Published on *The National Law Review* https://natlawreview.com

FDA Notifies Congress of Framework for Long-Awaited Guidance on Laboratory Developed Tests and Issues Final Guidance on Companion Diagnostics

Article By:

Linda D. Bentley

Laboratory Developed Tests

After many years of promising that it would be providing guidance on the regulation of laboratory developed tests (LDTs), the **Food and Drug Administration (FDA)** provided notice to Congress on July 31, 2014 that it intends to issue a draft guidance document entitled, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" and an accompanying draft guidance document entitled, "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)." The notice, which may be found here, includes the anticipated details of the draft guidance documents ("Draft Guidance").[1]

The FDA has consistently claimed that it has the authority to regulate LDTs, which it defines as in vitro diagnostic tests (IVDs) intended for clinical use and designed, manufactured and used within a single laboratory, as medical devices. As long as the single laboratory was a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA), however, the FDA generally exercised enforcement discretion in not otherwise regulating most LDTs. For a variety of reasons, including the increasing growth of personalized medicine and the introduction of technological advances that have enabled the use of IVDs in guiding critical patient care decisions, the FDA has decided that additional and more consistent and predictable regulatory oversight is necessary.

In the Draft Guidance, the FDA describes its proposed regulatory framework as a phased-in risk-based approach to the regulation of LDTs in a manner that is consistent with the FDA's current regulation of IVDs. This means that new LDTs could be subject to requirements for premarket review of higher-risk LDTs that have the same intended uses as IVDs that were (i) cleared for marketing by the FDA under section 510(k) of the Food, Drug and Cosmetic Act, or (ii) approved for marketing after submission, review and FDA approval of a premarket approval application, or PMA.[2]

For high-risk or Class III devices, the FDA has indicated that registration and listing requirements (with a notice option) and adverse event reporting will begin 6 months after the Draft Guidance is finalized with premarket review requirements (PMAs for Class III devices) beginning 12 months after the Draft Guidance is finalized for the highest risk devices. A 4-year phase-in will apply to the remaining high-risk devices. Devices that are already on the market would be allowed to remain on

the market during FDA's review and consideration of applications. The FDA's initial focus will likely be on (i) LDTs that act like already cleared or approved companion diagnostics, (ii) LDTs with the same intended use as an FDA-approved Class III medical device, and (iii) certain LDTs for determining the safety or efficacy of blood or blood products.

For moderate-risk or Class II devices, FDA registration and listing requirements (with a notice option) and adverse event reporting will begin 6 months after the Draft Guidance is finalized. Premarket notice requirements (510(k)s for Class II devices) will begin after the high-risk LDTs are completed (or 5 years after the Draft Guidance is finalized) with a 4-year phase in.

There will be a 12-month phase-in period for LDTs on the market at the time that the Draft Guidance is finalized which may be extended if an appropriate premarket application is made during that period.

For some manufacturers of LDTs, notification to FDA that they are developing LDTs 6 months after the Draft Guidance becomes finalized may take the place of registration and listing, although they will still be required to begin reporting significant adverse events.

The FDA will continue to exercise enforcement discretion for LDTs used solely for forensic purposes, certain LDTs for transplantation, low-risk LDTs, as well as LDTs intended for rare diseases and unmet needs where there is no FDA-cleared or approved alternative. However, the FDA may require compliance with certain non-review requirements such as registration, listing and adverse event reporting.

Additional details regarding the proposed framework for regulation and procedural and timing information are provided in the Draft Guidance and will be helpful for planning purposes, but the Draft Guidance will not be considered "issued" until at least 60 days after the July 31, 2014 notice to Congress. Although FDA received comments on its anticipated guidance for many years preceding the notice to Congress, it will consider additional comments for some period of time before the Draft Guidance is finalized.[3] Also, as is the case with all guidance documents, the final guidance will be a statement of the FDA's thinking on a particular topic and recomendations at the time that it is issued, and does not create or confer any rights nor bind the FDA. Alternative approaches may be used if they satisfy the applicable law and regulations.

Companion Diagnostics

On the same day the FDA provided notice regarding its intended LDT regulatory framework, it also issued a final guidance document entitled, "In-Vitro Companion Diagnostic Devices" (the Guidance). The Guidance, dated August 6, 2014, found here, made few revisions to the draft guidance which was issued 3 years earlier. The Guidance is intended to assist companies developing in vitro companion diagnostic devices (IVD Companion Diagnostics) and companies developing therapeutic products that depend on the use of a specific IVD Companion Diagnostic for the safe and effective use of the therapeutic product.

The FDA defines an IVD Companion Diagnostic as a device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. If the FDA determines that an IVD Companion Diagnostic is essential to the safe and effective use of a new drug or a new indication for an already approved drug, it will not approve the new drug or the new indication unless the IVD Companion Diagnostic is also cleared or approved for that indication. The FDA expects that the therapeutic sponsor will address the need for an approved (PMA) or cleared (510(k)) IVD

Companion Diagnostic in its product development plan in most cases, but recognizes that there are certain situations in which contemporaneous clearance or approval of the drug and IVD Companion Diagnostic may not be possible.

The FDA had already approved 18 IVD Companion Diagnostics, all of which were linked to cancer drugs, as of the date of the Guidance, and it encourages sponsors of IVD Companion Diagnostics and the related therapeutic drugs to meet early with the relevant review divisions at the FDA to solicit pre-submission feedback.

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[1] The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) required the FDA to provide Congress with at least 60 days' notice of its intent to issue draft guidance on the regulation of LDTs.

[2] The FDA acknowledged that many tests being marketed as LDTs don't meet its definition of an LDT and therefore are out of compliance with the Food Drug and Cosmetic Act. Nevertheless, it intends to apply the same risk-based approach set forth in the Guidance Documents to any IVD being offered as an LDT by a CLIA laboratory.

[3] The FDA has on occasion published draft guidance documents that have never been finalized.

National Law Review, Volume IV, Number 237