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BY ELECTRONIC DELIVERY

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Administrator
Centers for Medicare and Medicaid Services
Hubert H. Humphrey Building
200 Independence Avenue, SW
Room 314G
Washington, DC 20201

Margaret A. Hamburg
Commissioner
Food and Drug Administration
10903 New Hampshire Ave.
Room 2217
Silver Spring, MD 20993

Re: Parallel Review of Medical Products [FDA-2010-N-0308]

Dear Dr. Berwick and Dr. Hamburg:

The Biotechnology Industry Organization (BIO) is pleased to submit the following comments on the notice and request for comments from the Centers for Medicare and Medicaid Services (CMS) and Food and Drug Administration (FDA) regarding parallel review of medical products.[1] 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.

As the representative of an industry that is devoted to improving health care through the discovery of new therapies, BIO shares CMS's and FDA's desire to "accelerate consumer access to new, particularly innovative, safe and effective

[1] 75 Fed. Reg. 57045 (September 17, 2010).

medical products."[2] To achieve this goal, CMS and FDA propose to create a parallel review process in which CMS would begin its national coverage determination (NCD) review process while the FDA completes its premarket review, and play a role in discussions regarding investigational products under development.

As a general matter, BIO does not believe that the existence of separate, serial FDA and CMS review processes has resulted in significant problems in the review and coverage of drugs and biologicals, and questions whether there is any need for a new parallel process. Sponsors who wish to involve both FDA and CMS in clinical development and premarket review discussions may do so voluntarily under current practice, and we encourage both agencies to maintain this opportunity for early consultation, outside of any formal parallel review process, where it is desired by sponsors.

If such a parallel review process can be developed and implemented, CMS and FDA recognize that there are many important issues that must be resolved. *BIO recognizes these issues and believes that there are many potential problems with the proposed process, including our concern that the unique missions of these two agencies remain distinct, and not be comingled or compromised in the course of any parallel review.* Congress deliberately bestowed FDA and CMS with distinct authorities and standards for approval and coverage decisions respectively, consistent with the different missions and constituencies of the agencies. As noted in the Federal Register notice, "FDA premarket review and CMS national coverage determinations differ significantly. Each process operates under different statutory standards and each asks different questions to meet its respective mandates."[3] Indeed, it is critical that the integrity of these authorities continue to be maintained and respected. BIO's specific concerns are detailed below.

I. A Parallel Review Process Should Not Be Used to Determine Medicare National Coverage of Drugs and Biologicals:

BIO believes the proposed parallel review process is not appropriate or necessary for drugs and biologicals for several reasons.

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[2] Id. at 57046.
[3] 75 Fed. Reg. 57045 (September 17, 2010).

First, developing a new parallel review process potentially resulting in more NCDs for drugs and biologicals is not necessary because under current law, Medicare coverage of most drugs and biologicals is determined appropriately by local contractors. CMS's longstanding policies allow contractors to cover both approved and off-label uses of other drugs that are approved by the FDA and are "reasonable and necessary for diagnosis or treatment of an illness or injury."[4] In practice, contractors make most coverage determinations for drugs and biologicals and are able to do so in an appropriate and timely manner. Further, local contractors often are best placed to assess the reasonableness and necessity for their respective and unique constituents, and more NCDs are not necessarily better. In addition to being unnecessary, a parallel review process that would shift responsibility for these determinations from the contractors to CMS would unnecessarily increase demands on CMS's limited resources.

Second, a new parallel review process is not needed to improve timely access to new drugs and biologicals because current processes are adequate to ensure that result. With CMS's encouragement, manufacturers currently approach CMS prior to approval of their products to discuss coverage, coding, and payment. CMS accepts applications for Healthcare Common Procedure Coding System (HCPCS) codes for new drugs and biologicals when FDA approval is expected within three months of the application deadline.[5] CMS also allows drug and biological manufacturers to apply for pass-through status under the hospital outpatient prospective payment system when FDA approval is imminent, and if pass-through status is granted, the Agency creates a new code for the drug or biological to be effective in the next quarter. These processes allow CMS to create new codes to be effective soon after FDA approval of the drug or biological, while ensuring that the Agency does not commit its resources to consideration of codes for products for which approval is not imminent. Until CMS grants new codes, CMS facilitates timely access to new drugs and biologicals billed with HCPCS codes for "unclassified" codes, such as J3490 (unclassified drugs) and J3590 (unclassified biologicals). The proposed parallel review process does not address coding and payment and is not needed to improve collaboration between manufacturers and CMS on these issues.

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[4] Medicare Benefit Policy Manual, ch. 15, §§ 50.4.1-50.4.3.
[5] HCPCS Level II Code Modification Request Process, 2012 Update, http://www.cms.gov/MedHCPCSGenInfo/Downloads/2012HCPCSSApplications.pdf.

Third, Medicare coverage determinations for drugs and biologicals can be made appropriately under current guidance without access to pre-approval data. As instructed by CMS, contractors determine whether the drug or biological is "reasonable and necessary" by consulting the "advice of medical consultants and with reference to accepted standards of medical practice and the medical circumstances of the individual case."[6] This consultation does not require CMS to have access to confidential product information and data prior to FDA approval of the therapy. As noted above, there currently exists a process where a sponsor can request early consultation with CMS and FDA if the sponsor determines that such discussions would be beneficial; therefore, we do not believe there is additional value in the formal parallel review process contemplated in the notice. CMS or its contractors can make these determinations by reviewing the approved label and prescribed use of the product and generally do not need to play a role in pre-approval discussions and processes. It is incumbent solely on sponsors to design development programs specific to each new drug or biological including incorporation of guidance from appropriate government agencies as provided for in existing laws and regulations.

Fourth, Medicare's statutory requirements for coverage of certain drugs and biologicals obviate the need for such a process. By statute, for drugs used in an anticancer chemotherapeutic regimen, the FDA-approved uses and uses supported by certain compendia are "medically accepted indications" that should be covered by Medicare. The statutory definition of "drugs and biologicals" that may be covered by Medicare includes "any drugs and biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication." The statute explicitly recognizes any use that has been approved by the FDA as a "medically accepted indication"[7] of a drug or biological used in an anticancer chemotherapeutic drug regimen.[8] Congress clearly intended to protect access to approved drugs and biologicals used to treat cancer. Once CMS determines that a use of a drug or biological is a "medically accepted indication," as defined by the statute, no further review is necessary to determine whether the therapy should be covered.

Finally, we understand CMS' desire to ensure that clinical studies are designed to adequately address both FDA and CMS questions. However, we are

[6] Id.
[7] Social Security Act (SSA (1861(t)(2)(A).
[8] SSA 1861 (t)(2)(B).

concerned that the proposed parallel review process could involve CMS assuming responsibility for an expanded mission that it lacks the resources and expertise to fulfill. As CMS acknowledges in the notice, FDA is responsible for assessing the safety and efficacy of new medical products, and CMS is responsible for determining coverage and payment for those therapies. By seeking to be involved earlier in the process, we are concerned that CMS could potentially be involved in the designing of pre-approval clinical trial protocols, assuming a role in issues well beyond its statutory authorities and expertise. Sponsors seeking to involve both FDA and CMS in clinical development and premarket review discussions may voluntarily do so under current practice. BIO believes that CMS' involvement in clinical trial design should remain at the request of the sponsor.

CMS admits that it has limited resources for reviewing new technologies, and these resources likely are going to be increasingly strained as the Agency works to implement the requirements of the Patient Protection and Affordable Care Act (ACA). Given the lack of a parallel review imperative or need, CMS may be better served focusing on improving its current NCD process rather than seeking to assume a broader mission. For instance, CMS could improve the current NCD process by ensuring appropriate expertise is involved in the decision-making process both internally and within the Coverage and Analysis Group (CAG), as well as improving processes around its interactions with external advisors, including the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC). CMS could better assure that its advisors have the appropriate expertise, qualifications, and resources necessary to analyze all of the information necessary to make informed decisions on the new technologies to be considered and to do so in a timely manner.

II. The Integrity of FDA's Safety and Efficacy Authorities Must be Maintained

BIO has significant concerns that a parallel review process could compromise the independence and integrity of FDA drug and biological approval standards and decisions. FDA's approval of a new prescription drug is based upon the safety and efficacy of a drug and the safety, purity, and potency of a biological. CMS' standard for coverage determination, on the other hand, is based upon what is "reasonable and necessary." To support FDA's overarching mission, Congress has reinforced the Agency's core statutory mission by providing FDA with additional authorities to promote the safety and efficacy of drugs and maximize

respective products' benefit/risk profile. For example, the FDA Modernization Act of 1997 directed FDA to work more closely with sponsors to develop clinical protocols and the FDA Amendments Act of 2007 provided FDA with authority to require, under certain circumstances, post-market labeling changes or clinical studies and trials,[9] or mandate Risk Evaluation and Mitigation Strategies (REMS).[10] These authorities are carefully balanced to address the determination and maintenance of a benefit-risk balance for drugs and biologicals, and should not be influenced by CMS's unique standards, interests and inquiries pertaining to coverage determinations for elderly and disabled populations.

The Federal Register notice states that sponsors "may undertake clinical studies that are designed to address FDA questions but do not adequately address CMS questions concerning the impact of the technology on Medicare beneficiary health outcomes. This omission can slow the developer's quest for Medicare coverage. We believe that a parallel review process can in some instances furnish an opportunity to educate developers regarding clinical study designs that are more likely to simultaneously address both FDA and CMS questions."[11] However, a formal parallel review process is not required to address this concern. Under current practice sponsors may invite CMS officials into meetings with FDA on a voluntary basis to agree upon clinical protocols that meet the regulatory requirements of both FDA and CMS. Therefore, it is not necessary to implement a new parallel review process for drugs and biologicals to allow FDA, CMS, and the sponsor to agree upon premarket or post market trial design, when appropriate to satisfy the agencies' respective standards. Seeking advice on trial design should not be contingent on the parallel review process and if a sponsor chooses to invite CMS into pre-market discussions with FDA, the process for consideration of those clinical trials designed to meet the needs of both FDA and CMS should not be binding on the sponsor but rather advisory in nature.

BIO cautions that a proposed parallel review process should under no circumstances misappropriate or alter FDA's authority or otherwise delay its intended mission to ensure the safety and efficacy of drugs and biologicals to address CMS questions regarding the cost, clinical value, and medical necessity of the product. Nor should such a process influence the standard for FDA drug approval. A parallel review process could create undue pressure to use pivotal

[9] 21 USC §355 (o)
[10] 21 USC §355-1
[11] 75 Federal Register 57045, 57046.

studies to satisfy comparative or healthcare outcomes questions of interest to CMS that are more appropriately the subject of later analyses or research. Outcome data are typically collected in real world settings rather than clinical trials and shifting outcome research to the pre-approval clinical setting will lead to access delays for patients particularly for those patients with unmet medical needs. Clinical trials cannot in all cases be designed to generate adequate information for both FDA approval and CMS coverage determinations. To do so in many cases would dilute the study's ability to support safety and efficacy determinations, or would likely result in unduly large or complex clinical studies that would be prohibitive from a drug development perspective. Congress provided FDA authority to introduce flexibility into the approval process (such as through the use of surrogate endpoints and adaptive trials) in order to get new treatments to patients faster. The introduction of CMS demands on the drug approval process to facilitate value judgments regarding the cost and clinical utility of a product could actually prevent sponsors from using such approaches to develop a new medicine, and create significant delays in the availability of new treatments for patients.

For example:

- The outcome data typically utilized to process NCDs, such as effects on overall survival, may not be available at the time of FDA approval. In fact, FDA statutory and regulatory provisions allow for the market approval of serious and life-threatening diseases based on surrogate endpoints, such as progression free survival rather than overall survival, ensuring the earliest access for patients with unmet medical needs.[12] Additional outcome data is collected post-approval in studies typically not completed until years past the initial approval. Current clinical standards within oncology under such a parallel process could lead to requirements for survival as the primary endpoint – requiring much larger and longer trials. Such trials can also raise ethical concerns if a strong effect is observed with a surrogate endpoint and crossover to the experimental arm is not allowed.

- To reduce the potential for biases in FDA's safety and efficacy determination, clinical trials for the purposes of market authorization may exclude certain co-morbidities, while post-market outcomes analyses are based on broader utilization of the product. Trials that incorporate

[12] 21 CFR 314 - Subpart H

additional confounding factors for the purposes of coverage decisions may limit FDA's ability to make a scientifically sound safety and efficacy determination and limit patient access to novel treatments.

- Additional barriers could result for those drug and biological products where the relative safety and efficacy are established at the time of FDA's approval decision, but additional refinement of the benefit/risk profile may be warranted in a post-market setting. In this scenario, FDA requests or requires post marketing studies to obtain long-term clinical outcomes data and further define the relative risk and incidence rates of a serious adverse events or toxicities associated with use of the drug.[13] Pre-market regulatory approval and reimbursement decisions should not be delayed for those efficacious drug and biological products that need further refinement of the benefit/risk profile in a post-market setting.

- Finally, we note that FDA and CMS have unique constituencies that must be taken into account during clinical trial design. For example, a trial designed for an elderly patient will by definition under serve the safety needs of a pediatric patient and the parallel review process should not delay the access of innovative products to other significant patient sub-populations.

Similarly, post-market FDA authorities, such as REMS, labeling changes, and post-market studies and trials were framed by Congress to help ensure that medicines with a favorable benefit/risk profile are available for patients. Despite that laudable goal, such post-market requirements already disincentivize patient beneficial innovations because of the significant burden that they place on sponsors desiring to invest in therapies. In many cases, requirements in current REMS are already presenting considerable obstacles to physician prescribing and patient access to therapies for both labeled and legitimate off-label uses. As a general matter, such authorities should not be used in furtherance of CMS goals such as the collection of data supportive of coverage decisions or limiting the patient population. Rather, such studies/trials and REMS should be required solely when mandated under the Federal Food, Drug, and Cosmetic Act. Should a sponsor

[13] FDA Draft Guidance for Industry on *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act*, July 2009, p. 6, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf

agree to adapt a study, trial or REMS data collection effort to satisfy CMS needs relating to a coverage decision, such changes can be negotiated on an ad-hoc, case-by-case basis.

BIO also has significant concerns regarding the confidentiality implications of a parallel review process. Under FDA's regulations, a premarket application is generally considered confidential commercial information before approval or clearance is granted (unless the sponsor has publicly acknowledged the application). However, CMS makes it public when the Agency opens a National Coverage Analysis for a particular product. Although the current Memorandum of Understanding[14] between FDA and CMS creates a process for information-sharing and reiterates applicable standards for protecting proprietary sponsor information, the transfer of data between agencies and potential use of highly sensitive premarket data by CMS creates opportunities for lapses in such confidentiality protections. Inappropriate disclosure of confidential commercial or trade secret information would be a clear detriment to public health by chilling product development and innovation. By granting competitors insights into a rival compound's development process, disclosure would accelerate the process for competitors to enter the market and thereby diminish the incentives available to innovators, resulting in fewer new drugs being brought to market. The high stakes, for example, loss of product value, associated with any disclosure of confidential data further discourage our interest in pursuit of a parallel review process that is not even needed.

III. Considerations for any Potential Pilot Program:

For these reasons, BIO believes that the parallel review process described in the notice is not appropriate or necessary for drugs and biologicals. However, in the notice, CMS and FDA propose a pilot program for medical devices, which may be a more appropriate product area for a parallel review process. While it is likely that a separate process would need to be developed for parallel reviews of drugs and biologicals due to the nature of the studies involved in the approval process and applicable FDA and CMS authorities, experience in parallel medical device reviews may aid in further consideration of whether use of such processes for drugs and biologicals is appropriate.

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[14] See *http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm217585.htm*

We propose that the medical device pilot program be initiated with a limited number of companies in order to assess how the process would work in practice. As the two agencies work to develop the pilot and any parallel review process, please consider our previous comments and the following elements which taken together address many of the issues raised in the notice:

- Any parallel review process must be entirely voluntary for the manufacturer, CMS, and FDA.
    - The manufacturer must be the only entity that can request parallel review. If other entities were allowed to initiate parallel review, the process would not be voluntary for the manufacturer, could harm development of new technologies by leading to premature review, and could result in inappropriate use of limited Agency resources.

- We encourage the agencies to clarify that they will continue to provide for early consultation outside a formal parallel review process, or that it will modify the parallel review process so that it does not automatically initiate an NCD.

- The manufacturer must determine which uses of its therapies should be subject to parallel review. The review process should consider only the indications for which the manufacturer has sought FDA approval and maintain existing discretion for the local Medicare Administrative Contractors to provide for physician flexibility to meet patients' needs.

- The manufacturer must be allowed to terminate the parallel review process at any time without penalty or consequences for future decisions on this product or other products by either Agency. Further, voluntary participation by a sponsor on any given application should not be misinterpreted as precedent of that sponsor's intention to do so on other applications for the same or other products.

- The parallel review process must not change or influence either Agency's review criteria or processes.
    - Any parallel review process must not delay FDA approval of the new technology.

  - FDA's review of safety and efficacy must not be affected by CMS's concerns about whether the product is reasonable and necessary.
  - FDA must not be involved in decisions, such as coding or payment determinations, which are CMS's responsibility.
  - CMS data needs, or objectives with respect to issues such as limiting prescribing or treatment practices and associated costs, should not impact decisions by FDA with respect to post-market studies or trials, labeling, or REMS requirements.
  - BIO does not believe that the agencies should convene a joint advisory committee. The criteria and processes of the two agencies should remain separate. Further, sponsors seeking input from both FDA and CMS on early clinical development should have such an opportunity to seek input from both agencies without requiring a parallel review during the regulatory approval process.

- The confidentiality of manufacturer's proprietary information must be protected throughout the process.
  - The parallel review process should be kept confidential until the product has received FDA approval.
  - CMS should have access to only the limited data it needs to answer specific coverage questions.

- After considering the comments on this notice, if the agencies wish to proceed with a parallel review process between manufacturers, the FDA, and CMS, they should publish proposed regulations, receive public comment, and finalize the regulations after considering the public comments.

- BIO opposes any new user fees or increases in current user fees to facilitate parallel reviews.

- BIO urges CMS and FDA to consider the significant resources and training that would be warranted should the agencies move forward with the proposed parallel review process.

Conclusion

BIO understands and fully supports the need to minimize the length of time between marketing approval and commercial availability of new drugs and biologicals. Creating a new review process that brings FDA reviewers and CMS personnel into the clinical development process would not be expected to reduce the interval between approval and patient access as sponsors may already reach out to either Agency during clinical development.

BIO appreciates the opportunity to offer these comments on the proposed parallel review process. We hope you find these comments to be helpful, and look forward to working with you on this issue. Please contact Andrew Emmett or Laurel Todd at (202) 962-9200 if you have any questions regarding our comments. Thank you for your attention to this very important matter.

Respectfully submitted,

/s/

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/s/

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cc: Dockets Management Branch
Food and Drug Administration