American Association for Cancer Research
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October 6, 2016

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

Re: Docket No. FDA-2016-D-1703 for Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication, and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the July 2016 draft guidance, "Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product."

Aligning the therapeutic product and diagnostic test development process will undoubtedly have a dramatic impact on the speed and efficiency with which patients gain access to safe, effective, and novel life-saving therapies. The AACR supports the development of high-quality NGS tests with high analytic performance characteristics, and we commend the FDA for its commitment to advancing this critical area of precision medicine that holds great promise for dramatically improving patient care.

In June 2011, the FDA issued a draft guidance, "In Vitro Companion Diagnostic Devices," and the AACR, as well as other organizations, were fortunate to have the opportunity to submit public comments. In our comments to the Agency, we asked the FDA to expedite guidance on the codevelopment process of therapeutics and diagnostics. We appreciate the Agency's efforts to consider feedback from various stakeholders and commend the Agency for following through with our request by providing such a thoughtful and detailed draft guidance. The AACR recognizes that this draft guidance represents a tremendous step forward in modernizing the regulatory process for the codevelopment of an in vitro diagnostic device with a therapeutic product. We believe that early and frequent consultation with the FDA will help to foster this transparency and applaud the Agency's commitment to transparency in the contemporaneous review process.

Ultimately, the key to speeding safe and effective therapies to patients will be a flexible regulatory framework. Therefore, the AACR applauds the FDA for its flexible approach to the oversight of this codevelopment process. More specifically, in **Section III.C: Planning Ahead for IVD Validation in Potential Codevelopment Programs,** we praise the FDA for allowing the use of intended for research use only (RUO) products as part of Clinical Trial Assays (CTAs), and the use of contrived samples in

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validation studies when it is not possible for sponsors to obtain specimens containing a particular marker. Additionally, we appreciate that the FDA will allow for the use of representative samples for establishing analytical validity of NGS panels. The AACR believes that this flexible approach will allow for new and innovative mehods to be explored while still ensuring that the codevelopment process will culminate in the development of safe and effective products.

In these comments, the AACR respectfully asks the FDA to consider the following three points for additional guidance and clarification.

In **Section III.B.1: Risk Assessment and IDE Requirements and Section III.F.1: Coordinating Review Timelines**, the FDA discusses risk classification of IVD companion diagnostics as Class III and the possibility of reclassification into Class II upon 510(k) clearance or de novo request. The AACR supports this risk-based approach; however we believe that further clarity is needed on the criteria that must be met in order to reclassify an IVD companion diagnostic as Class II. We ask that the Agency further outline the steps that a sponsor of a moderate-risk IVD companion diagnostic would have to take in order to succeed in this reclassification.

In Section III.C.3: IVD Prototypes in Early-Phase Therapeutic Product Clinical Trials, the FDA will allow the use of CTAs in early-phase trials. The draft guidance states that *"when a CTA is used to inform the management of clinical trial subjects (e.g. enrollment, assignment to treatment arm, dose, etc.), FDA recommends that a single testing protocol be used in the trial, and that the CTA be fully specified (i.e., all components, protocols, instrumentation, etc. are specified and fixed)."* The AACR commends the flexibility of the FDA in allowing CTAs to be used in early phase clinical trials. Care must be taken to ensure that CTAs used in the management of clinical trial subjects are accurate; therefore, the AACR would appreciate if the FDA can provide further guidance on what standards such CTAs will have to meet for use in allocating patients to therapy in clinical trials (e.g. analytic validation to the degree of laboratory developed test or less). Additionally, regarding the "*single testing protocol to be used in the trial*," the AACR suggests that this does not necessarily mandate testing by a single central laboratory; rather local lab testing might be performed using harmonized testing protocols. Finally, it is unclear when CTAs would require an Investigational Device Exemption (IDE), and we would appreciate further clarification from the Agency.

In **Section III.E.3: IVD Bridging Studies**, the FDA states that the sponsor should show that an IVD "*performs very similarly*" to the test used in the trial (i.e. a CTA). The AACR asks for further clarification as to what the agency means by "*performs very similarly*" and would like the Agency to outline the criteria necessary to establish this similarity.

In conclusion, this draft guidance reflects a concerted effort by the FDA to develop a practical guide to assist therapeutic product and IVD sponsors in developing a therapeutic product with an accompanying companion diagnostic. The AACR commends the FDA for its commitment to incorporating scientific

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advances into its regulatory framework and is pleased to extend its resources and broad expertise to the FDA as the Agency further refines its guidance for codevelopment of an in vitro companion diagnostic device with a therapeutic product.

If you have any further questions, please contact Anna Sadusky, PhD, Director, Regulatory Science and Policy, at 267-765-1028 or anna.sadusky@aacr.org.

Sincerely,

George D. Demetri, MD
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