Biotechnology Industry Organization

November 12, 2014

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

Re: Docket No. FDA–2014–N–0926: Advancing the Use of Biomarkers and Pharmacogenomics; Notice of Public Meeting; Request for Comments

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on "Advancing the Use of Biomarkers and Pharmacogenomics; Notice of Public Meeting; Request for Comments." BIO appreciates the Agency's commitment to advancing biomarker science and agrees that biomarkers offer the potential to realize much greater efficiency in, and a more personalized approach to, drug development.

BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BACKGROUND:

There are significant challenges for Sponsors of individual drug development programs seeking to utilize biomarkers, surrogate biomarkers and, particularly, alternative endpoints ***within*** their specific drug development programs. The processes through which advice/consultation can be sought from additional FDA offices and staff (*i.e.*, Office of Translational Sciences, Study Endpoints and Labeling Development staff, *etc.*) to augment the experience/expertise of the FDA review divisions is not transparent. Additionally, the lack of timelines for receiving input or decisions from those support offices or staff makes it difficult for Sponsors to plan their drug development programs. Finally, there is no formal mechanism through which external scientific expertise can be leveraged by FDA to evaluate novel biomarkers, surrogate biomarkers and, particularly, alternative endpoints proposed early during drug development.

The current FDA Biomarker Qualification Program that supports regulatory qualification of biomarkers ***across*** drug development programs also presents significant challenges.

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Chiefly, there are no timelines or responsiveness requirements associated with the steps of the Qualification Process for Drug Development Tools[1], creating unpredictability for biomarker sponsors. Also, rather than prospective evidentiary standards, the program relies upon a Consultation and Advice stage that is designed to align FDA and submitters on *the standards for qualification to be used in each qualification submission* (*i.e.*, achieve regulatory consensus).[2] The transit time through the Consultation and Advice stage of the process is long, and the outcomes from this stage are unpredictable. Qualification submissions since the inception of this process have been challenged to move beyond this stage, and this stage often re-evaluates (and contradicts) scientific consensus previously achieved through external scientific expertise and collaboration. Specifically, as of 2013, FDA had received 23 submissions to the Biomarker Qualification Program, with only three of those submissions receiving regulatory qualification. More concerning, though, is the fact that nearly 60% of those submissions (13) are mired in the Consultation and Advice stage of the Biomarker Qualification process, unable to align scientific consensus with regulatory consensus for qualification.[3]

While these challenges are important, the overarching problem central to both processes is the lack of prospective evidentiary standards for biomarker acceptance or qualification. Without guiding, prospective evidentiary standards tied to context of use, it is impossible to have a consistent, coherent view of biomarker acceptance or qualification, regardless of access to external expertise or review timelines. Once prospective evidentiary standards for biomarker acceptance or qualification have been developed, their employment with appropriate risk-benefit calculus can be monitored through a transparent process, such as an Advisory Committee.

PROPOSALS:

BIO offers the following proposals for creating a more predictable, transparent, and scientifically sound process for qualifying biomarkers for general drug development and for accepting biomarkers, surrogate biomarkers and alternative endpoints for use within individual drug development programs:

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[1] FDA Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools (2014), available online at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf

[2] Goodsaid F. (2013) Impact of Biomarker Qualification Regulatory Processes on the Critical Path for Drug Development. *Biomarker Qualification* [Digital], Goodsaid and Mattes (Eds). Elsevier Press.

[3] Amur S (2013) *Biomarker Qualification at CDER/FDA*. QIBA Annual Meeting, available online at: http://www2.rsna.org/re/QIBA_Annual_Meeting_2013/Index_files/PDF%20slides%20for%20posting%20Tuesday/3.%20AMUR.pdf

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A. Prospective Evidentiary Standards for Regulatory Qualification / Acceptance of Biomarkers for Exemplary Contexts of Use

BIO believes that effectively leveraging the expertise of the broader scientific and health care community will enable the Agency to develop prospective evidentiary standards for regulatory acceptance/qualification of biomarkers and surrogate endpoints. BIO recommends that FDA engage stakeholders (including patients, industry, health care providers, academia, and government) and conduct workshops to develop scientific and regulatory consensus on prospective evidentiary standards for acceptance or qualification of biomarkers for various contexts of use (including surrogate biomarkers and alternative endpoints). Further, BIO encourages FDA to issue these prospective evidentiary standards, as well as the criteria to be used to evaluate the robustness of those data, as regulatory guidance for public comment.

B. Improving the Process for Utilizing Biomarkers, Surrogate Biomarkers, and Alternative Endpoints within Individual Drug Development Programs

BIO recommends that FDA create a more predictable, and transparent process for accepting biomarkers, surrogate biomarkers, and alternative endpoints within individual drug development programs. To achieve this end, BIO believes that Sponsors considering the use of a novel biomarker, surrogate biomarker, or alternative endpoint within a drug development program should be able to, at their discretion, request a meeting with FDA exclusively reserved to discuss these approaches (Biomarker and Endpoint Development Meeting), which could optionally include external scientific expertise, as necessary and appropriate. The participating Sponsor and FDA could coordinate to determine appropriate external scientific expertise to attend the meeting, in accordance with established guidelines on conflicts of interest and maintenance of confidentiality.[4,5] The goal of the meeting would be for the Sponsor and FDA to reach agreement on the specific testing required for the proposed biomarker, surrogate biomarker, or alternative endpoint in the development of the product, guided by the prospective evidentiary standards published in guidance by the Agency. Once development and data analysis are completed, FDA review, informed by external meeting attendees, should take place on a standardized timeline to promote a more predictable process.

C. Improving FDA's Public Biomarker Qualification Program

BIO envisions an improved FDA Biomarker Qualification Program wherein external scientific expertise can be leveraged in biomarker development and evaluation, resulting in a process that would achieve parallel scientific and regulatory consensus for

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[4] FDA Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: *Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees* (2008), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf

[5] Regulation Certification for Special Government Employees (2002), http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048287.pdf

biomarker development with predictable timelines and outcomes of regulatory review. Consortia or Sponsors of individual development programs could engage FDA in a process that would initially result in an agreed Biomarker Qualification Plan (BQP). FDA, Sponsor, and scientific experts would agree up-front on the context of use, evidentiary requirements, and data development plans to justify use of the biomarker prior to the initiation of large-scale data collection and analysis, guided by the prospective evidentiary standards published in guidance by the Agency. The agreed BQP would align the scientific consensus on biomarker development with clear expectations and evidentiary criteria necessary to support the use of a novel biomarker for regulatory purposes. Engaging scientific expertise in parallel with regulatory expertise would facilitate a more informed discussion of the current and projected state of science, realistic/acceptable levels residual uncertainty after qualification, and the appropriate evolution of qualification as additional evidence is generated. BIO believes that this could be achieved using a public process, such as an Advisory Committee, which would promote transparency and illuminate any differences in determination of benefit-risk associated with fulfillment of the evidentiary standards for biomarker and surrogate endpoint qualification.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Advancing the Use of Biomarkers and Pharmacogenomics; Notice of Public Meeting; Request for Comments." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization