy.

RUO or IVD?

The seeming status quo notwithstanding, there continue to be developments that bear upon this key regulatory issue.

First, on November 22, 2013, FDA issued a warning letter to 23andMe. That warning letter attracted considerable attention, including major stories in the mainstream media. Given the national prominence of the laboratory and its offerings, the intensive coverage was not surprising.

One key point, though, that got overlooked was that FDA had challenged an LDT. There may be a variety of reasons why FDA decided not to exercise enforcement discretion here; for example, the agency has long viewed direct access consumer testing differently than tests ordered through physicians. That factor was cited in the letter. (Since the warning letter was issued, a new federal regulation allows consumers to obtain their test results directly.) Nevertheless, at its core, 23andMe was providing an LDT, and FDA publicly and explicitly took the position that this test was a device subject to the FDCA. The unusual facts and circumstances notwithstanding, the 23andMe warning letter rested on FDA’s assertion of its statutory authority over LDTs.

Second, on November 25, 2013, FDA issued its long-awaited Research Use Only (RUO) final guidance. One of the key goals of the document was to assist companies and FDA in determining whether a product was an RUO, which is essentially unregulated by FDA, or an in vitro diagnostic (IVD), which is subject to full regulation as a device. RUOs are important to the laboratory industry in developing and
running tests. A substantial curtailing of the sale of RUOs would affect the ability of laboratories to develop diagnostic tests, including LDTs.

FDA’s earlier draft RUO guidance had raised many questions. One of the principal questions concerned the agency’s position that a product labeled as an RUO could be considered an IVD because the laboratory was using the RUO in a diagnostic test. That is, FDA was saying that the regulatory status of the product could be governed by actual use, not just the manufacturer’s intended use. This approach ran contrary to well-established law and raised many practical concerns, such as whether RUO manufacturers were obligated to “police” their customers.

FDA seemed to have backed away from this approach in the final RUO guidance. The document does not say intended use is based on actual use. While the guidance does contain multiple restrictions on the behavior of RUO manufacturers, the controversial language equating actual use with intended use was excised.

That textual change seemed to resolve the controversy. And yet, the regulatory relationship between RUO manufacturers and laboratories post-Guidance remains fraught.

One key passage of the RUO guidance cites the “[s]olicitation of business from clinical laboratories” as a factor indicative of IVD status, not RUO status. The RUO guidance does not purport to say that an RUO-labeled product sold to a laboratory that does not conduct research is automatically a device. Still, this section is likely to make some RUO companies more wary about transactions with certain clinical laboratories.

In addition, the RUO guidance limits the ability of RUO companies to provide validation and other technical support to laboratory customers. As a result, many RUO manufacturers are retraining technical support staff and sales personnel on the way they interact with laboratories. The upshot will be that more laboratories will receive less help from RUO suppliers than in the past.

But even beyond the wording of the RUO guidance, FDA officials have continued to express discomfort with some activities of RUO manufacturers vis-a-vis laboratories. For example, at a conference on February 26, 2014, FDA officials indicated concern over manufacturers supplying RUOs to laboratories if they know the product will be used in an LDT. While in the four months since the issuance of the Guidance document FDA has not issued any warning letters or taken public enforcement action against RUO companies, it would be surprising if this pattern persisted. FDA has persistently expressed discomfort with industry practices regarding RUOs.

Wait, What Are They, Exactly?

The third important development relates to a fundamental aspect of LDTs: What, exactly, are they? Although FDA and industry have been talking about LDTs for years, there is no formal definition of that term. While FDA has said it would exercise enforcement discretion over LDTs, the agency has never provided a formal definition of an LDT.

That omission can be critical, and lead to some surprising outcomes. In recent months, there have been instances in which FDA has said that a test developed by a laboratory and run in that laboratory did not qualify as an LDT.

For example, FDA officials have now asserted that if a laboratory participated in the manufacturing or designing of an instrument used in the assay then the test is not an LDT. FDA has explained that the “enforcement exemption” applicable to LDTs does not extend to situations in which a laboratory is directly involved in these activities. The stated rationale is that laboratories did not engage in these kinds of activities when FDA began to exercise enforcement discretion.

From a purely semantic perspective, this position is puzzling. What test could be more truly “laboratory developed” than one where the laboratory itself—rather than a third party—developed the instrument? One could reasonably claim that this situation presents a “purer” LDT than a test incorporating materials not developed by the laboratory. In addition, the agency’s position appears inconsistent with one of its rare public statements as to what constitutes an LDT: “a class of [IVDs] that are manufactured, including being developed and validated, and offered within a single laboratory.” Nevertheless, FDA appears to be saying—at least informally—that a test offered by a laboratory may not be an LDT because the laboratory played a “nontraditional” role in test development. Similarly, FDA officials have publicly questioned the boundaries surrounding the permissible transfer of information and knowledge from the laboratory that initially developed the test to another laboratory that wishes to develop a test using the same markers.

Taken together, these developments do not fundamentally remake the legal landscape regarding LDTs. FDA has developed a proposal, though, that would substantially revise the regulation of LDTs. That proposal has not been released by the Administration. While its release would surely precipitate a battle in Congress and probably the courts before it could be finalized, the issuance of the document would have an immediate impact on LDTs, e.g., by heightening concerns by investors, and focusing more public attention on LDTs.

In the meantime, it remains clear that FDA strongly believes it has the authority to regulate LDTs. By curtailing RUO sales and support, FDA may reduce access to some of the tools used by some laboratories in developing LDTs, or at least the assistance the laboratories receive from vendors. And by establishing further restrictions on which tests are eligible for LDT status—albeit in a nonpublic fashion—FDA is nibbling away at the tests that can be provided as LDTs.

One can debate what FDA’s appropriate role is in regulating LDTs. There can be no debate, though, that FDA intends to play a role in regulating tests developed and then offered by laboratories.