PMC
PERSONALIZED
MEDICINE COALITION

October 14, 2016

Robert M. Califf, M.D.
U.S. Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2016-D-1703

Principles for Codevelopment of an In Vitro Companion Diagnostic Device With a Therapeutic Product

Dear Dr. Califf:

The Personalized Medicine Coalition (PMC) appreciates the opportunity to submit comments regarding the U.S. Food and Drug Administration (FDA)'s draft guidance document, *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product*.

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.

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 work best for each patient. By combining this information with an individual's medical records, circumstances, and values, personalized medicine allows doctors and patients to develop targeted treatment and prevention plans.

Our members have long had interest in the topic of how FDA will coordinate review of targeted therapeutic products and the diagnostic tests that support their use. We commend FDA on this work and for engaging a diverse set of stakeholders and incorporating their various perspectives into this developing draft over the past decade.

Since the agency published its 2014 final guidance on the regulation of in vitro companion diagnostic devices, PMC has urged FDA to publish a detailed guide to aid product sponsors in coordinating the review of drugs and diagnostic products. We are pleased that FDA responded to that suggestion with an outstanding draft on the topic.

This guidance is especially important now given that nearly one-third of FDA's new drug approvals are personalized medicines. We expect that trend, which is already having a

tremendous impact for patients, to continue. These advances are enabling more accurate diagnoses, better prediction of individual susceptibility to disease based on genetic or molecular factors, improved detection of disease at early stages, greater use of targeted treatments, and, more broadly, greater efficiency and effectiveness for the health care system.

Scope and Statement of Neutrality

These comments focus on novel therapeutic and diagnostic products that are being developed and regulated simultaneously. PMC responded separately to FDA's recent draft guidance documents on next-generation sequencing (NGS). Furthermore, the draft guidance document addresses the rather new concept of "complementary diagnostic." While this concept is compelling, we will not address it in this letter other than to suggest that it might be considered as a topic for another draft guidance focused on that topic specifically. We also will not comment on the different types of medical devices outside of diagnostic testing nor will we comment on issues pertaining to the regulation of laboratory-developed tests. Finally, many of PMC's members will present their own responses to the agency and will actively advocate for those positions. PMC's comments are designed to provide feedback so the general concept of personalized medicine can advance. These comments are also intended to support and augment comments made by our members.

In this letter, PMC will identify areas where FDA could provide more detail through examples, points that FDA could clarify, and where terms should be defined.

Areas Where Examples Would Be Helpful:

Timelines: FDA urges both therapeutic and diagnostic product sponsors to meet with the appropriate FDA review centers while planning, and before launching, a clinical trial designed for regulatory purposes. Perhaps FDA could develop a hypothetical example and publish a sample timeline to aid sponsors. Such a timeline could allow therapeutic and diagnostic partners to work together in a timeline consistent with FDA's expectations. It would also be helpful if the timeline allowed for multiple partners on drug or diagnostic development.

Prescreening: In the field of personalized medicine, physicians and medical centers often use advanced diagnostic tests to determine treatment paths for patients. Many patients consider clinical trials only after receiving those test results. Thanks to the increased use of NGS testing for treatment selection, this trend is growing. Because of this transformation in health care, prescreening is likely to be a factor in a clinical trial for a new targeted therapeutic. We suggest FDA develop a hypothetical example on how sponsors should manage designing, populating, and conducting clinical trails where prescreening is a factor. This may include approaches to analyzing data in a study where prescreening has occurred.

Inter-center consultation: In the draft guidance document, FDA makes note that at times, communications will be shared between the different FDA centers and the sponsors of the therapeutic and diagnostic. To streamline product development and review, we suggest that the agency provide procedural details regarding under what circumstances, when and how the agency will share communications between the centers and product sponsors. It would be helpful if FDA elaborated on how the diagnostic and review teams at FDA will coordinate their respective reviews and provide feedback to sponsors. FDA suggests that both therapeutic and diagnostic

representatives participate in reviews of the partner product. We also suggest that FDA coordinate reviews so that center representatives could be present at meetings with sponsors of both products.

Areas Where Clarification Would Be Helpful

In some instances, FDA's recommendations or suggestions on possible approaches are unclear to sponsors, and we encourage FDA to clarify subjective statements that have been highlighted by other commentators. Below, PMC outlines some examples of where clarification may be necessary.

Stratification and bridging studies: It is currently unclear what stratification by assay cut off trial design would look like. Perhaps the agency could outline some examples of acceptable trial design so that sponsors can better understand what characteristics an acceptable trial design might entail. Furthermore, it would be helpful to understand how the agency would like to establish the cut off for the IVD companion diagnostic in bridging studies.

Banked samples: According to the draft document, use of banked samples could be acceptable if they are from adequate, well-conducted studies, yet no details are provided. Perhaps the agency could provide some attributes of an "adequate" and "well-conducted" study so that trial designs provided to the agency would better conform to expectation.

Areas Where Term Definitions Would Be Helpful

The terms "candidate IVD," "early prototype test," and "precursor IVD," are all used throughout the draft guidance document. If those terms are meant to be synonyms, it would be helpful to use consistent terminology in the final guidance document. However, if they refer to IVDs in different stages of development or refer to different tests, it would be helpful to define each term. Throughout the document some other terms are not defined. Consistent and clear use of language will aid the coordination of regulatory review of diagnostic and therapeutic products. We suggest FDA provide a list of terms with definitions in an appendix or in footnotes. Please include the following: analytical studies, ICD, investigational plan, investigator role, protocol.

Conclusions/Recommendations

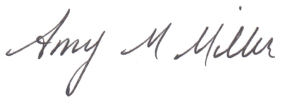
This draft guidance document provides a useful, thoughtful, and well-constructed guide to the codevelopment of drugs and diagnostics. PMC recognizes and appreciates that the process described in the draft guidance document could drastically improve the ease of coordination for codevelopment. Furthermore, we appreciate the significant work and experience that went into the development of the document. Clearly, FDA has worked very hard to aid innovators in bringing new products to market. The impact on personalized medicine is quite clear.

Individual members of the PMC are likely to comment with specific suggestions that will assist them in bringing targeted therapies to market. Those detailed suggestions should be given careful consideration by the agency. If the agency received conflicting yet well reasoned suggestions, publishing a rationale for agency decisions in the supporting document would prove very helpful to product sponsors.

PMC appreciates the opportunity to provide these comments and complements and encourages stakeholder engagement by the agency. PMC and FDA are united by a shared goal of providing patients and health care

providers with safe and effective technologies that will best serve the needs of patients. If you have any questions about the content of this letter, please contact me at amiller@personalizedmedicinecoalition.org or (202) 589-1769. We look forward to further opportunities to provide feedback.

Sincerely yours,



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