

7, July, 2014

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-N-0530

Attachment: AACR response to FDA Docket No. FDA-2011-D-0215

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 May 2014 notice to the public on **Center for Devices and Radiological Health (CDRH) Guidance Development and Prioritization**.

Progress in our understanding of the molecular underpinnings of cancer has given rise to a new generation of therapies that target cancer cells more effectively and offer new hope to patients. Companion diagnostics allow the stratification of patients to efficiently tailor treatments to the right population of patients and avoid treating patients who are not likely to respond to a given treatment. It is, therefore, imperative to create a regulatory environment that does not stifle innovation, allowing the speedy development of life-saving medical products while protecting the safety of patients.

The AACR applauds the agency on its release of the list of prioritized medical device guidance documents to be developed in FY2014 and is pleased to comment on the list of documents that the Agency intends to publish. In particular, the AACR urges the FDA to finalize guidance to industry on the topic of "In Vitro Companion Diagnostic Devices". The guidance addresses a need for greater consistency in how FDA will evaluate and regulate these products which are increasingly becoming a crucial part of cancer treatment and care. The AACR previously submitted detailed comments on the topic of "In Vitro Companion Diagnostic Devices" in response to agency docket no. FDA-2011-D-0215, "Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices" on October 12, 2011 and refers the agency and its staff to the input offered therein. The AACR respectfully asks FDA to consider modifications to the draft guidance as suggested in our attached comment letter and to clarify how the

agency will approach unapproved tests that are already standard of care in oncology practice.

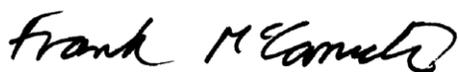
The AACR notes that FDA has not included **Co-development of Therapeutics and Diagnostics** in either the “A” or “B” lists of prioritized medical device guidance documents to be developed in FY2014. Since the majority of oncology drugs in development today are targeted therapies with a companion diagnostic, the AACR courteously suggests that the agency consider revising the list of priority guidance documents for FY2014 to include said guidance in the “A” list. The AACR also urges guidance development staff at CDRH to align their views on co-development of a diagnostic with a therapeutic and/or biologic with their colleagues in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). The AACR stands ready to provide any input, assistance and support to the agency to further the above objectives.

The AACR applauds the speed with which the FDA has been approving targeted cancer therapies like mekinist (trametinib) and taflinar (dabrafenib) along with their companion diagnostics. While these drugs and their companion diagnostics exemplify the success that is possible with coordinated review and approval of personalized cancer medicines, it is vitally important that the FDA continues to be flexible in its approach towards review of these complicated medical products, and that approval of a needed drug is not delayed because its companion diagnostic test lacks sufficient validation.

Representing cancer researchers across the discovery and development continuum—from the laboratory to the clinic, the AACR is committed to working with all stakeholders to facilitate and speed the delivery of medical advances to cancer patients. The AACR commends the FDA for its commitment to incorporating scientific advances into its regulatory framework and is pleased to extend its resources and broad expertise to the FDA as the Agency works on developing guidance documents.

If you have any further questions or require follow up, please contact Rasika Kalamegham, PhD, Director, Regulatory Science and Policy, at 267-765-1029 or rasika.kalamegham@aacr.org.

Sincerely,



Frank McCormick, Ph.D., F.R.S.
Chair, Regulatory Science & Policy
Subcommittee



Margaret Foti, Ph.D., M.D. (h.c.)
Chief Executive Officer

October 12, 2011

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0215, "Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices"

Dear Sir or Madam:

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 2011 draft guidance, "In Vitro Companion Diagnostic Devices."

Progress in our understanding of the molecular underpinnings of cancer has given rise to a new generation of therapies that target cancer cells more effectively and offer new hope to patients. Linking treatment effects with a particular molecular biomarker or biomarker signature will increasingly become the norm and is the foundation of personalized cancer medicine. Companion diagnostics allow the stratification of patients and avoid treating patients who are not likely to respond to a given treatment. It is imperative to create a regulatory environment that does not stifle innovation, allowing the speedy development of life-saving drugs while at the same time protecting the safety of patients.

In general, the AACR is supportive of the draft guidance, "In Vitro Companion Diagnostic Devices," and considers it a welcome step forward in acknowledging the importance of companion diagnostics. The guidance addresses a need for greater transparency and consistency in how FDA will approach this burgeoning scientific area. The AACR commends FDA for its enduring commitment to incorporating scientific advances into its regulatory framework.

In these comments, the AACR respectfully asks FDA to consider modifications in the draft guidance to clarify how FDA will approach unapproved tests that are already standard of care. Additionally, the AACR urges FDA to develop guidance on the process of codevelopment of therapeutics and diagnostics, and we provide details below on several issues particularly important to address in such guidance.

Recommendation to Clarify the Draft Guidance Re “Standard-of-Care” Tests

Current oncology treatment embodies the trend toward personalized medicine as numerous tests are now performed to determine whether certain targeted therapies would be the appropriate course of treatment for a given patient. Some of these “standard-of-care” tests are not FDA-approved, although they would now be considered to be companion diagnostics, based on the definition set forth in the draft guidance. Thus, the AACR asks for clarity as to whether FDA will require approval of existing “standard-of-care” companion diagnostic tests that are used in clinical studies for therapies in the control arm or in combination with investigational agents.

This uncertainty presents particular concern for oncology clinical trials, where the control arm is typically the standard-of-care treatment, which may require the use of such an unapproved diagnostic. It is also a concern when the companion diagnostic test is relevant to an approved therapeutic that is being combined with an investigational agent.

A concrete example is the combination of an investigational agent with cetuximab for treatment of colon cancer patients. As a result of local laboratory testing, the KRAS mutation status of colon cancer patients is often known before enrollment in a study. Because patients with KRAS mutations do not respond to cetuximab or panitumumab, it would be unethical to enroll a patient with a KRAS mutation if the study is randomized and includes a cetuximab/panitumumab -only control arm. In this case, it would seem inappropriate to expect the sponsor to submit an application for a KRAS companion diagnostic that is relevant for cetuximab/panitumumab, but is not relevant for the investigational agent. Analogous scenarios can be envisioned for other “standard-of-care” companion diagnostic tests that are not FDA-approved, such as for estrogen receptor status or presence of the BCR-Abl translocation.

The AACR suggests that FDA clarify its intent to require the approval of “standard-of-care” companion diagnostic tests currently in use for treatment and clinical research so as not to obstruct development of new drugs and new combinations of drugs.

Recommendations Related to Codevelopment of Therapeutics and Diagnostics

The draft guidance describes under what circumstances FDA will require the approval of a companion diagnostic device when approving a new therapeutic or new indication. The guidance implies that the therapeutic and diagnostic will have to be codeveloped, but does not discuss the process by which a therapeutic and its diagnostic are developed. The regulatory uncertainty surrounding codevelopment is a huge disincentive to the development of therapies and diagnostics which are very much needed by patients suffering from life-threatening diseases, such as cancer. Realizing that this issue is beyond the intended scope of the current draft guidance, the AACR strongly urges FDA to expedite guidance on the

codevelopment process and offers for consideration two critical issues for inclusion in such guidance.

Data on Biomarker-negative Patients

The AACR urges FDA to delineate its expectations for clinical trials in which diagnostics play an integral role in stratifying patients for treatment. For example, FDA should clarify whether, for a companion diagnostic that is used in a dichotomous manner (i.e., patients are defined as “positive” or “negative” for a biomarker), and for which early studies of a new therapeutic show dramatic activity in the biomarker-positive population, it is necessary to show with statistical rigor that the biomarker-negative patients are less responsive to the new therapeutic. We have received conflicting reports as to whether the FDA will require proof that there is no activity in the biomarker-negative population in order to approve a companion diagnostic. This is a concern for the development of both the therapeutic and the diagnostic.

The FDA should clarify, for example, whether a codevelopment path similar to that of the HER2 diagnostic test and trastuzumab is acceptable. A recent example is the approval of crizotinib for ALK-mutant lung cancer, which was based on an enrichment trial design where biomarker-negative patients were not included. In this case, FDA did not require the testing of the drug in biomarker-negative patients. In the case of cetuximab, however, FDA initially requested additional data, exceeding the requirements of other regulatory bodies, to show that cetuximab lacked activity in KRAS-mutant patients.

While it is true that the predictive value of a test could be questioned if the biomarker-negative population is not tested, the alternative is exposing patients to ineffective and potentially harmful treatments and slowing down the delivery of drugs to the patients who would likely respond. On a case-by-case basis, where a strong biological rationale, supported by preclinical and early clinical studies, indicates that the biomarker-negative population is not likely to respond, it seems reasonable to focus on the targeted population as clinical trials proceed.

If testing in biomarker-negative patients will be required by FDA in some cases, the circumstances and the pathway should be clearly delineated. Clarity on whether such testing would be required for approval or as a postmarketing commitment will also be important.

From Laboratory Test to IUO

Clarification with respect to data requirements will help developers to determine when to begin to submit an investigational device exemption (IDE) application. It is a huge expense for a diagnostic developer to meet the requirements of an FDA investigational use only (IUO) test. Thus, in practice, a laboratory developed test (LDT) is used initially, when risks

are extremely high for the developer. At some point in the development process, a test can be converted into an IUO test for commercialization. The FDA should clarify whether evidence generated in bridging or concordance studies with an LDT or other versions of the assay will be applicable when the test transitions to IUO and commercialization. Knowing these requirements will allow researchers and developers to seamlessly flow from research to use in patients. It is important that the FDA reflect on the fact that strict adherence for an IUO test could slow the development of a targeted agent with a companion diagnostic.

Conclusion

The AACR applauds the speed with which the FDA recently approved the cancer drugs, crizotinib and vemurafenib, and their companion diagnostics. While these two drugs exemplify the success that is possible in personalized cancer medicine, it is vitally important that the FDA be flexible such that approval of a needed drug is not delayed because a test lacks sufficient validation.

Representing cancer researchers across the discovery and development continuum—from the laboratory to the clinic, the AACR is committed to working with all stakeholders to facilitate and speed the delivery of drugs to cancer patients. Thus, the AACR is pleased to extend its resources and broad expertise as the FDA further considers the issues of companion diagnostics and codevelopment.

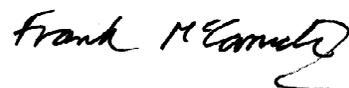
The AACR again thanks FDA for the opportunity to comment on the draft guidance and looks forward to contributing its collective expertise to the further deliberation of these and other issues.

If you have any further questions or require follow up, please contact Pamela Bradley, Ph.D., Director of Science Policy, at (202) 898-6499 or pamela.bradley@aacr.org.

Sincerely,



William S. Dalton, Ph.D., M.D.
Chair, Science Policy and Legislative Affairs
Committee



Frank McCormick, Ph.D.
Chair, Task Force on Regulatory Science & Policy



Margaret Foti, Ph.D., M.D. (h.c.)
Chief Executive Officer

The mission of the American Association for Cancer Research is to prevent and cure cancer. Founded in 1907, the AACR is the world's oldest and largest professional organization dedicated to advancing cancer research. The membership includes 33,000 laboratory, translational and clinical researchers; health care professionals; and cancer survivors and advocates in the United States and more than 90 other countries. The AACR marshals the full spectrum of expertise from the cancer community to accelerate progress in the prevention, diagnosis and treatment of cancer through high-quality scientific and educational programs. It funds innovative, meritorious research grants, research fellowships and career development awards to young investigators, and it also funds cutting-edge research projects conducted by senior researchers. The AACR has numerous fruitful collaborations with organizations and foundations in the U.S. and abroad, and functions as the Scientific Partner of Stand Up To Cancer, a charitable initiative that supports groundbreaking research aimed at getting new cancer treatments to patients in an accelerated time frame. The AACR Annual Meeting attracts more than 17,000 participants who share the latest discoveries and developments in the field. Special Conferences throughout the year present novel data across a wide variety of topics in cancer research, treatment and patient care, and Educational Workshops are held for the training of young cancer investigators. The AACR publishes seven major peer-reviewed journals: *Cancer Discovery*; *Cancer Research*; *Clinical Cancer Research*; *Cancer Epidemiology, Biomarkers & Prevention*; *Molecular Cancer Therapeutics*; *Molecular Cancer Research*; and *Cancer Prevention Research*. In 2010, AACR journals received 20 percent of the total number of citations given to oncology journals. The AACR also publishes *Cancer Today*, a magazine for cancer patients, survivors and their caregivers, which provides practical knowledge and new hope for cancer survivors. A major goal of the AACR is to educate the general public and policymakers about the value of cancer research in improving public health, the vital importance of increases in sustained funding for cancer research and biomedical science, and the need for national policies that foster innovation and the acceleration of progress against the 200 diseases we call cancer.