American Association for Cancer Research

615 Chestnut Street • 17th Floor • Philadelphia, PA 19106-4404
Telephone: (215) 440-9300 • Fax: (215) 440-9313 • www.aacr.org

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

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

Re: Docket No. FDA-2012-D-1145, "Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products"

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the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the December 2012 draft guidance on "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products."

The AACR applauds the FDA for developing detailed, forward-looking draft guidance on many of the key issues associated with clinical trial enrichment. There are, however, a few areas in which we believe additional guidance would be beneficial. Specifically, the AACR requests the FDA to provide additional information with respect to the definition of enrichment, the circumstances in which different types of enrichment strategies should be used, standards for screening strategies and biomarker development, and testing in marker-negative populations among other issues. We have elaborated on these concerns below. With these additions, we believe this document will enable innovative approaches to trial enrichment, accelerate drug development and create new hope for cancer patients worldwide.

Narrow the definition "enrichment"

For the purposes of this guidance the Agency defines "enrichment" as the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population (lines 44-48). We believe this definition to be too broad. Unless a random sample from an unselected population is taken, most clinical trials would qualify as "enrichment" trials by this definition. Therefore, we request that the Agency provide a more narrowly tailored definition clearly indicating that the use of standard inclusion/exclusion criteria, composite endpoints and re-randomization of trial design should not be thought of as enrichment strategies.

Elaborate on the use of enrichment strategies to assess safety and clinical effectiveness

The draft guidance states that "Although this guidance focuses on enrichment directed at improving the ability of a study to detect a drug's effectiveness, similar strategies can be used in safety assessments" (lines 56-58). Nevertheless, it would be helpful for the Agency to elaborate on the use of strategies to assess safety. We also ask the Agency to distinguish between using enrichment strategies to assess efficacy and clinical effectiveness since the two are distinct measures. Moreover, assessment of the two may be quite different, especially since potential participants with multiple comorbidities and those who are taking concurrent medications are routinely excluded from efficacy trials.

Reinforce flexibility in approaches to trial enrichment and biomarker development

We suggest that the background to the final guidance explicitly state that the differences between development of different therapeutic products (e.g., biologics versus small molecules) might necessitate different enrichment strategies. Likewise, biomarkers include a wide variety of analytes that could be individual, panels, static, or time-varying. This multi-dimensionality means that different strategies may be necessary for different types of biomarker development in different tumor types, different anatomical settings and different products.

Establish standards for screening strategies and developing biomarkers

We request the Agency provide clarity on how and to what detail a sponsor must establish performance characteristics of a screening strategy for selecting patients in enrichment studies. Specifically, we request that the Agency consider the recommendations made in the Institute of Medicine's 2012 report, "Evolution of Translational Omics: Lessons Learned and the Path Forward" in setting performance standards for "omics"-based tests that may be used to enrich populations for a clinical study.[1] The report recommends that development of "omics" based biomarker tests and panels include well-documented stages of discovery and confirmation, analytical validation and then, after stringent review and discussions with the FDA, validation for clinical utility.

We also request that the Agency provide greater detail as to the level of evidence (qualitative and quantitative) needed to develop and validate a biomarker and biomarker-based assays within a clinical trial or simultaneously with a trial for development of the therapeutic product. For example, it would be valuable to be able to use biomarkers discovered in the pre-clinical and/or early clinical phase of the study to distinguish between sub-populations for trial enrollment, though not necessarily to make treatment decisions. After the exploratory discovery phase, if a candidate biomarker is chosen for further development, its role in the enrichment process should be explicitly stated, whether it is to predict favorable or unfavorable course of illness (prognosis), assess the results of biomarker assays and classifiers in predicting the response to specific therapy and/or direct the choice of therapies within the study.

[1] IOM (Institute of Medicine). 2012. Evolution of Translational Omics: Lessons Learned and the Path Forward. Washington, DC: The National Academies Press.

Another issue for consideration is differentiating between biomarkers discovered independently from those which might emerge from within the trial itself. There is a risk of over-fitting multi-analyte data such as those for "omics"-based tests, especially when the number of patients or specimens is much smaller than the number of measurements. There is also a risk that results of embedded biomarker studies may be over-interpreted to have analytic or clinical value or may be used prematurely in the next stage of enrichment, potentially endangering patient outcomes. We would welcome additional guidance on these concerns.

In addition, development of biologics and some small-molecule therapies may employ continuous evaluation of multiple biomarkers. In these cases, it may be appropriate, or even advisable, to accrue patients with a given condition regardless of initial biomarker status, conduct exploratory analyses of (single or multiple) biomarker status and subsequently stratify the trial patient population into appropriate arms of the study which could include multiple test therapies. Further, these scenarios may lend themselves to using biomarker panel platforms as opposed to single tests, and we request that the Agency, in its clarification, distinguish its evidence requirements for development between the two.

Address the complexities of human genetics

We request that the Agency explicitly address the point that multiple alleles at relevant gene loci and multiple protein products from protein-coding genes can affect treatment outcomes. The current document, we suspect for reasons of simplicity, appears to treat a locus as having only one allele of therapeutic significance, although, as is well known, a single locus can be the source of multiple alleles, splice forms, non-synonymous polymorphisms and other variations of differing therapeutic and clinical significance. These emerging data have not yet been leveraged to their fullest extent by researchers and developers for the benefit of patients, but the Agency should acknowledge and inform readers of these sources of biological variation, which have an impact on clinical trial design and treatment outcomes.

Clarify prospectively defining retrospective analyses

A laudable feature of this guidance is that it allows a sponsor to conduct prospectively defined retrospective analyses. This is of great importance in situations where biomarker selection as well as cut-off values for biomarker selection and/or validation, and thereby patient selection and enrichment, can be (and increasingly are) based on large, initial, exploratory studies. This approach will also allow for selection and validation of multiple biomarkers for different sub-populations within a given disease type and setting. An appropriate enrichment strategy in these cases would be to enroll patients into a study based on the status of various pre-determined biomarkers, determine which of those biomarkers have clinical and/or analytic value and interest, and subsequently enrich for patients with the biomarkers of interest.

Although the draft guidance allows for prospectively defined retrospective analyses, the Agency states that "With few exceptions, the enrichment characteristics used in confirmatory studies should be measured at baseline, and patients who are classified as having, or not having, the predictive marker should be stratified and randomly assigned to treatments if both subgroups of patients are to be included" (lines 954-57). Therefore, we request that the FDA provide additional guidance as to when prospective stratification (with retrospective analysis) would not

be necessary. For example, in cases in which the final assay may not be available at baseline (enrollment) it may not be feasible to take the approach outlined above. We do note that the Agency has provided some guidance by stating that with large enough populations enrolled, randomization without stratification will not affect final outcome, and we agree. The caveat here is that enrichment strategies are carried out precisely to avoid large population trials and thus, we request further clarification from the Agency.

Testing in a marker-negative population

We seek greater clarity from the Agency with regards to testing in the biomarker negative population. This is especially important when the mechanism of action of the product is unknown or the product has multiple mechanisms of action and therefore may, in fact, have beneficial effects even in the biomarker-negative population. Biomarker assay panels may have particular utility in these situations, since populations negative for one biomarker may be positive for another. Further, the mechanism of action of a product may vary depending on the tumor site or organ, thus excluding the marker negative population in one setting may not be appropriate for all settings. Adaptive trial design may be of benefit in scenarios wherein the entire (marker positive and negative) patient population could be treated in an earlier/initial phase of the study while simultaneously conducting exploratory biomarker analyses. Based on patient responses in the initial phase and risk and benefit to the marker positive and negative populations, a biomarker-selected population could potentially be enrolled in the later phase of the study for validation.

We also encourage the Agency to elaborate on the clinical utility of tests and products with respect to marker negative patient populations. The Agency should prescribe how much data is required to show lack of or no response in the marker negative population. The clinical utility of the test should be considered in the context of the specific disease area, other available treatment options, their effectiveness and the positive and negative predictive value of the test along with its sensitivity.

The Agency should also explicitly recognize in the guidance that response rates to an intervention vary across therapeutic areas, and thus cut-off values for defining the sub-population to enroll in studies should also reflect the same (e.g., a 20 % response rate greater than placebo in a disease with few or no treatment options may be acceptable for treating the "all patient" population without biomarker enrichment).

The AACR commends the FDA for its commitment to incorporating scientific advances into its regulatory framework. The AACR is pleased to extend its resources and broad expertise to the FDA as the Agency further considers the use of various trial enrichment strategies to support the approval of human drugs and biological products as well as other critical issues. If you have any further questions or require follow up, please contact Rasika Kalamegham, Ph.D., Senior Science Policy Analyst at 267-765-1029 or rasika.kalamegham@aacr.org.

Sincerely,

Frank McCormick Margaret Foti

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

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