



July 16, 2013

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

**Re: Docket No. FDA–2013–N–020: Center for Drug Evaluation and Research  
Medical Policy Council; 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 the “Center for Drug Evaluation and Research Medical Policy Council; Request for Comments.” BIO commends the FDA for reaching out to the public and regulated industry to seek input on topics for discussion by the Medical Policy Council. In light of the rapid pace of biomedical advancement and the complexity of modern drug and biologic development, it is important for FDA to systematically assess existing policies, develop new regulatory approaches, and ensure consistent and predictable implementation of medical policies across various FDA offices and review divisions.

The CDER Medical Policy Council serves a positive function in this process as a forum for senior management input into novel medical policy issues to promote the most efficient and effective methods for demonstrating the safety and efficacy of new therapies. We welcome additional clarity regarding the upcoming agenda topics and objectives for Medical Policy Council consideration.

BIO represents more than 1,100 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.

BIO is pleased to suggest the following topic areas for consideration by the FDA Medical Policy Council.

**A. Pathways for Expedited Drug Development:**

BIO welcomes FDA’s recent release of the draft guidance for industry on “Expedited Programs for Serious Conditions – Drugs and Biologics”, which provides an overview of the four primary expedited development programs: Accelerated Approval, Fast Track, Breakthrough Therapies, and Priority Review. This guidance will be helpful in explaining

the differences between the four pathways, the eligibility and designation processes, and various methods to speed the development of life-saving and life-enhancing therapies. BIO is currently evaluating the guidance and intends to provide written comments.<sup>1</sup>

While this initial guidance appears to focus on many procedural considerations as a first step in implementation of the expanded pathways under the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), we encourage the Medical Policy Council to further engage in an ongoing discussion of the scientific and medical issues underlying these pathways to inform future guidance and consistent implementation of the pathways across various diseases and indications.

For example, under Accelerated Approval, what is meant scientifically for a surrogate endpoint or an intermediate clinical endpoint to be “reasonably likely to predict a clinical benefit” and how can review divisions promote the adoption of new and novel endpoints? How will FDA take into account the “severity, rarity, or prevalence of the condition” and “the availability or lack of alternative treatments”, particularly for rare diseases and therapies that have not traditionally been considered under the Accelerated Approval Pathway?

Under Breakthrough Therapies, we appreciate the Medical Policy Council’s engagement in the designation process to ensure senior level input. We encourage FDA to adopt a transparent, structured process to continue to facilitate senior level input throughout the development process for Breakthrough Therapies. Additionally, we request that FDA elaborate upon the threshold of what constitutes a “substantial improvement over existing therapies on 1 or more clinically significant endpoints.” Post-designation, we welcome additional clarity on the various clinical options available to Sponsors to expedite drug development through novel clinical trial designs and approaches. Furthermore, we support an ongoing dialogue on how manufacturing requirements can be streamlined to accommodate a shorter clinical development program.

## **B. Standards for Qualification of Biomarkers and other Drug Development Tools:**

BIO recognizes and appreciates FDA’s ongoing commitment to advance regulatory science and believes a re-examination of the biomarker qualification process would be an extremely valuable exercise toward streamlining drug development.<sup>2</sup> Qualified biomarkers have the potential to improve public health and yield major impacts on the efficiency of drug development programs and their regulatory review, enabling life-saving or -improving therapies to be delivered to targeted patient populations more expeditiously.

Despite this enormous potential, and a commensurate expenditure of resources, very few biomarkers have been successfully qualified. Coalitions of stakeholders remain committed to the development and qualification of biomarkers, however, which illustrates the importance of prioritizing the improvement of the qualification process,

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<sup>1</sup> “Expedited Programs for Serious Conditions – Drugs and Biologics”, June 2013, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>2</sup> “Guidance for Industry: Qualification Process for Drug Development Tools”, October 2010, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

even in the current resource-limited environment. Increasing the efficiency of the qualification process could greatly benefit many of these stakeholders, and most importantly, patients. In addition, public-private partnerships, foundations, and patient advocacy organizations directly involved in the development of biomarkers, as well as FDA regulatory scientists and biopharmaceutical companies, would also benefit from a more efficient qualification process.

BIO suggests that FDA leadership and the Medical Policy Council work with key stakeholders to develop prospective evidentiary standards for the qualification of biomarkers, facilitate Sponsors' determination of appropriate contexts of use based upon available data, and promote a harmonized qualification process to support global drug development programs.

### **C. Regulation of Tests for Precision Medicine:**

Significant advancements have been made in the development of targeted therapies and molecular diagnostics that have ushered in an era of precision medicine, which will play an integral role in current and future drug development. Precision medicine will be predicated upon multiplex technologies capable of testing wide arrays of biomarkers and gene mutations, which is particularly important in guiding selection of patient subsets likely to benefit from a molecularly-targeted therapy.

While CDRH has played a primary role in the approval of diagnostic tests, BIO encourages FDA to ensure the coordination of processes in CDRH, CDER, and CBER as regulatory policy evolves to ensure consistent and standardized approaches across Centers. A high percentage of targeted biologic therapies and oncology treatments under development are being paired with companion diagnostics, which will necessitate a coordinated approach between two or more Centers, including CBER in many instances.

In addition, an issue of particular concern is the criteria for when one must also conduct trials in the test negative population.

### **D. Acceptable Clinical Trial Approaches for Disease Subsets**

Modern drug development is increasingly focusing on targeted patient sub-populations and BIO also encourages FDA to further clarify clinical trial standards for certain disease subsets. For example:

BIO requests greater flexibility in the selection of endpoints for many slowly progressive degenerative diseases, as it may be prohibitive to measure longer-term clinical endpoints that may not develop for several years or decades. For example, FDA guidance on the use of "intermediate" clinical endpoints that can be measured earlier in drug development would be welcome.

We also suggest that FDA further clarify standards for drug development and sub-setting in high unmet need populations within much larger populations. For example, FDA's definition of morbidly obese patients versus those with less severe disease is unclear. In some cases, concern over off-label use may be preventing early approval of drugs for narrow populations with high unmet need, which is a negative public policy outcome.

Additional guidance is also requested on acceptance of extrapolation among populations. This is highly relevant to drug development for certain sub-populations, such as pediatrics and rare diseases, through the use of rational pharmacokinetic / pharmacodynamic (PK/PD) extrapolation in some instances.

#### **E. Post Marketing Requirement (PMR) & Post Marketing Commitment (PMC) Tracking:**

Under PDUFA IV, FDA made significant progress in updating the database for tracking PMRs and PMCs, but experience has suggested that the tracking system often does not reflect modifications to timelines and trial designs agreed between Sponsors and the responsible review division, particularly for pediatric trials. This can lead to PMRs and PMCs being listed as “delayed” despite meeting agreed upon timelines. Commitments under PREA appear to represent a disproportionate component of commitments listed as “delayed” according to FDA’s methodology. We encourage the Medical Policy Council to revisit the process for tracking post-market commitments and requirements to ensure that studies and their completion timelines are appropriately documented and are reflective of the feasibility of trial conduct for certain challenging diseases and sub-populations.

#### **F. Standard for Imposing, and Removing, Safety Study Requirements:**

BIO also encourages the FDA Medical Policy Council to consider the level of evidence necessary to justify significant new post-market study requirements to address a safety question and, conversely, when and how to end such requirements.

#### **G. Proprietary Name Review:**

BIO also encourages the FDA Medical Policy Council to revisit the review and approval of drug and biologic proprietary names. BIO supported efforts under PDUFA IV to improve the consistency and predictability of the proprietary name evaluation process by the FDA Division of Medication Error Prevention and Analysis (DMEPA) to reduce medication errors caused by look-alike or sound-alike names. Although some improvements have been made in recent years, the current process provides limited transparency on its methods for proprietary name review. The 2010 CDER Guidance describes components of the agency proprietary name review process, but there is no formal guidance describing methods validation or standards.<sup>3, 4</sup> We also suggest enhancements to the appeals process so that Sponsors may challenge DMEPA decisions at a higher Office level rather than through a second DMEPA review.

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<sup>3</sup> Guidance for Industry on the Contents of a Complete Submission for the Evaluation of Proprietary Names February 2010, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf>

<sup>4</sup> PDUFA Pilot Project Proprietary Name Review Concept Paper, September 2008 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072229.pdf>

## **H. Output of the Medical Policy Council Deliberations:**

Finally, we request greater clarity regarding the process that the Medical Policy Council will utilize to communicate its decisions and determinations back to the public. BIO believes that FDA needs internal forums at which senior leaders and review staff can have open and frank discussion of scientific and process issues related to drug review. However, we expect that any new and significant policy decisions will be published in the Federal Register for public comment or notice. Where appropriate, it would also be beneficial for stakeholders to understand how non-policy decisions, implementation decisions, and other issues that may not be regularly published in the FR would be communicated externally.

### **Conclusion:**

BIO appreciates this opportunity to comment on the *Center for Drug Evaluation and Research Medical Policy Council; Request for Comments*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

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