



January 5, 2015

The Honorable Fred Upton (R-MI)
Chairman
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Diana DeGette (D-CO)
Member
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

Sent via email: Cures@mail.house.gov

Re: Request for Information Regarding *21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests*

Dear Chairman Upton and Representative DeGette:

Thank you for engaging the community on the 21st Century Cures initiative. Your focus on accelerating the pace of medical breakthroughs is generating ideas that could greatly improve the quality of patient care in the United States, including proposals to promote personalized medicine, which is on the cutting edge of biomedical innovation.

The Personalized Medicine Coalition (PMC), representing innovators, scientists, patients, providers and payers, promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health system. We thank the Committee for including PMC in its work so far and for this opportunity to engage.

As you know, personalized medicine is an emerging field that uses diagnostic tools to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will be best for each patient. By combining this information with an individual's medical records and circumstances, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans. The goal is to provide the right treatment to the right patient at the right time.

In *21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests*, a list of questions is posed along with a request for answers to them. We understand that the Committee has been working on an extensive legislative package to advance health care innovation generally. Although the request for information covers issues related to all diagnostic tests, PMC's comments focus on personalized medicine diagnostics in particular. Our answers are also heavily focused on FDA's recent notice to Congress and subsequent publication of two draft documents related to the regulation of laboratory developed tests, *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, and *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)*.

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PMC's answers are designed to suggest policy improvements that will help personalized medicine advance. Many of PMC's members will present their own responses to the Committee, and will actively advocate for those positions. To support the work of our member organizations we therefore note the following disclaimer: nothing in this letter is intended to impact adversely in any way the ability of individual PMC members, alone or in combination, to pursue separate comments, litigation, or other remedies with respect to FDA's proposed regulatory framework for LDTs, responses to the Committee's questions, or related issues.

We greatly appreciate the thoughtful and important questions that the Committee has raised, but given the short timeline, we have elected at this time to address only some of the Committee's questions. For clarity, we have maintained the original numbering and restated the entire question for each of the questions we are addressing.

3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?

PMC supports a risk-based approach to diagnostic test regulation. Risks posed by diagnostic tests are very different from a therapeutic medical device. Traditional medical device classification, therefore, is not entirely appropriate for diagnostic tests. FDA plans to develop a risk-classification system for LDTs. A new risk-classification for diagnostics, developed with significant stakeholder input, that provides for a more flexible balance between the relative risks posed by diagnostic tests and the potential benefit of the information that tests provide would be most appropriate and would logically fit within FDA's activities designed to promote personalized medicine and the regulatory science behind it.

As acknowledged above, FDA has issued a draft framework for the regulation of LDTs that is risk-based and tiered so that the highest risk tests must comply with FDA regulatory structure first. However, the draft framework proposes to apply the therapeutic medical device risk classifications to diagnostics initially as the classification system for LDTs is developed. The FDA currently intends to release its risk-classification draft guidance document 24 months after the finalization of the current guidance documents. The risk and classification piece is of tremendous importance to any potential regulatory oversight. PMC thinks it is vital that the concepts of risk and classification be resolved before the framework is finalized. This will substantially alleviate much of the uncertainty that currently exists around the FDA's proposed draft guidance. We request that FDA issue a risk-classification draft guidance document along with a second draft of the framework so that the public can consider and comment on both together.

4. The current pre-market review standards that apply to in vitro diagnostics use the same terminology of safety and effectiveness that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?

Pre-market review standards should be risk-based. Evaluation of traditional medical device concepts like safety and effectiveness should likewise be risk-based and might not be completely appropriate for all diagnostic tests or LDTs. Diagnostic tests provide information to a treating physician, who makes decisions based on test information, clinical information, disease state, prior diagnosis and many other patient-specific factors. Therefore, the risk profile for a diagnostic differs substantially from that of a therapeutic medical device, and the application of existing pre-market standards for safety and effectiveness may have to be modernized so that they are more appropriate when applied to diagnostic test kits and LDTs.

5. Are there areas where the balance between pre-market reviews versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

Shifting the focus of diagnostic regulation by some degree from pre-market review to post-market controls should be considered for the vast majority of LDTs and should also be considered as an appropriate path for the regulation of LDTs. Personalized medicine diagnostic tests often enter the market and evolve from or reflect scientific advances and constantly evolving clinical research. Therefore, this focus shift from pre-market review to post-market control has two distinct benefits. First, it allows tests to enter the market in response to medical need. Second, it allows tests to develop along with the science and advances in clinical research.

FDA has, for some devices and diagnostics, used an expedited pre-market approval (PMA) process, which has been welcomed by innovators and has been a great success. Significant expansion of the expedited PMA process would be welcome as changes to the current FDA system for test regulation are considered.

We are concerned that the current medical device statute is too inflexible to allow FDA to adjust or modify the current standards for clearance or approval to allow personalized medicine tests or changes to them based on rapidly evolving clinical information to reach patients. To the extent that the FDA does not have the flexibility necessary to make this shift under current statutory authority, Congressional action might be necessary. Stakeholders would likely support a legal remedy that enables the agency greater flexibility in the de novo application process.

6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?

We, too, are concerned about how FDA proposes to handle test modifications by clinical laboratories. For example, sometimes clinical laboratories must alter a test to improve its performance characteristics by making small technical adjustments that do not change the intended use of the test. Furthermore, as mentioned above, personalized medicine diagnostic tests often evolve rapidly in response to scientific advances. Modifications that do not change the intended use, but provide additional information that may enhance or improve treatment decision-making should be allowed by FDA in a streamlined manner. Finally, personalized medicine is already in the process of moving from a one-marker, one-test field to one in which hundreds and perhaps soon thousands of bits of information are discovered from a test. While the test might not change, the clinically actionable information will change over time. It is not clear that under the current statute FDA has the ability to address these near-future changes regarding actionable information in the least burdensome manner without impacting patient access. A flexible, modular system for approving modifications would help personalized medicine maintain its current pace alongside clinical and scientific advancements.

7. We have heard a lot about the practice of medicine and its relationship with medical product “labeling.” What should comprise “labeling” for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?

Within the FDA draft framework for LDT regulation, it is unclear how FDA would handle redundancies and conflicts with the CLIA program, under which clinical laboratories are now regulated, including labeling requirements. Below, we explain two examples of why FDA medical device labeling does not necessarily fit LDTs, and make suggestions for how labeling issues for LDTs might be resolved.

Because the rules for device labeling conflict with the CLIA program, FDA should provide a comprehensive explanation of how it would apply device-labeling requirements to LDTs. A laboratory should be permitted to fulfill any mandatory labeling requirements solely through its online directory of services. Section 502(f) of the

FDCA (21 U.S.C. § 352 (f)(2)) authorizes the use of electronic labeling in lieu of paper-based labeling under certain circumstances. This provision states, in part:

[r]equired labeling for prescription devices intended for use in health care facilities or by a health care professional and required labeling for in vitro diagnostic devices intended for use by health care professionals or in blood establishments may be made available solely by electronic means, provided that the labeling complies with all applicable requirements of law, and that the manufacturer affords such users the opportunity to request the labeling in paper form, and after such request, promptly provides the requested information without additional cost.

FDA should not require clinical laboratories to maintain labels or labeling in formats required for distributed/shipped products.

Furthermore, current FDA device labeling regulations will have negative consequences on the practice of medicine if applied to LDTs. Laboratory physicians, such as pathologists, advise treating physicians about available tests, test results, and possible treatment decisions that follow testing as part of the practice of medicine and based on their medical training and expertise. Current device regulation will hamper this aspect of the practice of medicine, an aspect upon which personalized medicine depends, because of potential off-label concerns. Briefly, pathologists or laboratory physicians routinely discuss options, which appear to modify FDA-approved or cleared devices. When physicians are treated as manufacturers, rather than medical professionals, such off-label uses cannot be discussed. When a test has been “labeled” for one use but is appropriate for another use, a manufacturer is prohibited from revealing that use, but physicians are permitted to discuss off-label uses. We are concerned that the agency intends for such other uses to be treated as off-label until “labeling” requirements are met again based on the new intended use. Thus, clarification is required regarding the extent to which the agency intends for this prohibition to apply to physicians who identify alternative uses that could require changes to labels. We suggest that the agency create a carve-out for off-label promotion for LDTs, so that laboratory physicians can discharge their duty to advise treating physicians seeking advice on relevant testing options. Laboratory-based physicians have both an ethical and legal obligation to serve as a resource to treating physicians on the most appropriate testing methods based on patient medical needs.

8. The Section 1143 guidance documents raise important questions about the relationship between the FFDCA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA’s quality systems regulations compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?

PMC notes that many laboratories have concerns about the potential for duplication between the regulatory requirements that laboratories are subject to under CLIA and new requirements that would be imposed by the FDA’s proposed framework. Duplicative regulations represent an unnecessary burden and cost for laboratories and the federal government. We are further concerned that FDA may move to finalize the proposed framework before outlining how these duplicative requirements will be streamlined.

FDA should be directed to harmonize its requirements with those already in existence under CLIA, and only impose regulatory requirements where the existing CLIA requirements are insufficient to achieve a specific regulatory goal. Particularly in the area of QSR, PMC notes substantial overlap in the regulatory requirements under FDA medical device regulation in 21 CFR §820 and the existing regulations under CLIA in 42 CFR §493 in relation to quality system requirements, design controls, document controls, purchasing controls, production and process controls, acceptance activities, nonconforming products, corrective and preventative actions, and records. It is critically important that FDA be required to identify the least burdensome approach to QSR, deferring to CLIA where regulatory goals overlap and are adequately met.

Likewise, CMS and FDA should be directed to issue a joint draft guidance document in conjunction with a public process for comment consideration from all stakeholders. We propose that draft guidance documents should clearly state that the CLIA program will suffice where there is overlap and that FDA will start where CLIA ends. Conflicts between the two programs should be fully resolved before the framework is finalized, since it is our understanding that before a PMA is filed, a quality system inspection must be completed. Therefore, requirements should be fully articulated, with opportunity for stakeholder comments first, so that laboratories can develop appropriate internal systems.

9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g. Ebola)?

PMC has long argued that the United States needs a creative, dynamic and flexible diagnostic test industry to support the future of health care and protect the public health from emerging threats. For optimal diagnostic industry capability, we must ensure that regulatory systems are designed in a way that protects patient safety in a flexible manner responsive to both emerging medical needs and the evolving science of personalized medicine.

Conclusion

Thank you again for recognizing and tackling this important set of issues. PMC appreciates the opportunity to provide comments now and in the future as the Committee continues its work to identify the appropriate legislative balance between regulation, innovation and access to personalized medicine diagnostic tests.

We would like to take this opportunity to conclude with a request. As you know, FDA has issued a draft framework for the regulation of LDTs and an accompanying notification process. We referenced the framework many times in the letter above. During public meetings, FDA staff members have stated that FDA intends to issue a second draft of the framework only if changes are significant.

PMC has requested additional information on risk classification, harmonization between the CLIA program and FDA inspections, technical test modifications and labeling issues.

Alone, each of these issues is significant; yet together it is clear that, at the very least, a second draft of the framework should be issued together with draft guidance documents clarifying the missing pieces for the review and public engagement process to be complete. We request that FDA resolve outstanding issues, publish draft guidance documents on risk and CLIA-FDA harmonization, open a docket for the collection of public feedback and engage in a series of public engagement activities such as a webinar and public meeting.

We have many other requests of and suggestions for the agency, but this one is most critical. If you have any questions or require more information, please contact Amy Miller by phone at 202-589-1769 or email at amiller@personalizedmedicinecoalition.org.

Sincerely yours,



Edward Abrahams, Ph.D.
President