PMC
PERSONALIZED
MEDICINE COALITION

February 2, 2015

Via Electronic Submission
Margaret Hamburg, M.D.
Commissioner
United States Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 3128
Rockville, MD 20857

Re: Docket No. FDA-2011-D-036

Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) and *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests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),* herein referred to as the *Framework.*

Dear Commissioner Hamburg,

The Personalized Medicine Coalition (PMC) represents innovators, scientists, patients, providers and payers, and promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health care system.

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

Our interest in the *Framework* pertains to how it can support this emerging field. Personalized medicine can benefit the health care system by improving the quality, safety, accuracy and effectiveness of treatments. For example, in breast cancer, colorectal cancer and non-small cell lung cancer, diagnostic testing of tumor samples allows oncologists to target treatments to the particular biomarker(s) expressed by a given tumor. Testing improves the quality of the patient's care by providing the most appropriate therapy for arresting the progression of the cancer. Furthermore, the health care system saves on the considerable resources spent on ineffective treatments for a particular patient as well as the associated costs for visits to the doctor and the hospital. Furthermore, every newborn baby in the United States undergoes screening for genetic diseases that, if not detected within the first days of life, will cause substantial morbidity and sometimes mortality. These tests save lives, reduce the costs of treating babies whose conditions would be undetected without screening and ultimately improve the overall health of the public.

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While examples of personalized medicine are exciting, these kinds of innovations must be balanced with patient safety. Providing optimal access to high-quality diagnostic tests will help deliver on the promise of personalized medicine while preserving patient safety and public health.

Scope, statements of neutrality and disclaimer

Many of PMC's members will present their own responses to this agency and will actively advocate for those positions. PMC's comments are designed to suggest improvements to the draft guidance documents so that the general concept of personalized medicine can advance. To support the work of our member organizations, we therefore note the following disclaimer: nothing in these comments 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 the proposed regulatory framework or related issues.

Since our comments are focused on improving the proposed FDA oversight process for laboratory developed tests (LDTs), and because of the differences of opinion within our membership, PMC will not take a position on whether FDA has the statutory authority to regulate LDTs or on the processes by which FDA will regulate them (e.g., whether regulation should be promulgated through notice and comment rulemaking versus guidance documents).

PMC's response is focused exclusively on personalized medicine issues, like those pertaining to molecular diagnostic and pharmacogenomic tests, which are the hallmarks of personalized medicine.

FDA's attempts to address stakeholder concerns and outstanding issues

PMC recognizes that FDA has attempted to address stakeholder concerns such as those brought to their attention at the July 19 and 20, 2010 public workshop on the regulation of LDTs. [1]As suggested by some stakeholders, FDA has agreed to take a risk-based, phased-in approach to FDA regulation of LDTs, focusing first on the highest risk tests. Furthermore, FDA has called out exemptions for rare diseases and for unmet health care needs. Finally, in recognition of registration and listing concerns, FDA has outlined a notification process that is separate from the usual registration and listing process.

Some outstanding issues with the proposals do remain, however. They include those discussed below.

Compliance timeline: Of foremost concern is the timeline for regulation of the highest risk tests. There seems to be a discrepancy between when active regulation of the highest risk tests will begin (12 months after the *Framework* is finalized) and when FDA intends to issue a risk-classification draft guidance document (24 months after the *Framework* is finalized).

As we will articulate in this comment letter, there are a great many outstanding issues that should be addressed before the *Framework* is finalized. Since most of the highest risk tests will be what we consider personalized medicine diagnostics, we ask that FDA add granularity to what tests will be regulated by FDA first, so that laboratories with menus full of those types of tests can prepare now to come into compliance with the accelerated timeline.

We understand that the first LDTs to be actively regulated by FDA are those that are equivalent to an FDA-cleared or approved companion diagnostic test or have the same intended use as an approved Class III medical device, as well as certain LDTs used to determine safety/efficacy of blood or blood products.

[1] FDA/CDRH Public Meeting: Oversight of Laboratory Developed Tests (LDTs). Available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm.

However, it is not clear what FDA considers to be high-risk when there is not an FDA-cleared or approved equivalent. Laboratories may need longer than 12 months to come into compliance for the highest risk tests, for a variety of reasons.

It is critical that FDA resolve outstanding timeline issues before finalization, so that laboratories that must comply first have a reasonable timeframe to develop programs and processes that conform to FDA's regulatory requirements. To do otherwise may result in laboratories inadvertently developing processes that do not comply with FDA regulation, ultimately depriving patients' access to crucial medical tests.

We propose that a two-year grace period take effect after FDA's quality systems regulations are first applied to laboratories, which is when initiation inspections and reviews take place. We suggest that laboratories not be sanctioned or penalized during this time, but are rather granted reviews that are learning opportunities as the two groups, clinical laboratories and FDA, start to learn from one another.

Use of existing literature: According to the *Framework,* FDA may allow laboratories to use existing literature to support clinical validity. We note that this is a very positive response to stakeholder suggestions. We ask FDA for a commitment on the use of existing literature and to expand the allowance by also permitting the use of laboratory accreditation information for the demonstration of analytical validity, and in the case of New York state accreditation, additional clinical validity information, in a confidential manner to the extent possible and appropriate.

Exemptions: While the community appreciates the carve-outs for rare diseases and for unmet health care needs, we request clarification on this point. For a traditional humanitarian use device (HUD) designation as defined in 21 C.F.R. §814.100(b), fewer than 4,000 patients per year can be tested with a medical device. Given the difficulty in communicating the number of tests performed across laboratories and organizations, one solution could be that the HUD exemption applies to tests when fewer than 4,000 patients are tested per year for a specific condition by a single laboratory. This exemption, however, might not be sufficient to cover newborn screening programs or testing during an infectious disease outbreak. The agency could consider additional exemption language to cover these situations.

Furthermore, to maintain the current state of health care, we suggest that FDA consider defining "unmet health care needs" as diagnostics that have an intended use for which there is no FDA-cleared or approved equivalent. This exemption would help maintain the current state of health care quality through testing access.

Notification process: The notification process outlined by FDA addresses some community concerns regarding registration and listing, including possible application of the medical device tax. However, once an LDT is cleared or approved, the laboratory will be subject to device listing and registration, the applicable registration fees and the medical device tax; therefore the notification process is a limited and temporary solution to the burden that FDA fees and medical device taxes will place on clinical laboratories. Furthermore, the proposed notification process should be no more onerous than registration and listing; yet, as proposed, it is more onerous in that it requires information beyond what is required by registration and listing.

Areas where further clarity is needed

Definition of LDTs and risk: FDA should redefine "LDT" to be consistent with the manner in which it intends to apply the *Framework,* which is by considering any test marketed by a laboratory as an LDT to be an LDT, whether it meets FDA's original draft definition as stated below[2] or not:

> *…an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory. 4,5 The following is an example of an LDT:*
>
> - *A laboratory uses peer reviewed articles to guide development of a new diagnostic device. The laboratory uses general purpose reagents and analyte specific reagents combined with general laboratory instruments and develops a testing protocol, that together constitute a test system which is then verified and validated within the laboratory. Once validated this device is used by the laboratory to provide clinical diagnostic results.*
>
> *FDA does not consider devices to be LDTs if they are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them. The following are some examples of devices that FDA does not consider to meet the definition of an LDT:*
>
> - *An entity that owns several clinical laboratories develops a device in one of its clinical laboratories and then transfers the device to several clinical laboratories within its network.*
> - *An academic institution develops a device, which it then licenses to or signs an exclusivity agreement with a private corporation that owns a CLIA-certified laboratory. The private corporation's CLIA-certified laboratory then begins manufacturing and using the device to provide clinical diagnostic results.*
> - *A laboratory contracts with a third party manufacturer to produce a key component (e.g., coated microtiter plate, specialized specimen collection kit) used in its device.*

While PMC recognizes that FDA has recently issued a final companion diagnostic guidance document, In Vitro Companion Diagnostic Devices, Guidance for Industry and Food and Drug Administration Staff (August 6, 2014), ambiguity remains in the LDT framework documents as to how the agency intends to categorize LDTs that are not true companion diagnostics, but are instead considered "companion diagnostic-like" tests. It is critical that FDA clarify where the lines will be drawn between tests that provide useful, but not essential, information and those that are considered true companion diagnostic tests.

Incorporating new scientific discoveries: Because personalized medicine has frequently benefited from newly identified correlations between existing recognized biomarkers and clinically relevant conditions, additional guidance about LDTs offered for a new intended use would be helpful. For example, an LDT intended to detect a disease may later be found valid for providing essential information for changing drug dosage regimens. FDA should clarify when such alterations would lead to changes in risk categorization and when continued enforcement discretion may be warranted. Furthermore, guidance is required regarding processes for inclusion of newly identified biomarkers that enhance or improve clinical decision-making in multi-biomarker diagnostic platforms.

[2] *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) DRAFT GUIDANCE* (October 3, 2014), page 5 at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf.

Right now, the CLIA path to market allows for LDT biomarker panels to be changed when new, valid markers are identified and published in the clinical literature. For example, since initial FDA approval of an in vitro diagnostic (IVD) for the detection of KRAS codon 12 and 13 mutations to aid in the identification of colorectal cancer patients for treatment with cetuximab, clinical practice has evolved to require testing of additional codons in KRAS as well as the NRAS gene. FDA's current device regulations do not yet appear to allow for these types of advancements without significant additional time, even after the validity of a new biomarker or new use for an existing biomarker has been widely established in clinical experience and communicated broadly in peer-reviewed literature.

Furthermore, there are instances when clinical laboratories alter a test to improve its performance characteristics by making small technical adjustments that do not change the intended use of the test. 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. We recognize that this can be a challenge. For example, there are many different mutations in the EGFR, BRAF and KRAS genes. While we cannot assume that a new test that can detect additional mutations is superior to an FDA-cleared test for identifying responders to a therapeutic, FDA should be willing to accept a reasonable level of evidence to qualify the new test for clinical application.

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 meaningful 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 and without impacting patient access. A flexible system for approving modifications would help personalized medicine maintain its current pace alongside clinical and scientific advancements. We urge FDA to address this important issue.

LDTs used in new drug applications: To strike an appropriate balance between the need for continued innovation in drug development and the need for patient protections, FDA should continue to exercise some enforcement discretion with respect to LDTs used in investigational phase I, phase II or other early-phase drug clinical trials, while applying Investigational New Drug (IND) and/or Investigational Device Exemption (IDE) requirements for clinical investigational studies only to LDTs used in clinical trials after phase III, as warranted. Regulatory oversight of LDTs used in phase I, phase II or other early-phase drug clinical trials should follow 21 CFR Part 56 for institutional review board (IRB) approval as well as applicable requirements in 21 CFR Part 50 for informed consent from the study subjects.

PMC also requests that FDA address whether the *Framework* will apply solely and apart from IND and IDE requirements for LDTs that are used in phase III clinical studies for one use but are also available as LDTs for other distinct uses. Specifically, PMC suggests that LDTs subject to IND and/or IDE requirements when being evaluated for companion diagnostic applications should not also be viewed as high-risk LDTs, and should be subject to continued enforcement discretion with respect to other clinical non-investigational uses.

Gaps in the current *Framework* draft

Defining risk

Given that LDTs are a new category for FDA, PMC suggests that FDA circulate a draft guidance document on risk classification before finalizing the *Framework.* FDA currently proposes to publish the risk-classification draft guidance document within 24 months of finalization of the *Framework,* while the

highest risk tests must comply with regulation within 12 months of finalization. We believe that additional detail is needed in advance of finalization. For example, FDA should outline a timely process by which a lab knows when its self-described evaluation of risk-level is accepted by FDA. FDA should also outline a process by which it will adapt risk classification for both diagnostic kits and LDTs that are related to submissions for further indications of approved tests and for modifications that may be made to various types of tests during their life cycles. Finally, it is not clear what will happen to the classification of a marketed LDT when a kit for the same intended use is cleared by FDA.

It is also critical that FDA publish a draft guidance document on risk-classification before finalization of the *Framework,* because compliance is predicated on a test's risk classification. Laboratories should not have to guess which tests will be classified into which risk pool. Knowing in advance which tests are likely to be classified into each risk pool will allow laboratories to prepare for and comply with the final *Framework,* rather than leaving them to react to FDA risk assessments during the implementation process.

CLIA and QSR harmonization

PMC notes that many laboratories have concerns about the potential for duplication and conflict between the regulatory requirements that laboratories are subject to under the Clinical Laboratory Improvement Amendments (CLIA) and the new requirements that would be imposed by the FDA's proposed framework. Duplicative and conflicting regulations represent an unnecessary burden and cost for laboratories and government.

To address these concerns, FDA should harmonize its quality system regulations (QSRs) with the quality standards that already exist under CLIA, and only impose regulatory requirements on labs where the existing requirements are insufficient to achieve a specific, clearly defined and rationally necessary regulatory goal in the least burdensome manner. PMC notes substantial overlap in the regulatory requirements under FDA medical device regulation in 21 CFR Part 820 and the existing regulations under CLIA in 42 CFR Part 493 as it pertains to quality system requirements, design controls, document controls, purchasing controls, production and process controls, acceptance activities, nonconforming products, corrective and preventive actions and records. PMC urges FDA to identify the least burdensome approach to QSRs by using existing CLIA regulatory oversight to the fullest extent possible, which means deferring to CLIA regulations where regulatory goals overlap and are adequately met.

Additionally, PMC requests that an explanation of the harmonization of the FDA QSRs and those quality standards existing under CLIA be put forth jointly by FDA and CMS for public comment and be fully resolved before the proposed *Framework* is finalized.

Adverse event reporting: The section of the *Framework* on adverse event reporting is not entirely clear. Specifically, please clarify how FDA intends to apply to LDTs the definitions of reportable events in the existing Medical Device Reporting regulations at 21 C.F.R. Part 803. PMC suggests that FDA clarify that a reportable event occurs when a lab becomes aware that a test has reported an incorrect answer (e.g., an analytical validity error) likely to result in patient harm. FDA should clarify that laboratories do not have to actively seek/survey for adverse events, but that they do have the responsibility to create and present for inspection the process they have designed to vet and address reports of adverse events and customer complaints.

User fees: FDA should clarify how it will comply with its MDUFA III commitment to avoid imposing new user fees on laboratories or LDTs during the MDUFA III period (ending October 1, 2017).

Labeling: Within the FDA *Framework* it is unclear how FDA plans to handle redundancies and conflicts with the CLIA program in relation to labeling requirements. Below, we explain 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 CLIA requirements for laboratory clinical consultation, and because LDTs are not marketed as physical products in packages to which labels are readily affixed, 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.

False Claims Act: Due to False Claims Act constraints, current FDA device labeling regulations may have negative consequences on the practice of medicine if applied to LDTs. Physician laboratory directors and laboratory medicine experts 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. This is an aspect of medical practice upon which personalized medicine depends. Current device regulation may impede physicians and laboratory medicine experts from effectively doing their job because of potential False Claims Act concerns.

Briefly, physicians and laboratory medicine experts routinely discuss options that may appear to modify FDA-approved or cleared devices or the instructions for their use. When physicians and laboratory medicine experts are treated as manufacturers, such alternative uses cannot be discussed. When a test has been "labeled" for one use but is appropriate for another use, a manufacturer is, under almost all circumstances, prohibited from revealing that use, while physicians and laboratory medicine experts are still permitted to discuss and use them. 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, following developments in the scientific and clinical literature, identify alternative uses that could require changes to labels.

PMC suggests that the agency develop policy for discussions between treating physicians and laboratory medicine experts for LDTs, so that they can discharge their duty to advise treating physicians seeking advice on relevant testing options. Physician laboratory directors and laboratory medicine experts 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.

Requests related to FDA's process

Release another draft before finalization: Given the scope of the *Framework,* the questions that laboratories have regarding it and the challenges compliance poses to the laboratory industry, we strongly

urge FDA to release another draft of the *Framework* for public comment before a final version is issued. Specifically, we request the publication of second versions of the *Framework* draft guidance documents, a joint draft guidance document that harmonizes CMS and FDA regulations, and a draft guidance document on how FDA proposes to classify LDTs into different risk categories. We ask that the release of these documents be coupled with a list of public comments and agency responses, as described below. After the release of this package, we ask FDA to engage in another public comment period that includes a webinar and a public meeting.

Publish list of comments and responses: We understand that FDA will receive a number of suggestions from specific stakeholders and groups. Since laboratories are unfamiliar with FDA regulation, we suggest that the agency publish a detailed response to stakeholders' comments, something akin to a "preamble to a regulation," which is often issued during notice and comment rulemaking. We think a document that summarizes major areas of feedback, suggestions and comments, and clarifies FDA's thinking as to whether or how the draft guidance can or should be modified to address the comments will serve to educate stakeholders on details, add nuance to the community's understanding of the documents and make the second round of comments more useful to FDA. Clinical laboratories and stakeholders can best address FDA's evolving requirements if the agency's thought process is outlined in a transparent way. Waiting to issue a final guidance that only briefly summarizes some comments will therefore make it harder for stakeholders to comply with the new regulations.

Economic impact analysis: An analysis of the regulatory proposal should be conducted to assess the economic impact on all affected entities and to identify the least economically burdensome regulatory path for clinical laboratory compliance. This should include an analysis of how this proposal will or will not impact the future of personalized medicine and health care quality overall.

Risk classification: Defining risk levels for various types of diagnostics used for different purposes poses a challenge for laboratories as they work to understand how FDA will catalog tests into specific risk categories.

It would be useful for FDA to work with stakeholders to define a framework for gathering data for different intended uses. Furthermore, FDA should address how existing literature and data requirements for clinical laboratory accreditation may be leveraged to support FDA's requirements and how such data should be conveyed to the agency in the least burdensome, yet confidential way.

Advisory committee: We suggest that FDA convene a multidisciplinary, multi-stakeholder panel to address outstanding issues before the *Framework* is finalized. The committee should address the harmonization between CLIA quality standards and FDA's QSRs as well as how to categorize different types of diagnostic tests with different intended uses.

While we recognize that FDA has significant disclosure and conflict-of-interest rules, PMC suggests that the agency be as expansive and inclusive as possible in recruiting key opinion leaders with relevant clinical laboratory and personalized medicine experience when empaneling the advisory committee.

We suggest the following composition:

- Expert in personalized medicine
- Physician who orders personalized medicine tests
- Physician who conducts tests and reports results
- Representative from the diagnostics kit manufacturing industry
- Representative from a sole source/proprietary lab

- Representative from a hospital, academic medical center or clinic-based lab
- Representative from a large, national reference lab
- Representative from a pharmaceutical manufacturer
- Patient who has benefited from advanced personalized medicine diagnostics
- Representative from CMS' CLIA program involved in laboratory regulation
- Representative from the Centers for Disease Control and Prevention who is experienced with laboratory regulation
- Third-party accreditor with deemed status within the CLIA program

Finally, we strongly recommend that FDA include ex officio representatives from FDA's Center for Drug Evaluation and Research (CDER), one of whom is an expert in oncology and another who is an expert in a disease state outside of oncology.

Unintended implications of these policies

Drastic changes in the regulatory processes for laboratories might cause unintended consequences. We outline them below with the hope that understanding them will be a step toward protecting the field against them.

Contraction in the industry: Personalized medicine and public health rely on a strong, vibrant and diverse laboratory community to address unmet and evolving health needs, develop innovative approaches to care and respond to public health threats. Regulations that do not appropriately balance risks and benefits may threaten the existence of some laboratories or drastically reduce their menu of offerings. Industry contraction could cause patient access issues for existing tests, prevent other tests from being developed and drive up the cost of testing in general. Regulatory burdens may also cause a delay in laboratories submitting tests to FDA for approval, further hampering the field. Loss of access to targeted therapeutics due to laboratory industry contraction and reduced availability of their associated personalized medicine diagnostics is of significant concern to our community.

Access issues: Presently, patients have access to evolving diagnostic tests that are changing health care. We fear loss of access to existing, valid personalized medicine diagnostics due to economic infeasibility of FDA regulation and the loss of future evolutions of those tests as developers find difficulties in navigating them through the existing FDA medical device process. Furthermore, in the interim, we are concerned about patients losing access to tests as rules change because of agreements with health insurance plans. If the only "in-network" laboratory for a particular health plan stops providing high-complexity molecular tests, a patient's health care quality could suffer through delayed or denied access to a test.

Standard of care taking backward steps: Many patients have benefited from innovative personalized medicine tests that have drastically changed how disease is treated. We are concerned, however, that much work needs to be done to ensure that these tests remain on the market as FDA and industry work through outstanding issues.

Conclusions/recommendations

FDA and the community realize that the *Framework,* when implemented, represents a paradigm shift for how laboratories are operated and regulated. For this reason, PMC has a number of suggestions to ease the industry into regulatory oversight by FDA.

Laboratory education: FDA should work with established academic societies, laboratory trade and professional associations, and third-party accreditors to develop and share information. This should

include a multifaceted education process to assist laboratories in achieving compliance with any FDA guidance or regulation resulting from this process. Examples are below:

- FAQs: FDA should publish Frequently Asked Questions (FAQs), especially on risk categorization for different types of diagnostic tests used for different intended uses. For example, the same biomarker might be tested for therapeutic selection or for diagnostic purposes. FAQs should cover data submissions type and quality for each type of diagnostic used for different purposes and classified by different risk-levels.

- Workshops: FDA should develop educational programs in live and virtual workshops to explain compliance and implementation. These activities should be implemented nationwide and coordinated with large meetings designed to attract laboratory personnel. It might be helpful if, when possible, workshops focus on how FDA regulations fit within different settings, such as hospital-based laboratories, large reference laboratories and sole-source/proprietary laboratories.

- Real-time support: FDA should staff a toll-free number from 9 a.m. ET – 5 p.m. PT to answer questions from the industry beginning at the time of guidance document finalization and throughout the phase-in period. This should be an outlet for quick user questions and informal answers from the agency, and should cover the full business day across the country.

- Guidance document and regulation list for laboratories: FDA should develop, publish and maintain a listing of all relevant guidance documents and applicable regulations to provide laboratories with easy access to reference materials including other relevant guidance documents and regulations. FDA has done an excellent job of using its website to communicate important LDT updates to the broader community. A list of appropriate regulations and guidance documents would be a useful addition to the website. We suggest that this be done as soon as possible, because as laboratories become familiar with them, they might have clarification questions. These questions should be addressed before the *Framework* is finalized.

Medical device modification regulation: While discussing the *Framework* with PMC members, it became clear that the current medical device regulatory framework should be altered and improved to take into consideration the specific challenges posed by diagnostic tests. For example, modifications to existing tests should be accelerated in a way that allows efficacious products to evolve while protecting patient safety. FDA should provide guidance as to when changes can be implemented through memoranda to file versus new 510(k) notices, annual reports versus 30-day notices, real-time supplements, or standard (180-day) PMA supplements, and suggest under what circumstances each is advisable.

Health care costs: While it is beyond the purview of FDA, PMC would like to briefly discuss health care costs. FDA regulation will cost laboratories money. They will have to focus attention on educating their current workforce on FDA regulations, hire new staff or cut back their menu of testing services to lower their regulatory burden. All of these expenses, coupled with the user fees that will one day be imposed, raise the cost of diagnostic tests. Yet the laboratory industry has been decimated by recent changes in coverage and payment policies by both the public and private health plans. When considering the regulatory options, one more burdensome than the other, we strongly urge FDA to select the less burdensome option.

Concluding requests

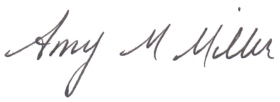
PMC appreciates the opportunity to provide comments now and in the future as the agency continues its work to identify the appropriate balance between regulation, innovation and access to personalized medicine diagnostic tests.

Along with many others, PMC has requested additional information on risk classification, harmonization between the CLIA program and FDA QSRs, how technical test modifications would be handled, 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. During public meetings, FDA staff members have stated that the agency intends to issue a second draft of the *Framework* only if changes are significant. However, PMC has requested that comments from stakeholders and the agency's response to them be as transparent as possible to allow further improvement to the *Framework.* Specifically, 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.

Thank you for allowing PMC to comment on the draft *Framework.* We look forward to working with the agency on revisions. If you have any questions about the content of this letter, please contact me at amiller@personalizedmedicinecoalition.org or 202-589-1769.

Sincerely yours,



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