American Association for Cancer Research

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February 14, 2011

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

Re: Docket No. FDA-2010-D-0616, "Guidance for Industry: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination"

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the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the December 2010 draft guidance, "Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination." Fostering codevelopment of combinations will undoubtedly have a dramatic impact on the speed with which patients gain access to novel life-saving therapies. We commend the FDA for its commitment to advancing this critical area that holds great promise for dramatically improving cancer therapy.

The draft guidance represents a tremendous step forward in modernizing the regulatory process. We are delighted that the FDA is taking a proactive approach to integrating the growing wealth of information about the underlying biological mechanisms of the cancer cell and its microenvironment into the regulatory environment. The draft guidance provides reasonable and balanced criteria to determine when codevelopment of drugs is appropriate and recommends nonclinical and clinical development strategies. Importantly, the FDA acknowledges the great deal of variability in the codevelopment process and urges sponsors to consult with the appropriate review divisions to seek specific recommendations. Early and frequent consultation with FDA will facilitate transparency on this complex issue.

In these comments, we respectfully ask the FDA to consider two minor modifications to the draft guidance. In addition, the AACR is pleased to extend its resources and broad expertise as the agency continues to define appropriate parameters to design innovative trials that capitalize on the biological understanding of disease.

Addressing the Path to Fixed-Dose Combinations

We are aware that the draft guidance is not intended to apply to fixed-dose combinations (i.e., drugs that are physically combined), which are addressed in the "Combination Rule," 21 CFR 300.50; however, it would be helpful for the FDA to indicate how this draft guidance relates to the "Combination Rule." In particular, it would be useful to understand the agency's expectations for

how to develop a fixed-dose combination following approval of a codeveloped drug combination. For example, FDA could clarify whether it anticipates that any bridging studies would be necessary. At a minimum, the AACR feels it would be reasonable for the final guidance to state that the sponsor should discuss the path to fixed-dose combinations with the FDA.

Clarifying Expectations for Additional Phase 3 Dose Arms

The draft guidance states: "In this and other situations, it will often be useful to study more than one dose of the more active drug in phase 3 studies," (page 8, lines 342-3). The AACR is concerned that, as written, it implies an expectation to add a separate second-dose arm to phase 3 studies. While we agree that additional dose arms may sometimes be necessary, we suggest the following edit to clarify that this is not a requirement: "In this and other situations, it **may** be useful to study more than one dose of the more active drug in phase 3 studies."

Partnering with AACR to Further Define Data Requirements

In its initial comments, the AACR sought FDA's guidance concerning data requirements for determining the appropriateness of adaptive randomized phase 2b trial designs that aim to rapidly eliminate underperforming monotherapy arms. We are pleased that the FDA agrees that in certain circumstances the four-arm factorial trial design will have limited utility.

The draft guidance lays out, in broad terms, scenarios where the typical design may be altered. We fully appreciate that some parameters cannot be defined as simple rules and that deep consideration of the issues will be required. The AACR hopes that the FDA will continue to seek stakeholder involvement and offers to assist in development of reference cases, collection of data, and/or discussion of issues that FDA would find useful to continue to move forward.

In particular, the AACR offers its broad expertise and resources to help the FDA:

- Define the required statistical rigor for the data. For example, define what is required to demonstrate that a single agent is ineffective if there is a strong biological rationale suggesting it will only be effective in combination.
- Characterize acceptable surrogate endpoints, such as tumor shrinkage on CT scans (measured by RECIST or other criteria), in assessing clinical activity of the combination and each monotherapy component, recognizing that multiple endpoints are informative for different purposes. For example, clarify whether endpoints for determining activity of single agent versus combination can be different from endpoints for determining clinical benefit.
- Consider assessment of absolute response and differential response. For example, define the threshold for significance of clinical benefit if a combination provides a 30% response rate while individual drugs provide a 0% response rate, or in the case when a combination provides a 70% response rate while individual drugs provide a 40% response rate.
- Reconcile cases in which investigators believe that data are clinically meaningful but do not meet the FDA criteria for safety and efficacy determinations.

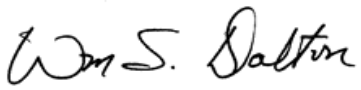
The regulatory process for codevelopment of investigational drugs is complicated by the fact that the issue intersects with many other complex issues facing drug development more broadly, including appropriate use of adaptive designs, biomarkers, surrogate endpoints, and multiple, flexible endpoints. These issues should be considered concomitantly to move the entire drug development enterprise forward as rapidly as possible. The AACR strongly urges the FDA to continue to show leadership in modernizing the regulatory process by also addressing these related issues.

Concluding Remarks

We deeply appreciate the clarity provided in the draft guidance and feel it is a major step forward for the cancer field. The fast pace of progress in science and technology drives a continual evolution of our understanding of cancer biology and innovation in our approaches to cancer treatment. Such rapid change necessitates flexible modernization of regulatory approaches. That the FDA is pursuing this complex and challenging issue speaks volumes about its forward-thinking leaders.

Representing cancer researchers across the discovery and development continuum, the AACR again thanks the FDA for the opportunity to comment and looks forward to contributing its collective expertise to further consideration of these and other issues.

Sincerely,



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

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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 basic, 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. The AACR Annual Meeting attracts more than 18,000 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. Including Cancer Discovery, the AACR publishes seven major peer-reviewed journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; Cancer Epidemiology, Biomarkers & Prevention; and Cancer Prevention Research. AACR journals represented 20 percent of the market share of total citations in 2009. The AACR also publishes CR, a magazine for cancer survivors and their families, patient advocates, physicians and scientists.