Combination Products Coalition

February 2, 2015

VIA ELECTRONIC DELIVERY
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0360
Comments on Draft LDT Framework

Dear Commissioner Hamburg:

The Combination Products Coalition welcomes the opportunity to comment on FDA's draft LDT framework. The Coalition's focus in submitting these comments is on securing regulatory reforms that advance access to companion diagnostic tests that get patients the right drug at the right dose.

When FDA first released its framework to Congress in July 2014, the Agency explained how patients would benefit from "a better balanced approach for all diagnostics," stating that –

> Labs and conventional manufacturers serve as vitally important sources of innovative test development. Through smart, appropriately tailored oversight, we can best promote product development by all test developers and best serve patients and their healthcare providers. When everyone plays by the same rules, innovation and society benefit.[1]

The Coalition agrees with these sentiments. We also recognize the vital role that laboratories play in providing access to tests when FDA-approved or -cleared IVDs are unavailable. FDA has recognized this as well by proposing to extend enforcement discretion to LDTs for unmet needs and rare diseases. Potentially, many of these tests could serve a companion diagnostics-like function in guiding therapeutic choices that are crucial to a patient's health.

However, enforcement discretion only treats the symptoms, and not the regulatory causes, of limited access to FDA-approved and -cleared companion diagnostic tests. To improve access, FDA and stakeholders must work together to find that "better balanced approach for *all*

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[1] Jeffrey Shuren, M.D., Ph.D., *Curbing Risk, Not Medical Innovation, in Personalized Medicine*, *available at*, http://blogs.fda.gov/fdavoice/index.php/2014/07/curbing-risk-not-medical-innovation-in-personalized-medicine/#sthash.45pqzIJz.mq5d2aaI.dpuf.

diagnostics" to which the Agency aspires. We urge FDA to look beyond LDTs and get to the root cause of delays in IVD innovation. We believe that by doing so, and developing a comprehensive and efficient diagnostic framework for all tests, both laboratories and traditional manufacturers can bring the best tests and quality of care to patients in the quickest possible way.

With that in mind, we offer the following specific comments for the Agency's consideration.

I. RESTRICTING IVD DEVELOPMENT WITH REQUIREMENTS THAT GO BEYOND LDT REQUIREMENTS IS NOT IN THE BEST INTEREST OF PATIENTS

According to its proposed framework, FDA believes the benefit-risk ratio for diagnostics regulation supports the manufacture and use of tests for unmet needs and rare diseases by certain laboratories without premarket review and FDA quality systems. However, other high complexity laboratories and/or traditional IVD manufacturers must continue to meet burdensome requirements. FDA has not provided a reasonable basis for treating these similarly situated parties so differently, and restricting innovation that could benefit patients.

For example, FDA would limit enforcement discretion for tests that serve "unmet needs" to labs within a "healthcare system," such as a hospital. According to FDA, the reason enforcement discretion should be limited to these laboratories is that the healthcare system is "responsible for the patient's outcome," and therefore has some greater interest in the patient's well-being. We understand the need to give healthcare facilities flexibility in testing as part of their practice of medicine, and don't question a healthcare system's dedication to their patients. However, clinical laboratories outside of healthcare systems and traditional manufacturers also take great care to ensure their tests will work as intended and will help patients. Why exclude these expert test developers from an abbreviated, less burdensome pathway to bring these types of tests to patients? If FDA's risk-benefit analysis favors rapid access with less regulation, why not address access concerns by reducing regulatory burdens for everyone?

Similarly, for rare diseases, enforcement discretion would encourage innovation by clinical laboratories, but offers no incentive to traditional manufacturers for bringing new tests to these populations: traditional manufacturers are still constrained by full FDA requirements, including a lengthy PMA or 510(k) process, or a humanitarian-use device pathway which carries significant burdens and comes with cost-recovery restrictions that prevent a return on investment. Why exclude traditional manufacturers, who have considerable expertise and FDA-compliant quality systems, from a less burdensome regulatory process for rare disease test development?

Proposed Solutions

A. Couple the development of the LDT Framework with a "Transitional" IVD approach that could give faster access to tests that are developed by both laboratories and traditional manufacturers

For many years FDA and the IVD industry have discussed the feasibility of a "transitional" IVD framework, which would allow a limited initial FDA clearance or approval

for a test based on *analytical* validity, without claims regarding the clinical validity of those tests. Over time, innovators could then seek clinical claims for their diagnostics based on growing scientific knowledge. In 2012, FDA committed as part of MDUFA III to "work with industry to develop a transitional In Vitro Diagnostics (IVD) approach for the regulation of emerging diagnostics."[2] This program could provide a means to accelerate development of and access to diagnostics that aid in guiding therapeutic decision-making, and would be a valuable addition to a comprehensive regulatory framework for diagnostics that could benefit patients. Also, such a program could be designed to be "manufacturer neutral," meaning *all* high-complexity CLIA laboratories and traditional manufacturers could use this approach to bring innovative tests to patients.

B. Couple development of the LDT Framework with development of an Agency-wide guidance on companion diagnostic development

In recent years there have been case-by-case successes in the field of companion diagnostics, including FDA-approved LDTs. However, there is not a uniform published set of FDA recommendations that considers the intricacies of companion diagnostic development. FDA recognizes a need for such guidance and has, in fact, been working on a cross-Center therapeutic-diagnostic "co-development" guidance for the last several years. A co-development guidance of this kind could improve the uniformity of decision-making, and establish clearer and more consistent FDA expectations for development of companion diagnostics. Releasing this guidance should be part of any diagnostic reform plan for LDTs or IVDs.

II. THE PROPOSED FRAMEWORK LIMITS LABORATORY TEST QUALITY

FDA has suggested that enforcement discretion would apply only to those tests for rare diseases and unmet need that are designed and manufactured within a single clinical laboratory. We are concerned that the "single laboratory" requirement may lead to lower quality diagnostic tests for patients. Currently, laboratories make LDTs using articles that are contract manufactured under FDA-compliant quality systems, but these LDTs appear to fall outside of FDA's proposed enforcement discretion because some manufacturing would take place outside of the laboratory.

In addition, limiting the exemption to tests designed entirely in-house will discourage potentially beneficial collaborations between laboratories and other laboratories or traditional manufacturers that could lead to better tests for patients. The proposed framework further suggests FDA intends to leave speech restrictions that hinder exchange of scientific ideas (such as those for analyte-specific reagents) intact.

If FDA considers both laboratories and traditional manufacturers to be "manufacturers," why maintain barriers to collaboration, innovation, and better quality tests? We expect the answer is that the barriers will help keep pressure on laboratories and traditional manufacturers to go through a long and expensive FDA premarket review, and comply with FDA quality

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[2] MDUFA Performance Goals and Procedures: Process Improvements (Apr. 2012), *available at*, http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf.

system requirements. That may be true, but it is not fair to patients. Anything that can be done to improve tests design and quality, even incrementally, should be done today, not tomorrow (or possibly years down the road).

The true solution to FDA's concerns about the use of the FDA process is to improve it for everyone so that it is seen as a more attractive option for test development – implementing the Transitional IVD approach or other reforms that would accelerate beneficial innovation. However, even if FDA decides to use enforcement discretion it should not condition that discretion on using lower quality test components and avoiding beneficial collaborations.

Proposed Solution: ***Do not, under any circumstances, limit (1) exchange of ideas or interactions between multiple laboratories or between laboratories and traditional manufacturers, or (2) access to the highest quality components for LDTs (such as contract-manufactured components), as part of an enforcement discretion policy.***

III. THE "UNMET NEED" AND "RARE DISEASE" DEFINITIONS PROPOSED BY FDA COULD PERPETUATE INEQUALITIES IN REGULATION THAT DISCOURAGE DEVELOPMENT OF COMPANION DIAGNOSTICS

One of the factors that weighed in FDA's decision to pursue LDT regulation was encouraging development of FDA-approved and cleared companion diagnostics. Under the current regulatory system, FDA recognized that IVDs for companion diagnostics come to market after years of research and investment only to face immediate competition from LDTs developed outside of FDA regulation that are being marketed for the same use. The proposed enforcement discretion for tests for unmet needs and rare diseases may perpetuate this practice. For example, assume FDA approves a companion diagnostic test for biomarker X. Subsequently, a laboratory develops an LDT for measuring the biomarker X, and does not make claims regarding companion diagnostic use, but some other use falling within the enforcement discretion category. Through lawful off-label *use* that is permitted under the framework, the LDT under enforcement discretion may continue to compete with the FDA-approved companion diagnostic.

Similarly, assume that a laboratory develops a more analytically sensitive test for biomarker X to guide therapeutic decisions, which could benefit certain drug responders who might otherwise go undetected. The laboratory decides to market the product as one satisfying an unmet need (e.g., identifying patients with low-level markers) or rare disease (e.g., if the low concentrations of biomarker are associated with a rare disease). Potentially, these tests would fall within enforcement discretion and discourage use of the FDA-approval and -clearance processes.

Proposed Solution: ***FDA should clarify how it will treat the unmet need and rare disease enforcement discretion categories, and the potential overlap of these categories with companion diagnostics, to ensure companion diagnostic development is not discouraged.***

IV. THE AGENCY MUST CLARIFY THE INTERRELATIONSHIP OF FDA AND CMS REQUIREMENTS

During the January 8th-9th public meeting on LDTs it was clear that many stakeholders who have long-operated under CLIA need further clarity about what will be required by an FDA

quality system. Public comments on this topic ranged from viewing FDA quality system requirements as being entirely foreign to laboratories, to being almost the same as CLIA quality systems. Also, there is considerable confusion about where laboratory services end and manufacturing begins. For example, during a meeting session on the topic of clinical validity, panelists noted that it was a standard practice to modify FDA-approved and -cleared tests to, e.g., analyze difficult-to-test samples. Under the proposed framework, at what point would those modifications go from being laboratory practice of medicine to test modifications that require 510(k), PMA or BLA submissions? In addition, concerns have been raised regarding the applicability of CLIA requirements to companion diagnostics being developed under an IDE – which was not a subject of the LDT Framework, but is an area that needs to be addressed.

Proposed Solution: ***FDA, in consultation with CMS and stakeholders, should develop a document detailing the metes and bounds of the (1) Food, Drug, and Cosmetic Act (and Public Health Service Act) and (2) CLIA requirements, to eliminate confusion and facilitate opportunities for developing efficient systems that satisfy all sets of requirements.***

Although the FDA and CMS authorities derive from complementary statutes imposing their own distinct requirements, there is potential overlap. Clarifying the relationship of the statutes at an operational level is important both for stakeholders and for regulators. For example, during inspections of clinical laboratories it is easy to envision confusion about overlapping requirements that could cause various problems for laboratories (e.g., FDA-483 observations or CLIA audit citations) that take a lot of time and expense to sort out. Developing public documents that can be referenced by the Agency and stakeholders alike will facilitate compliance and make diagnostics regulation run more smoothly.

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FDA and stakeholders should not limit their focus to LDTs and enforcement discretion. Let's look at the big picture and ways to get all test developers involved in bringing innovative, safe and effective tests to patients more quickly.

Sincerely,

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