

IOM Biomarker Discussion Forum
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CRN Comments
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Session III Speaker Questions

In a 5-minute presentation, please briefly address the following questions, focusing on scientific issues:

I want to thank the IOM and the organizers of this forum for giving me the opportunity to make a few comments regarding this important initiative, and I want to commend FDA (specifically CFSAN) as I have before, for initiating and funding this process.

1. How do biomarkers impact patients, consumers, or clients in your industry/stakeholder group?

Biomarkers (or their absence) represent one of the greatest obstacles to research on the role of diet and nutrition in health promotion and disease prevention. The lack of validated biomarkers for exposure to nutrition interventions and as surrogate endpoints for chronic disease limits the amount of research that can be conducted, especially using prospective randomized, controlled intervention trials, due to cost and logistical issues. This, in turn, limits the ability to derive answers to important questions relating to the ability of diet, food and food components to promote health and reduce the risk of chronic disease. For the industry, this translates into fewer health claims; for consumers and patients, this translates into less useful information they and their healthcare professionals have to make informed decisions. CRN has

commented to both FDA and NIH (both ODS and NCCAM) in the past about the urgent need for additional biomarkers as surrogate endpoints.

2. How does the recommended biomarker evaluation framework relate to biomarker evaluation processes currently in use within your industry/stakeholder?

Seeing that there was no formal evaluation process or framework established for biomarkers, the fact that we now have a framework to start with is seen by the supplement industry as a positive step. The lists of biomarkers validated as surrogate endpoints for disease and as markers of nutrient exposure (i.e. status) are disappointingly short and have been for some time. We hope that with the implementation of this new framework, those lists will eventually grow, although we recognize that this is a long and complicated process.

3. Will a prospective biomarker evaluation process add clarity to product development/consumer understanding?

We anticipate that a formal biomarker evaluation process will add clarity to product development, as companies that choose to invest in research will have a better understanding *a priori* that the research will have broader acceptability and applicability to public health recommendations, such as health claims. As far as consumer understanding, that will depend on whether and to what extent efforts are undertaken to build consumer awareness. In the end, consumers are not so much interested in the biomarker as they are the clinical endpoint that it represents.

4. To the degree it is possible to respond, if at all, what are the key concerns for implementation of the recommendations?

The primary concern regarding implementation of the recommendations is whether there will be adequate resources (both human and financial) made available to take the next steps. This is essential to realizing the value of the recommendations and all the work that went into developing them.

A secondary concern is how some of the recommendations may be misinterpreted. For example, Recommendation 3 (“The FDA should use the same degree of scientific rigor for evaluation of biomarkers across regulatory areas, whether they are proposed for use in the arenas of drugs, medical devices, biologics, or foods and dietary supplements. Congress may need to strengthen FDA authority to accomplish this goal.”). We interpret this statement to mean that when it comes to relying on a biomarker as a surrogate for a clinical endpoint, the product application--whether a food, drug or device--is irrelevant; and there should be a single standard, i.e. the reliance on LDL-cholesterol as a surrogate for heart disease; and the scientific rigor used to validate that relationship should not be modified by the product application (e.g. dietary fiber and statin drugs both lower LDL-cholesterol and both lower the risk for heart disease).

However, the text in the body of the report associated with this recommendation is not consistent with the aforementioned interpretation. Rather, the report states, for example, “...the FDA’s regulation of claims and the scientific standards for evaluating such claims are governed by different regulatory frameworks as compared to drugs; legislation may be required to revise the science-based standards and regulatory processes for these non-drug

products....” The regulation of and scientific standards for claims are much broader and go beyond the validation of biomarkers as surrogates, and in our opinion is outside the scope of the expertise of the IOM Committee and their mandate (see below).

5. To the degree it is possible to respond, if at all, which recommendations of the report are the most useful and/or important?

The most useful and relevant recommendations are those provided in the first part of the report, i.e. Recommendations 1 and 2. These recommendations represent what the IOM Committee was charged with accomplishing and they set a solid foundation for a scientific framework that can now be applied to the literature and future research efforts.

We find recommendations 3 and 4 unnecessary and even confusing, as noted in our earlier response to the previous question. The IOM Committee may have lacked an understanding of nutrition policy and food/dietary supplement regulation, and this is reflected in Recommendation 3. Biomarkers are not only important as surrogates for clinical endpoints but also essential in the assessment of nutrient exposure, which are not only used to inform decisions on health claims, but also for the Dietary Reference Intakes and statements of dietary guidance. The notion that the scientific and regulatory frameworks for these public health recommendations should be identical for those used in the drug approval process is nonsensical. Recommendation 4 is irrelevant to the Committee’s mandate and is inconsistent with Recommendation 3, because, for example, FDA does not currently evaluate dietary patterns that may be

associated with the use of a particular medication or device, although the potential for diet to interact with one or both of these is also quite high.

Ancillary Recommendation 5 (a and b) is totally irrelevant and completely outside the Committee’s mandate, which was not to dissect the regulatory framework for FDA-regulated products. FDA already has post-market surveillance authority over most of the product categories it regulates, including all of those listed in Recommendation 5, and FDA has already conducted research on consumers’ understanding and impression of label claims.

We feel Ancillary Recommendation 6a is important for the implementation of Recommendations 1 and 2 and it should be combined with these to reflect its importance. A number of different Federal agencies conduct research on and evaluate biomarkers, and in order to fully leverage all of these resources, these efforts cannot be “siloeed”, but instead should be consistently shared across the various agencies.

Thank you for your consideration.

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Summary of recommendations from the IOM Report

The Evaluation Framework

1. The biomarker evaluation process should consist of the following three steps:

1a. Analytical validation: analyses of available evidence on the analytical performance of an assay;

1b. Qualification: assessment of available evidence on associations between the biomarker and disease states, including data showing effects of interventions on both the biomarker and clinical outcomes; and

1c. Utilization: contextual analysis based on the specific use proposed and the applicability of available evidence to this use. This includes a determination of whether the validation and qualification conducted provide sufficient support for the use proposed.

2a. For biomarkers with regulatory impact, the Food and Drug Administration (FDA) should convene expert panels to evaluate biomarkers and biomarker tests.

2b. Initial evaluation of analytical validation and qualification should be conducted separately from a particular context of use.

2c. The expert panels should reevaluate analytical validation, qualification, and utilization on a continual and a case-by-case basis.

Scientific Process Harmonization

3. The FDA should use the same degree of scientific rigor for evaluation of biomarkers across regulatory areas, whether they are proposed for use in the arenas of drugs, medical devices, biologics, or foods and dietary supplements. Congress may need to strengthen FDA authority to accomplish this goal.

4. The FDA should take into account a nutrient's or food's source as well as any modifying effects of the food or supplement that serves as the delivery vehicle and the dietary patterns associated with consumption of the nutrient or food when reviewing health-related label claims and the safety of food and supplements. Congress may need to strengthen FDA authority to accomplish this goal.

"Ancillary" recommendations

Improving Evidence-Based Regulation

5a. Congress should strengthen the FDA's authority to request and enforce post-market surveillance across drugs, devices, and biologics when approvals are initially based on putative surrogate endpoint data.

5b. Congress should grant the FDA authority to request studies and sufficient authority to act on the results of studies on consumer understanding of claims on foods and supplements.

6a. The U.S. Department of Health and Human Services (HHS) should facilitate a coordinated, department-wide effort to encourage the collection and sharing of data about biomarkers for all uses, including drugs, biologics, devices, and foods.

6b. The FDA in coordination with other federal agencies should build needed data infrastructure and surveillance systems to handle the information necessary to gain sufficient understanding of the effects of biomarker utilization.