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ONE HUNDRED FOURTEENTH CONGRESS

Congress of the United States

House of Representatives

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MEMORANDUM

November 15, 2015

To: Subcommittee on Health Democratic Members and Staff

Fr: Committee on Energy and Commerce Democratic Staff

Re: Hearing on "Examining the Regulation of Diagnostic Tests and Laboratory Operations"

The Subcommittee on Health will hold a hearing on **Tuesday, November 17th, 2015, at 10:00 a.m. in Room 2322 of the Rayburn House Office Building**. The hearing is entitled "Examining the Regulation of Diagnostic Tests and Laboratory Operations."

I. BACKGROUND ON LABORATORY DEVELOPED TESTS

FDA defines the term "laboratory developed test" (LDT) as a type of *in vitro* diagnostic test that is designed, manufactured, and used within a single laboratory.[1] In 1976, Congress amended the Federal Food, Drug, and Cosmetic Act (FFDCA) to define "device" to include *in vitro* diagnostics, regardless of whether they are manufactured by conventional device manufacturers or laboratories.[2]

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[1] Food and Drug Administration (FDA), *Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories,* (July 31, 2014) (online at http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf).

[2] *See* Federal Food, Drug, and Cosmetic Act, Section 201(h). "(h) The term "device" (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is—

An *in vitro* diagnostic test can detect diseases, conditions, or infections. Studies or tests that are performed *in vitro* means that they are performed outside of the body, often using test tubes or other laboratory tools. Unlike *in vitro* diagnostic tests, *in vivo* tests are conducted within or upon the body.

LDTs are widely used and vary widely in complexity and type. The Centers for Disease Control and Prevention (CDC) has estimated, based on 2007 data from the Centers for Medicare and Medicaid (CMS), that approximately 6.8 billion laboratory tests are performed annually in the U.S. CDC also noted that "publically available information about the economic status and quality of the laboratory medicine sector remains limited."[3] Another analysis found that results from clinical laboratory tests influence around 70 percent of health care decision-making.[4]

Some LDTs, like those which measure sodium levels, are simple tests, while more complex LDTs can, for example, analyze DNA variations in helping diagnose a genetic disease or condition, or to detect a patient's risk for serious diseases, including breast cancer and Alzheimer's disease. FDA opted historically not to enforce medical device regulations that might apply to LDTs because they were simple tests that were not widely available.[5] However, over the years, the volume and types of LDTs has drastically increased and they have become more complex, presenting greater patient safety risks.[6]

FDA has discovered safety issues with certain LDTs, leading to agency concerns that patients might erroneously rely on these tests to delay or forgo treatment. Specifically, FDA has stated that it is "aware of faulty LDTs that could have led to: patients being over- or undertreated for heart disease; cancer patients being exposed to inappropriate therapies or not getting effective

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(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

[3] *Id.*

[4] The Lewin Group, *Laboratory Medicine: A National State Report* (May 2008) (online at https://www.futurelabmedicine.org/pdfs/2007%20status%20report%20laboratory_medicine_-_a_national_status_report_from_the_lewin_group.pdf)

[5] FDA, *Laboratory Developed Tests* (2014) (online at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm).

[6] *Id.*

therapies; incorrect diagnosis of autism; unnecessary antibiotic treatments; and exposure to unnecessary, harmful treatments for certain diseases such as Lyme disease."[7]

As a result of these concerns, FDA published draft guidance on October 3, 2014, outlining a modified, risk-based approach to overseeing these technologies. FDA notified Congress 60 days prior to issuance, as required under Section 1143 of the FDA Safety and Innovation Act, on July 31, 2014.[8]

II. ROLE OF CMS IN OVERSEEING LABORATORIES AND LDTs

Under the Clinical Laboratory Improvement Amendments (CLIA), CMS oversees laboratory testing (except research) performed on humans in the U.S.[9] Among other things, CLIA establishes quality standards for laboratory testing and an accreditation program for clinical laboratories. Requirements for laboratories vary based on the complexity of the test and the risk of harm in reporting erroneous results. Laboratories that perform low complexity, or waived, tests must enroll in CLIA, pay applicable certificate fees biennially, and follow manufacturers' test instructions, but they are not subject to the additional requirements specified for laboratories that perform moderate of high complexity tests. Laboratories that perform moderate or high complexity tests are subject to standards related to certification, personnel, proficiency testing, patient test management, quality assurance, quality control, and inspections.

With respect to LDTs that do not receive FDA approval or clearance, CLIA prohibits a laboratory from releasing any results from such tests, unless that laboratory establishes certain performance characteristics relating to the "analytical validity" of that test conducted within that particular laboratory.[10] In this analytical validity assessment, CMS looks at such things as the accuracy and precision of the specific LDT.[11] However, under CLIA, CMS does not address the "clinical validity" of the test—in other words, CMS does not assess whether a particular LDT can accurately identify, measure, or predict the presence or absence of a clinical condition or predisposition in a patient.[12] Instead, FDA is charged with looking at the clinical validity of a given LDT under its premarket clearance and approval processes.[13] CLIA also does not require:

1. Proof of the safety and effectiveness of the test;
2. Pre-market review of the test;

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[7] *Id.*

[8] FDA Safety and Innovation Act, Section 1143 (P.L. 112-144).

[9] P.L. 100-578.

[10] Center for Medicare and Medicaid Services (CMS), *LDT and CLIA FAQs* (October 22, 2013) (online at http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf).

[11] *Id.*

[12] *Id.*

[13] *Id.*

3. Adverse event reporting;
4. Removal of unsafe LDTs from the market; or
5. Demonstration of quality of the design and manufacture of the test.

III. FDA'S PROPOSED FRAMEWORK FOR OVERSIGHT OF LABORATORY DEVELOPED TESTS

In its October 2014 draft guidance, FDA proposed a risk-based regulatory framework that would be phased in over time. Specifically, FDA intends to continue to exercise enforcement discretion with respect to: (1) LDTs used solely for law enforcement purposes; and (2) for certain LDTs for transplantation when used in CLIA-certified, high-complexity histocompatibility laboratories.[14] FDA will continue to exercise enforcement discretion with respect to pre-market review requirements and quality systems requirements for (1) Low-risk LDTs; (2) LDTs for rare diseases and "traditional LDTs"[15]; and (3) LDTs for unmet needs when no FDA-approved or cleared equivalent device is available.[16] For these categories of LDTs, FDA would still require companies to notify the agency of the LDTs they are manufacturing or otherwise to register and list their products, as well as to conduct adverse event reporting.[17]

For all other high and moderate risk LDTs, FDA intends to enforce applicable regulatory requirements, including notification or registration and listing, adverse event reporting, premarket review, and quality system requirements. Specifically, for high-risk LDTs (which would be considered Class III medical devices), notification or registration and listing and adverse event reporting would begin six months after the guidance is finalized.[18] Premarket review requirements would begin 12 months after the guidance is finalized for the highest risk devices and phase-in over four years for the remaining high-risk devices.[19] Devices would

[14] *Supra,* note 2 at 11.

[15] FDA describes "traditional LDTs" as those that were originally the subject of FDA's enforcement discretion policy when it was implemented in 1976. FDA also considers the following factors when deciding whether an LDT is a "traditional LDT": "(1) Whether the device meets the definition of LDT in this guidance (a device designed, manufactured and used by a single laboratory); and (2) Whether the LDT is both 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; and (3) Whether the LDT is comprised of only legally marketed components and instruments (e.g., analyze specific reagents (21 CFR 864.4020), general purpose reagents (21 CFR 864.4010), and various classified instruments); and (4) Whether the LDT is interpreted by qualified laboratory professionals, without the use of automated instrumentation or software for interpretation." *Supra,* note 2 at 20.

[16] *Supra,* note 2 at 11.

[17] *Supra,* note 2 at 11 and 16-19. In contrast to registration, notification does not require the payment of a registration fee.

[18] *Supra,* note 2 at 11.

[19] *Supra,* note 2 at 11.

remain on the market during review and FDA's consideration of applications.[20] FDA's focus on high-risk devices would begin with the following: (1) LDTs with the same intended use as a cleared or approved companion diagnostic; (2) LDTs with the same intended use as an FDA-approved Class III medical device; and (3) certain LDTs for determining the safety or efficacy of blood or blood products. For moderate-risk LDTs (which would be considered Class II medical devices), notification or registration and listing and adverse event reporting begin six months after the guidance is finalized.[21] Premarket review requirements would begin after the high-risk LDTs are completed (five years after the guidance is finalized) and phase in over four years.[22] FDA has estimated that the process of bringing all LDTs into compliance will take nine years to complete. FDA has also noted that the agency intends to issue further guidance within 24 months of finalizing the current guidance to describe what the Agency considers to be Class I, II and III devices. To date, FDA has not finalized this guidance.

IV. SUMMARY OF DISCUSSION DRAFT

Circulated with the notice for the hearing was a discussion draft that would establish a risk-based regulatory framework for *in vitro* clinical tests (IVCTs), which would be a new category under FFDCA. The discussion draft defines IVCTs as "any finished product or laboratory protocol intended by the developer to be used in the collection, preparation, analysis, or in vitro clinical examination of specimens taken or derived from the human body, solely or principally for the purpose of identifying, measuring, predicting, monitoring, or assisting in selecting treatment for, a disease or other condition." Tests that meet the definition of a "biologic" under Section 351 of the Public Health Service Act, and that are intended to screen human blood, human cells, tissues, cellular or tissue-based products, or organs for infectious diseases, or intended to determine the compatibility of a donor of patient to ensure the safe transfusion or transplantation of blood, human cells, tissues, cellular or tissue-based products, or organs are excluded. Further, tests developed solely for nonclinical use, such as forensic testing, drugs-of-abuse testing for employment, insurance, and genetic testing for nonclinical purposes are also excluded.

A. Regulatory Framework

The proposed regulatory framework, which is risk-based, demarcates which IVCT-related activities are to be regulated by FDA versus CMS. As outlined in the discussion draft, FDA will have jurisdiction over the development of IVCTs, which encompasses the design, development, validation, production, manufacture, preparation, propagation, assembly, and processing of an IVCT, as well as validation of an IVCT and any change to the design of an IVCT. The discussion draft proposes a new center at FDA that would have sole jurisdiction over IVCT finished products and laboratory test protocols. CMS, on the other hand, will have jurisdiction over laboratory operations, which encompasses the development of and performance of tests to standard operating procedures; verification of laboratory performance; pre-analytical

[20] *Supra*, note 2 at 11.

[21] *Supra*, note 2 at 12.

[22] *Supra*, note 2 at 12.

processes; preparation of reagents or other test materials; preparation and transfer of individual components; parts or raw materials between commonly owned facilities within the same state; collection, preparation, storage, and transport of patient specimens; and, reporting the output or results of an IVCT.

B. Risk Classifications

Under the proposal, new IVCTs will be classified based on the risk of the test's intended use and is divided into three categories: high-risk, moderate-risk, or low-risk. These categories are defined below:

High risk. An IVCT is considered to be high-risk if a clinically significant inaccurate result for the intended use would cause serious or irreversible harm or death, to the patient or public, based on failure to treat, incorrect treatment, invasive procedures, prolonged disability if such inaccurate result were undetected when used as intended in medical practice.

Moderate risk. An IVCT is considered to be moderate-risk if a clinically significant inaccurate result for the intended use would cause non-life-threatening injury, injury that is medically reversible, or a delay in necessary treatment if such inaccurate result were undetected when used as intended in medical practice.

Low risk. An IVCT is considered to be low-risk if a clinically significant inaccurate result for the intended use would cause minimal or no harm, immediately reversible harm, or no disability if such inaccurate result were undetected when used as intended in medical practice. If an IVCT meets the criteria of moderate or high risk, but the risk of adverse patient impact or adverse public health impact caused by an inaccurate result is remote, it also will be regulated as low risk.

C. Classification of Existing and New IVCTs

Initial classification for existing IVCTs will be based on the current risk classifications for devices: current IVCTs subject to premarket approval will be considered high-risk; current IVCTs subject to a 510(k) clearance will be considered moderate-risk; and current exempt IVCTs will be considered low-risk. An advisory panel, which will consist of physicians, consumers, industry, and lab representatives, will classify existing IVCTs into new risk classes. FDA and public stakeholders have the opportunity to identify IVCTs for which they believe a classification is either incorrect, or for which there is no classification currently.

Developers of new IVCTs will submit to FDA a proposed classification, with proposed mitigations if applicable, and a proposed description of the IVCT. FDA will have 60 days to respond to the developer's classification submission. If the agency does not act within this period, developers can appeal and seek a classification decision. IVCTs can be reclassified by FDA or in response to a petition.

D. Standard and Submission Process

Developers of an IVCT must demonstrate a reasonable assurance of analytical validity and clinical validity for the intended use before it can be marketed. Analytical and clinical validity must be demonstrated by valid scientific evidence for IVCTs. Clinical trials can only be required for high-risk IVCTs and FDA is required to demonstrate in writing, based on scientific criteria, that other evidence is insufficient.

Submission requirements for IVCTs vary based on risk classification. Developers of high-risk IVCTs must submit a summary of valid scientific evidence to demonstrate reasonable assurance of analytical and clinical validity prior to offering; the protocol and summary of results and conclusions from any studies performed; applicable performance standards, voluntary standards or mitigations relied upon; a summary of design controls and a declaration of conformity to such design controls; summary of relevant manufacturing process controls; a risk assessment; among other things. FDA must approve or disapprove the submission within 120 calendar days. Developers of moderate-risk IVCTs must submit prior to offering a summary of valid scientific evidence to demonstrate reasonable assurance of analytical validity and clinical validity; a summary of the protocol and results and conclusions of any studies performed; and a summary of the relevant risk assessment, among other things. If FDA does not disapprove the submission within 75 days, the IVCT is deemed to be approved. Developers of low-risk IVCTs are required to list the IVCT within 10 days of offering, and include the intended use and summary explanation of the IVCT.

An alternative pathway is also included in the framework for IVCTs for unmet needs, rare disease, and for moderate-risk IVCTs that offer a clinically significant advantage over an IVCT that has been previously approved. Under this pathway, a developer must submit an application that demonstrates reasonable assurance of analytical validity and either reasonable assurance of probably clinical validity or reasonable assurance of clinical validity. If the application only demonstrates probable clinical validity, the developer may offer the IVCT and collect post-market evidence, as agreed to by FDA and the developer, over a three-year period demonstrating a reasonable assurance of clinical validity. FDA must approve or disapprove of an IVCT for rare disease and unmet need IVCTs within 30 days, and disapprove of moderate-risk IVCTs within 75 days or the IVCT is deemed approved.

E. Modifications

Modifications that change the intended use or add a new intended use to an IVCT that is moderate-risk or high-risk, or results in a meaningful clinical impact to the IVCT, such as a meaningful increase in risk to the patient, a change in the diagnosis or therapy delivered to the patient, or changes the analytical or performance specifications from the approved specifications following verification and validation, must be submitted to FDA for approval. Modifications that comply with a recognized standard or FDA guidance and for specimen-related changes if validated and verified using protocols approved by FDA do not have to be submitted.

F. Quality Requirements

IVCT development and production would be subject to quality requirements to be established by regulation by FDA. In establishing such requirements, FDA shall consider requirements for design controls, production and process controls, purchasing controls, corrective and preventive action, and handling, storage, distribution, and installation, among others. FDA is also required to establish unique identifier requirements for finished products.

G. Post-Market Requirements

Developers of an IVCT will be required to report to FDA any adverse event known to cause patient death within five calendar days, and any adverse event that presents an imminent threat to public health within 15 calendar days. Developers will also be required to maintain adverse event files that contain information related to the adverse event, including documentation of the developer's deliberation about whether an IVCT error was reportable, and copies of all required adverse event submissions. Further, developers must submit a quarterly summary and trend report for all other adverse events.

H. Grandfathering and Transitional Provisions.

Moderate and low risk tests introduced 90 days prior to enactment are deemed to be approved by FDA as long as the IVCT developer lists their test with FDA. High risk tests introduced 90 days prior to enactment that have not been reviewed previously by FDA are deemed to be approved if the IVCT developer lists with FDA and also submits a summary of their available analytical validity and clinical validity evidence within four years.. Developers of new tests will use existing FDA approval processes during the three-year period following enactment, and will have the option to begin using the new submission process after three years. The new submission process is mandatory after four years.

I. Withdrawal Authority

FDA will have the authority to withdraw approval of an IVCT if the IVCT presents an unreasonable risk of illness or injury when used as intended, the submission contains material false statements, the IVCT quality systems are in violation, or if the IVCT labeling is materially false or misleading and is not corrected. FDA will also be able to mandate removal or correction of an IVCT if FDA finds there is a reasonable probability that an IVCT would cause serious, adverse health consequences or death.

J. Preemption and Fees

All state requirements that are different from, or in addition to, FDA or CLIA IVCT requirements would be preempted. The discussion draft includes a placeholder for FDA user fees; current fees assessed under CLIA would be credited against FDA user fees.

K. CLIA Modernization

Lab operations will continue to be regulated under CLIA, which will be updated to clarify activities regulated by FDA and CMS, and reflect updated accreditation requirements from external stakeholders. These changes include an expansion of the CLIA certificate to include specialties and sub-specialties, update to CLIA standards for the new specialties and sub-specialties, development of new CLIA standards for genetic testing, and greater requirements for laboratory computer systems. CLIA quality standards will also be updated to include criteria for purchasing controls for lab operations, enhanced quality requirements for reagents not for use as a finished product but as a component of an IVCT to ensure quality and consistency of the reagent, and to include common standards for identifying, investigating, assessing and addressing laboratory errors.

V. WITNESSES

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