Biotechnology Industry Organization

March 1, 2013

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

Re: Docket No. FDA–2012–N–1248: Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need; Public Hearing; Request for Comments

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit written comments on the proposal to create an alternative approval pathway for certain drugs intended to address unmet medical need, also referred to as a Special Medical Use (SMU) designation.

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 applauds the Administration and the FDA for seeking input on proposals focused on approaches to stimulate innovation and expedite access to medicines that will improve the quality of life for patients that need them the most. BIO has a long-standing position of supporting modern approaches to clinical development and effective review that will invigorate research, development, and availability of drugs to patients. This is consistent with FDA's dual role in both protecting and promoting the public health.

Both the President's Council of Advisors for Science and Technology (PCAST) 2012 report, "Propelling Innovation in Drug Discovery, Development, and Evaluation", and the FDA's January 15th public hearing notice underscore the importance of efficiently and effectively developing new therapies intended to treat targeted subpopulations,

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200
202.488.6306
bio.org

rare diseases, infectious diseases, and serious manifestations of a more common condition. We understand that the PCAST, FDA, and Infectious Diseases Society of America (IDSA) proposals are intended to facilitate more narrow, targeted, and expeditious clinical development programs in such cases. We also understand that the intent is for products approved through this new pathway to utilize an additional communication tool in the form of a special designation and logo that would inform healthcare providers and patients that the therapy was studied in specific subpopulations only, without interfering with the practice of medicine.

Following discussions of the SMU designation concept with BIO's member companies and consideration of the February 4th testimony of other stakeholders, BIO supports implementation of the SMU pathway for a broad range of potential diseases and conditions as scientifically appropriate *if* it can be structured in such a manner that it will promote biomedical innovation and contribute to improved health outcomes for patients suffering from serious, debilitating and life-threatening diseases. We are pleased to provide the following recommendations on how the SMU pathway can be designed to achieve this common goal. BIO looks forward to collaborating with the FDA, PCAST, the Administration, and other stakeholders to work through the details of this important proposal and any questions regarding its establishment and implementation. We would also look forward to the opportunity to comment further as FDA develops specific proposals.

In this regard, BIO notes that FDA currently has broad and flexible authority under its authorizing statute and accompanying regulations to develop streamlined approaches for the development and review of important new therapies, with appropriate labeling regarding the risks and benefits thereof. Thus, depending on the specifics of the SMU pathway, new legislative authority may not be necessary. Nonetheless, BIO stands ready to work with the Administration and Congressional leaders on any such legislation, as appropriate.

Key Elements of a Special Medical Use Pathway:

BIO believes that the following seven key factors are fundamental elements of a potentially successful SMU pathway:

1. Voluntary for Sponsors
2. Prospective and Available Early in Drug Development
3. Broad Eligibility for All Relevant Indications
4. Clear Eligibility Criteria
5. Clarity on Expedited Clinical Development Approaches
6. Focuses Clinical Research on Relevant Subpopulations
7. Does Not Infringe on the Practice of Medicine

We are pleased to provide more detailed comments on each of these elements below.

1. Voluntary for Sponsors

First, a fundamental element of the pathway is that it should be voluntary to the Sponsor. As noted in BIO's statement[1] to the FDA public meeting, the PCAST report recommends that:

> *"the FDA should implement a drug approval pathway under which Sponsors could propose, early in the development process, to study a drug for initial approval under a designation of Special Medical Use (SMU)".*[2]

It is our view that this pathway should be at the request of the Sponsor. We suggest a similar mechanism to that of the Fast Track process, in which a Sponsor requests designation during drug development with a justification of how the subpopulation and the investigational agent meet the criteria of the pathway. FDA could then grant or deny the request. The designation would then apply to the IND, unless the Sponsor chooses to withdraw the designation.

Under no circumstances – either formally or informally - should a Sponsor be compelled or coerced into utilizing this pathway. For example, BIO could not support this pathway if it were to be applied in the same manner as a Risk Evaluation and Mitigation Strategy (REMS), which is imposed by FDA during the review process as a condition of approval. Furthermore, it would be inappropriate for FDA reviewers to recommend informally to the Sponsor late in the development or review process that a product could only be approved if it were SMU designated for a narrow population, unless the Sponsor initiates the dialogue. Such approaches could inappropriately narrow the indication to such an extent that the product may not be commercially feasible; could rule out the possibility of a return-on-investment on large-scale clinical trials on the broader population; and could undermine current statutory incentives for innovators to develop novel products for broader indications. FDA management processes and training should help to ensure that Sponsors are not in any way channeled into the pathway against their judgment and commercial interests, and that the benefits of therapies for patients are not limited by inappropriate FDA application of the pathway.

2. Prospective and Available Early in Drug Development

It is also critical that the pathway be available to Sponsors early in development. The PCAST report elaborates that:

> *"This designation and pathway would be sought early in the development process to allow the sponsor and the FDA to agree upon a more narrow*

---

[1] BIO Statement on *Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need*, February 4, 2013, http://www.bio.org/sites/default/files/2013-02-04%20BIO%20SMU%20Statement%20-%20FINAL.pdf

[2] PCAST, "*Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation,", September 2012, p. 64, (emphasis added),* http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf

development program than required for traditional approvals. This pathway would not be intended as an alternative means to approve a drug that is late in development or in the review and approval process."[3]

That is, the SMU process should be treated as a prospective pathway, rather than a retrospective designation, to facilitate expedited drug development plans for the rapid advancement of innovative medicines to patients. By obtaining designation early in development, a Sponsor can design appropriate clinical studies for use under the pathway, for example by conducting clinical studies based upon only the most severe manifestation of the disease without having to progress through more moderate disease populations first.

We presume that an SMU approval would be granted based on a targeted or more focused safety and efficacy dataset and clinical trial plan designed to expedite access of innovative medicines to the patients who need them most. SMU indications and much broader indications could also be developed simultaneously, but as SMU indications may require substantially less time to accrue the needed safety data than a broader indication, they could conceivably be approved more expeditiously than a non-SMU indication.

To achieve these objectives, BIO suggests that the SMU process only be available to Sponsors prior to submission of the New Drug Application (NDA) or Biologics License Application (BLA) to ensure that these studies are designed with the deliberate, prospective purpose of seeking an SMU approval. After approval, the Sponsor could request that the SMU designation be lifted if the results of additional clinical studies justify use of the product in a broader population.

As a matter of principle, SMU designation should not be an option to Sponsors (nor should be proposed by FDA) during the review stage to retrospectively restrict the use of a product to a more narrow population that had been initially studied in broader populations. Appropriate labeling based upon relevant clinical data under this scenario should enable responsible FDA approval and Sponsor marketing of the product.

3. Broad Eligibility for All Relevant Indications

The 2012 PCAST report and FDA public hearing notice discuss several disease states for which an SMU approval pathway and communication tool would enable Sponsors to develop targeted clinical development programs for subpopulations. For example, a drug may have a favorable risk-benefit balance in patients with a severe manifestation of a disease, such as morbid obesity, but an unfavorable or uncertain benefit-risk balance in patients with a mild manifestation, such as being overweight. A second example presented was the approval of a drug designed to prevent a disease for use in a subpopulation at especially high risk, such as a genetic disposition to diabetes. A third example is products designed to treat antibiotic resistant pathogens where the approval of a product would be based on a targeted

[3] PCAST, p. 64

population and judicious prescribing is encouraged to protect against creating resistant pathogens. BIO also notes that the SMU pathway is consistent with the modern era of personalized medicine and genetically defined disease and therapy. For example, the SMU approval pathway might accelerate the advancement of breakthrough therapies for patients with genetically defined cancers where more narrowly focused data collection could serve as a basis for initially expediting access to a subpopulation of patients that could be broadened subsequently based on more studies. During the February 4th FDA public meeting, stakeholders presented additional examples of therapeutic areas, such as rare diseases, where this new pathway would also be beneficial.

At present, neither BIO nor any other stakeholder can project the state of science and medicine in five, 10, or 20 years, and what new medical therapies may be appropriate for use under the SMU pathway in the future. FDA's existing expedited approval pathways embody regulatory flexibility so that the pathway can adapt to new technologies and advancements in science. Likewise, a broad range of indications should be eligible for the SMU pathway on a case-by-case-basis so that it can adapt to novel technologies and emerging public health priorities.

We note, however, that FDA and infectious disease groups have made considerable progress in articulating the details of how this pathway would apply to therapies intended to treat drug-resistant pathogens, a serious public health problem. While the eligibility of the pathway should include a broad set of appropriate conditions, we suggest that FDA issue draft guidance on how the pathway would apply specifically to anti-infectives within 12 months of establishment to provide greater clarity to Sponsors on how to utilize the pathway to develop important new therapies to treat infectious disease. We would further suggest that FDA hold public hearings within 12 months articulating how this pathway would apply to other therapeutic areas. Neither of these conditions should prohibit Sponsors from utilizing the pathway for a broad range of conditions and medicines.

4. Clear Eligibility Criteria

BIO also recommends that the eligibility criteria for the pathway be clear with consistent use of terminology, and that consideration be given regarding how subpopulations will be characterized.

For example, a number of potential eligibility standards for the SMU pathway have been discussed publicly, including:

- "Serious or life-threatening conditions that would address an unmet medical need"[4]
- "Serious, high-risk manifestation of a common condition"[5]

---

[4] FDA, Federal Register Notice, January 15, 2013, p.1, http://www.gpo.gov/fdsys/pkg/FR-2013-01-15/pdf/2013-00607.pdf

[5] PCAST, p. 64

- "Serious or life-threatening conditions for whom the benefits of the drug have been shown to outweigh the risks"[6] or
- "The most serious infections where there exists an unmet medical need (i.e., where insufficient satisfactory therapeutic options exist)[7]

We appreciate the underlying intent of these proposed criteria, but believe that their exact wording may not be appropriate for a formal pathway. For example, BIO does not believe that the initial designation criteria should be based upon whether "the benefits of the drug have been shown to outweigh the risks" because SMU designation is intended to take place early in drug development before clinical data has been collected to demonstrate such a conclusive benefit-risk determination. BIO also does not believe the term "common condition" alone is appropriate. While this would include areas where there are serious manifestations of a condition (*e.g.,* morbid obesity), it may preclude use of the pathway with respect to rare disease subpopulations. It is also unclear whether language regarding "unmet medical needs" is a necessary criterion in this context.

In light of these considerations, BIO recommends the following criteria for consideration:

- "a drug, either alone or in combination with one or more other drugs, intended to treat a serious or life-threatening disease or condition in a targeted subpopulation, where such subpopulation is characterized by a different or more severe manifestation of the disease or condition than other patient populations with the same disease or condition."

We note that the terms "serious and life-threatening" are grounded in current Fast-Track and Accelerated Approval statute[8], and would be preferable given the established precedent.

In addition to supporting use of the SMU pathway for small subpopulations suffering from a severe manifestation of a more common disease or condition, this definition would also support use of the pathway in scenarios that might be precluded by more restrictive definitions. Consider for example, a situation where the severe form of a disease is prevalent in 60% of the patient population, while the milder form accounts for only 40%. If the criteria required that the milder form of the condition be prevalent in a *majority* of, or be more common in, the patient population, an important opportunity would be missed to develop a drug for the severe subpopulation.

---

[6] FDA, Federal Register Notice, January 15, 2013, p.2

[7] Infectious Diseases Society of America, (LDSA), "*Limited Population Antibacterial Drug (LPAD) Approval Mechanism Frequently Asked Questions, p. 1,* *http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/LPAD%20FAQs.pdf*

[8] FFDCA Section 506

Alternatively, a population could be characterized by two or more equally severe forms of the condition, but a genomic subset of patients may be more likely to respond to a targeted therapy. Under this scenario, an SMU designation should be available for a product targeted at the patients most likely to respond to the therapy, even though the broader population also suffers from a severe or equally severe manifestation of the disease.

5. Clarity on Expedited Clinical Development Approaches

It is important to recognize that the success of the pathway in providing for expeditious approval of new products for serious and life-threatening conditions will depend on the extent to which FDA and Sponsors work together on streamlining clinical development through smaller and more targeted studies.

First, more frequent and interactive communication between FDA and the Sponsor is fundamental to reaching agreement on a non-traditional development program that can promote the expedited development, approval, and commercialization of SMU products. Working in tandem with other designation processes, such as Fast-Track and Breakthrough Therapies, and the Agency's commitment to enhanced FDA-Sponsor communication under PDUFA V, FDA should encourage more frequent meetings and interactions for SMU products. BIO would like to emphasize the need for timely discussions around Sponsor design of clinical trials to support approval via the SMU pathway.

BIO recommends that FDA issue formal guidance, or modify existing guidelines, on various options for expediting clinical development under the SMU proposal to promote clarity to Sponsors, while continuing to maintain appropriate regulatory and statutory flexibility in meeting the existing standards for safety and efficacy. These approaches would be expected to include smaller, more targeted clinical studies and alternatives to the traditional sequential Phase 1-3 approach to clinical testing. However, the development of such guidance should not prohibit the FDA from moving forward and working with Sponsors on SMU designations and approvals in the near term.

6. Focuses Clinical Research on Relevant Subpopulations

The proposed SMU pathway should also maintain a core focus on developing therapies for the targeted subpopulation of the disease. While a Sponsor may choose to study the broader patient population to expand the label and lift the SMU designation in the post-market, FDA should not compel the Sponsor to study the broader population as a condition of approval or as a post-market commitment or requirement, unless in response to a known serious risk, signal of serious risk, or to identify an unexpected serious risk pursuant to FFDCA Section 505(o). In some instances, the underlying science and clinical experience may suggest that there is no expectation that the product will work in the broader population and it should continue to be labeled for the more narrow indication. In other instances, patient safety or financial considerations may preclude study in the broader population.

We note, for example, that Congress recently addressed this issue in the context of medical device regulation, and confirmed that the Sponsor should have significant flexibility and independence in determining the scope and staging of its proposed research program.[9]

7. Does Not Infringe on the Practice of Medicine

BIO supports efforts to help healthcare providers appropriately understand the information in product labels and to enable them to better evaluate the benefit-risk profile of different therapeutic alternatives, and how that pertains to the medical needs of their patients. BIO understands that FDA views an SMU logo as another tool to communicate to health providers the precise clinical development limitations surrounding an SMU product and help bring attention to the careful benefit-risk analyses that serve as a basis for SMU approvals. However, as noted in BIO's February 4th statement, Sponsor and FDA involvement in the practice of medicine should be kept to a minimum. It is the Sponsor and FDA's role to provide adequate labeling that best informs clinical use of the product.

This is consistent with recent statements made by FDA Commissioner Hamburg and CDER Director Janet Woodcock when discussing the SMU proposal:

> *"This is an issue of having the right science and data to assess risks and benefits but also a broader societal discussion about risks and benefits that individuals and communities are willing to take on and under what circumstances"*[10]
>
> *"...FDA is not seeking to ban off-label prescribing of drugs approved through a new limited-use pathway."*[11]

While BIO supports the opportunity that would be afforded by an SMU pathway to improve the communication of the appropriate use of drugs and the state of knowledge underlying FDA's benefit-risk assessments, BIO cannot support an SMU pathway that would include label warnings or other contraindications that are not supported by clinical data, or that would otherwise restrict or limit patient access to SMU therapies in circumstances beyond the narrow indication that healthcare providers deem to be medically appropriate and beneficial based on the best data available. Further, BIO does not believe it is appropriate for either the FDA or the Sponsor to play (or be required to play) an enforcement or oversight role over the practice of medicine, or in any way interfere with the patient-physician relationship. The emphasis of SMU should be on enhancing the communication of the best

---

[9] FFDCA Section 520(g) (21 U.S.C. 360j(g))

[10] Bloomberg, "*FDA Considers Faster Approval Process for Obesity Drugs",* October 11, 2012, http://www.bloomberg.com/news/2012-10-11/fda-considers-faster-approval-process-for-obesity-drugs.html

[11] *BioCentury, "Debating 'limited use'", January 28th, 2013, http://www.biocentury.com/biotech-pharma-news/coverstory/2013-01-28/fda-wants-public-dialog-on-new-limited-use-pathway-inhibiting-off-label-use-a1*

available information healthcare providers, not on restricting their exercise of judgment in any given patient's situation.

Whatever limits any institution places on SMU products should not prohibit judicious prescribing by trained physicians based upon their informed judgment of what they deem to be the best treatment for an individual patient based on his or her unique needs and circumstances. Limits found, for example, in formularies and health system guidelines should not foreclose physician exercise of such sound medical judgment. Accordingly, the Sponsor of an SMU product should not be subjected to any additional or special post-market restrictions solely by virtue of the SMU designation, and the SMU logo should not be presented in a way to discourages or limit the Centers for Medicare and Medicaid Services (CMS) or other Federal, State or private payer coverage and payment decisions with respect to responsible usage beyond the narrow indication where medically appropriate.

FDA's current initiatives related to education, outreach, and training, and improved professional and patient labeling are positive ways to ensure that healthcare providers appropriately understand and utilize the label and better understand benefit-risk for unmet medical needs. These initiatives should continue to be an element of the broader conversation.

Conclusion:

In conclusion, BIO believes that a proposed SMU pathway that meets these principles and criteria noted above could play a positive role in advancing the development of new therapies for serious and life-threatening diseases and promoting their responsible use. We look forward to engaging constructively with FDA and other stakeholders as these discussions progress, and we again applaud FDA for advancing this important discussion on a new pathway.

Sincerely,

/S/

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

/S/

E. Cartier Esham, Ph.D.
Senior Director, Emerging Companies,
Health and Regulatory Affairs
Biotechnology Industry Organization