2011-167
CDRH201130

4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-D-0360]

Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of the draft guidance entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)." This document describes a risk-based framework for addressing the regulatory oversight of a subset of in vitro diagnostic devices (IVDs) referred to as laboratory developed tests (LDTs), which are intended for clinical use and designed, manufactured and used within a single laboratory. This document describes FDA's priorities for enforcing pre- and post-market requirements for LDTs, and the process by which FDA intends to phase in enforcement of FDA regulatory requirements for LDTs over time. This draft guidance is not final, nor is it in effect at this time.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 120 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: An electronic copy of the guidance document is available for download from the Internet. See the SUPPLEMENTARY INFORMATION section for information on electronic access to the guidance. Submit written requests for single hard copies of the draft guidance document entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" to the Office of the Center Director, Guidance and Policy Development, Center for Devices and Radiological Health (CDRH), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5431, Silver Spring, MD 20993-0002, or the Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your request. The guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 240-402-7800.

Submit electronic comments on the draft guidance to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify comments with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: LDTframework@fda.hhs.gov; or Katherine Serrano, Center for Devices and Radiological Health, Food and Drug Administration, Bldg. 66, rm. 5646, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 240-402-4217; or Stephen Ripley, Center for Biologics Evaluation and Research Food and Drug Administration, 10903 New Hampshire Ave., Bldg.71, rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

In 1976, Congress enacted the Medical Device Amendments (MDA), which amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to create a comprehensive system for the regulation of medical devices intended for use in humans. At that time, the definition of a device was amended to make explicit that it encompassed in vitro diagnostic devices (IVDs): "The term 'device' … means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article…" (section 201(h) of the FD&C Act (21 U.S.C. 321(h)). The definition of device applies equally to IVDs manufactured by conventional device manufacturers and those manufactured by laboratories. An IVD, therefore, meets the device definition irrespective of where and by whom it is manufactured.

Since the implementation of the MDA of 1976, FDA has exercised enforcement discretion so that the Agency has generally not enforced applicable provisions under the FD&C Act and FDA regulations with respect to laboratory developed tests (LDTs), a subset of in vitro diagnostic devices that are intended for clinical use and designed, manufactured, and used within a single laboratory.

In 1976, LDTs were mostly manufactured in small volumes by local laboratories. Many laboratories manufactured LDTs that were similar to well-characterized, standard diagnostic devices, as well as other LDTs that were intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population. LDTs at the time tended to rely on the manual techniques used by laboratory personnel. LDTs were typically used and interpreted directly by physicians and pathologists working within a single institution that was responsible for the patient. In addition, historically, LDTs were manufactured using components that were

legally marketed for clinical use (i.e., general purpose reagents, immunohistochemical stains, and other components marketed in compliance with FDA regulatory requirements).

Although some laboratories today still manufacture LDTs in this "traditional" manner, the landscape for laboratory testing in general, and LDTs along with it, has changed dramatically since 1976. Today, LDTs are often used in laboratories that are independent of the healthcare delivery entity. Additionally, LDTs are frequently manufactured with components and instruments that are not legally marketed for clinical use and also rely more heavily on complex, high-tech instrumentation and software to generate results and clinical interpretations. Moreover, technological advances have increased the use of diagnostic devices in guiding critical clinical management decisions for high-risk diseases and conditions, particularly in the context of personalized medicine.

Business models for laboratories have also changed since 1976. With the advent of overnight shipping and electronic delivery of information (e.g., device results), a single laboratory can now easily provide device results nationally and internationally. Today, many new LDT manufacturers are large corporations that nationally market a limited number of complex, high-risk devices, in contrast to 1976 when hospital or public health laboratories used a wide range of devices that were generally either well characterized and similar to standard devices; used to diagnose rare diseases; or designed specifically to meet the needs of their local patients. Together, these changes have resulted in a significant shift in the types of LDTs developed, the business model for developing them, and the potential risks they pose to patients.

Because of changes in the complexity and use of LDTs and the associated increased risks, as described earlier, FDA believes the policy of general enforcement discretion towards LDTs is no longer appropriate. To initiate this step toward greater oversight, FDA held a two-

day public meeting on July 19 and 20, 2010, to provide a forum for stakeholders to discuss issues and concerns surrounding greater oversight of LDTs. Comments submitted to the public docket for the July public meeting have been addressed, as appropriate, in the draft guidance document.

Once finalized and implemented, this guidance document is intended to provide a risk-based oversight framework that will assure that devices used in the provision of health care, whether developed by a laboratory or a conventional IVD manufacturer, comply with the appropriate levels of regulatory controls needed to assure that they are safe and effective. Under the framework outlined in this guidance document, FDA intends to continue to exercise enforcement discretion for all applicable regulatory requirements for LDTs used solely for forensic (law enforcement) purposes as well as certain LDTs for transplantation when used in certified, high-complexity histocompatibility laboratories. Additionally, FDA intends to exercise enforcement discretion for applicable premarket review requirements and quality systems requirements, but enforce other applicable regulatory requirements, including registration and listing (with the option to provide notification instead) and adverse event reporting, for low risk LDTs (class I devices), LDTs for rare diseases, Traditional LDTs and LDTs for Unmet Needs, as described in the draft guidance document. For other high and moderate risk LDTs, FDA intends to enforce applicable regulatory requirements, including registration and listing (with the option to provide notification instead) and adverse event reporting, and phase in enforcement of premarket and quality system requirements in a risk-based manner.

On July 31, 2014, as required by Section 1143 of the Food and Drug Administration Safety and Innovation Act, FDA provided notification to Congress of its intent to issue this draft guidance and the accompanying draft guidance entitled "FDA Notification and Medical Device Reporting for Laboratory Developed Test (LDTs)" (the availability of the accompanying draft

guidance is announced elsewhere in this issue of the Federal Register). The anticipated details of these draft guidance documents were included in the notification to Congress.

Although FDA was not accepting formal comments on its notification to Congress, the Agency has received informal comments and questions regarding the anticipated details of this draft guidance provided in the notification to Congress. To give everyone an opportunity to provide formal comments on the anticipated details as part of the administrative record, the details of the draft guidance are identical to that which were included in FDA's July 31, 2014, notification to Congress with the exception of the following technical amendments: The definition of companion diagnostic has been updated for consistency with the final guidance on "In Vitro Companion Diagnostic Devices" issued on August 6, 2014, and the "Traditional LDT" factor regarding whether the LDT is comprised only of components and instruments that are legally marketed has been clarified to more accurately reflect FDA's intent of considering whether the LDT is comprised of only components and instruments that are legally marketed for clinical use.

To provide greater transparency on certain questions and issues that have been raised and to allow for broad public input, in addition to welcoming comments on all aspects of this draft guidance, FDA seeks feedback on the following specific issues:

- Traditional LDTs: In Section D.5.(a) of the draft guidance, FDA has proposed continued enforcement discretion for premarket review and quality system requirements for a category of LDTs called "Traditional LDTs" based on whether the device is: (1) an LDT (designed, manufactured and used within a single laboratory); (2) manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at that same health care facility or within

the facility's healthcare system; (3) comprised only of components and instruments that are legally marketed for clinical use; and (4) interpreted by qualified laboratory professionals without the use of automated instrumentation or software for interpretation. FDA believes that these factors appropriately mitigate risks associated with Traditional LDTs being used on patients so that continued enforcement discretion with respect to premarket review and quality system requirements is appropriate. However, FDA is seeking public feedback as to whether the following three factors may be sufficient to appropriately mitigate risk for this category of tests and whether they may also be sufficient to support continued enforcement discretion in full (i.e., for all regulatory requirements rather than just for premarket review and quality system requirements): (1) the test is an LDT (designed, manufactured and used within a single laboratory); (2) the test makes use of only components and instruments that are legally marketed for clinical use, which have a number of regulatory controls in place, including reporting of adverse events; and (3) the test is interpreted by laboratory professionals who are appropriately qualified and trained as required by the Clinical Laboratory Improvement Amendments regulations (e.g., 42 CFR 493.1449), without the use of automated instrumentation or software for interpretation.

- LDTs Used for Rare Diseases: In Section D.5.(a) of the draft guidance, FDA has proposed continued enforcement discretion for premarket review and quality system requirements for LDTs used for rare diseases, which are those tests that meet the definition of LDT in the guidance (designed, manufactured and used within a single laboratory) and meet the definition of a Humanitarian Use Device (HUD) under 21 CFR 814.102(a)(5). With these factors, FDA has attempted to balance the need to mitigate the

risks associated with these tests with their potential benefit for patients. FDA invites stakeholders to provide feedback on the suitability of these factors for LDTs for rare diseases. Further, FDA is seeking feedback on whether a factor other than the HUD definition should be considered, such as a factor based on the number of tests for a rare disease or condition that would likely (based on the prevalence of the condition) be conducted annually in the United States, and if so what the annual number of tests should be for the purpose of defining an LDT as an LDT for a rare disease. FDA also seeks feedback on whether enforcement discretion should be limited to tests that are designed, manufactured and used within a single laboratory.

- Healthcare System: In Section D.5. of the draft guidance, for the categories of tests called "Traditional LDTs" and "LDTs for Unmet Needs," FDA has identified factors it intends to consider in continuing to exercise enforcement discretion for premarket review and quality system requirements. One such factor is whether the LDT is both manufactured and used by a healthcare facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at that same healthcare facility or within that facility's healthcare system. To further clarify this factor, the guidance document explains that "healthcare system" refers to a collection of hospitals that are owned and operated by the same entity and that share access to patient care information for their patients, such as, but not limited to, drug order information, treatment and diagnosis information, and patient outcomes. While FDA invites feedback on all factors described in Section D.5. of the draft guidance, FDA specifically requests feedback on whether enforcement discretion should be limited, as proposed, to those LDTs that are both manufactured and used by a healthcare facility laboratory. FDA also

invites the public to provide feedback to the Agency on which types of facilities would or would not be considered within a healthcare system, or to offer an alternative description of healthcare system for Agency consideration.

- Quality System (QS) Phase-in: In Section D.6. of the draft guidance, FDA has proposed to continue to exercise enforcement discretion with respect to QS regulation requirements, codified in 21 CFR Part 820, until a manufacturer of a given LDT submits a Premarket Approval (PMA) or FDA issues a 510(k) clearance order for the LDT. Under this enforcement policy, the clinical laboratory manufacturing and using the LDT will be responsible for having a quality system in place that meets the minimum requirements codified in 21 CFR Part 820, either at the time of PMA submission (the facility that makes the device must pass an inspection as a condition of PMA approval as a matter of law (21 CFR 814.45(a)(3)), or prior to market launch for cleared devices, as applicable. FDA invites feedback on the timeframe for phase-in enforcement of QS regulation requirements. Specifically, FDA is considering whether those LDTs in the highest-risk category of devices (described in section D.5.(c) of the draft guidance), which FDA intends to generally enforce premarket review requirements 12 months following publication of the final Framework guidance, should remain under enforcement discretion for the design control requirements (21 CFR 820.30(a-h) and (j)) of the QS regulation for up to 24 months after publication of the final guidance.
- Notification: FDA notes that some laboratory networks (i.e., more than one laboratory under the control of the same parent entity) offer the same test in multiple laboratories throughout their network. Although devices in this scenario do not meet FDA's definition of an LDT (i.e., they are not designed, manufactured and used within a single

laboratory), FDA would like feedback on whether a single notification from the laboratory network for that test is sufficient, provided that the laboratory network indicates in the notification to FDA that the test is offered at multiple sites. In addition, FDA seeks comment on whether there are certain types of LDTs for which the Agency should neither enforce requirements for registration and listing nor request notification in lieu of registration and listing.

- FDA understands that members of the public may want more clarity around specific issues; such as how laboratory sponsors could interpret what elements make up a medical device, what might constitute the label or labeling for their device, whether or not unique device identifier requirements apply to LDTs, and how laboratory-physician communication about a test and its result would be viewed by FDA, among others. We invite public comment on these issues and any other issues or questions that should be addressed in the guidance, including how that issue or question should be addressed.

Additionally, FDA intends to hold a public webinar in late October, 2014 to summarize the proposed oversight framework and answer clarification questions from stakeholders. The webinar will not require registration and will be announced at least one week in advance on FDA's Web site. It will be recorded and made available on FDA's Web site shortly thereafter.

II. Significance of Guidance

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on oversight of laboratory developed tests. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative

approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

III. Electronic Access

Persons interested in obtaining a copy of the draft guidance may do so by downloading an electronic copy from the Internet. A search capability for all CDRH guidance documents is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm. Guidance documents are also available at http://www.regulations.gov or the CBER Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

Persons unable to download an electronic copy of "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" may send an email request to CDRH-Guidance@fda.hhs.gov to receive an electronic copy of the document. Please use the document number 1739 to identify the guidance you are requesting.

IV. Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 807 Subpart E have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 807 Subpart B and C have been approved under OMB control number 0910-0625; the collections of information in 21 CFR part 601 have been approved under OMB control number 0910-0338; the

collections of information in 21 CFR part 814, subparts B and E, have been approved under OMB control number 0910-0231; the collections of information in 21 CFR part 814, subpart H, have been approved under OMB control number 0910-0332; the collections of information in 21 CFR part 820 have been approved under OMB control number 0910-0073; the collections of information in 21 CFR part 812 have been approved under OMB control number 0910-0078; the collections of information in 21 CFR part 806 have been approved under OMB control number 0910-0359; the collections of information in 21 CFR 801 and 21 CFR 809.10 have been approved under OMB control number 0910-0485; and the collections of information in 21 CFR part 803 have been approved under OMB control numbers 0910-0291 and 0910-0437.

V. Comments

Interested persons may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

Comments will also be accepted at a public meeting, which will be held prior to finalizing this draft guidance. A 2-day meeting is tentatively scheduled for early January, 2015 and will be announced separately in the Federal Register.

Dated: September 30, 2014.

Peter Lurie,

Associate Commissioner for Policy and Planning.

[FR Doc. 2014-23596 Filed 10/02/2014 at 11:15 am; Publication Date: 10/03/2014]