August 23, 2004

Jeffrey Shuren, MD
Assistant Commissioner for Policy
Division of Dockets Management
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Stimulating Innovation in Medical Technologies. Docket No. 2004S-0233

Dear Dr. Shuren:

The Biotechnology Industry Organization (BIO) is pleased to respond to the Department of Health and Human Services' (HHS) request for comments on Stimulating Innovation in Medical Technologies. BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations in the United States. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. Our members are devoted to discovering new cures. Such policies include those that help streamline the process of bringing life-enhancing and life-saving therapies to market, and increase patient access to much needed drugs. Private investment in innovation is driven by the potential for financial return and will be undermined by policies that threaten the availability of these returns, including policies that breed confusion and uncertainty about the coverage and reimbursement process for new cures.

HHS asks how it and its agencies can work together to facilitate the development and approval of new medical technologies. BIO appreciates the many efforts that already have been undertaken to eliminate barriers to medical technology innovation, but believes more can be done. Our comments outline a number of areas we think deserve additional attention and we look forward to a continued dialogue with HHS and its agencies to seek additional creative approaches to this important issue. Our comments are divided into two main sections: (I) Coverage and Reimbursement for New Medical Technologies; and, (II) Government Support for Research and Facilitation of the Approval of New Technologies.

I. Coverage and Reimbursement for New Medical Technologies

BIO believes that HHS should develop and maintain an appropriate, predictable and stable reimbursement system. This will allow biotechnology companies to make informed research and development decisions, and allow investors to make

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knowledgeable investment decisions regarding the reimbursement parameters surrounding new products. Beyond that, maintaining a system that provides adequate reimbursement is crucial both to encourage innovation and investment and to ensure that Medicare and Medicaid patients will have access to cutting edge new therapies.

Current Issues with Medicare Reimbursement

BIO has worked over a long period of time with the Centers for Medicare and Medicaid Services (CMS) to ensure that reimbursement rates established for our members' products are appropriate and market based. We also have worked to ensure that Medicare payment systems adequately compensate physicians, hospitals, and other providers for their costs of acquiring, handling, and administering drugs and biological products. We continue to urge appropriate reimbursement as a crucial component of ensuring continued investment in the research and development of new medical technology and we remain concerned that reimbursement is still inadequate in a number of areas.

In general, we believe that the Healthcare Common Procedure Coding System (HCPCS) coding process is one area where HHS could take large steps to improve access to new therapies, particularly for Medicare beneficiaries. The process new products must traverse to receive Medicare reimbursement causes unnecessary delays in the availability of new products. For example, before receiving a new code, a company must collect six months of marketing data before a new application can be submitted. We believe this requirement is unnecessary, blocks access to new technologies, and discourages innovation. BIO urges CMS to eliminate the six month marketing requirement and establish a mechanism for multiple quarterly updates of the HCPCS system.

For example, the HCPCS system is updated only once a year after a prolonged review process. Applications that are received by April 1 of the current year are eligible for inclusion 9 months later in the January 1 update of the following year. When the additional 6 months for gathering marketing data is added to the 9 month review process, the time between FDA approval and issuance of a new code stretches to at least 15 months and can reach up to 27 months. For example, a therapy approved by the FDA on October 2, 2004 would not be eligible to apply for a new HCPCS until it has had 6 months of marketing experience, so its manufacturer could not apply until April 2, 2005. Because this therapy would have missed the April 1, 2005 cut-off for consideration for the January 1, 2006 update, the earliest the therapy could be represented by a new code is January 1, 2007, 27 months after the FDA approved it. Although we recognize that the National Panel has at times allowed manufacturers to supplement their marketing data if the end of the 6 month period is close to the HCPCS deadline, these timeframes are much too long. We urge you to implement the changes to the HCPCS process which BIO and others have advocated.

These steps would also improve the ability of biotechnology companies to continue to secure investment capital. The current coding application process creates the possibility of a more than two year delay from FDA approval before a HCPCS code is effective. Without these codes, providers face a more difficult time securing reimbursement,

potentially threatening patient access to breakthrough medicines—and threatening the ability of BIO's members to secure investment capital needed to discover future medicines.

Lastly, we hope that the recently launched Council on Technology and Innovation will consider ways to improve the coding process, and we would urge you and the Council to focus on ways that the coding process can be made significantly more efficient.

A. Hospital Outpatient Prospective Payment System (HOPPS)

When setting the rules for the Hospital Outpatient Prospective Payment System (HOPPS), Congress understood that adequate payment would be needed to protect access to drugs and biological products. They established transitional pass-through payments to provide adequate reimbursement to hospitals for various technologies, including oncology products and other important classes of medicines, while data on appropriate reimbursement rates were gathered. When these pass-through payments expired, CMS set rates that were woefully inadequate, particularly for higher cost drugs and biological products. Along with some of our members, BIO provided evidence that these shortfalls for higher cost therapies were the result of a problem in the CMS methodology that has since been labeled "charge compression." By assuming an average cost to charge ratio in its methodology, CMS specifically penalizes products that are subject to lower than average markups on hospital charge masters. Unfortunately, CMS continues to ignore this problem despite evidence detailing this problem.

As a result, BIO and others sought a legislative solution that again set temporary payment floors for single source drugs, pending implementation of a new methodology to create reimbursement levels that will adequately reflect hospital costs for acquiring, storing and administering these products. In the MMA, Congress enacted payment floors for single source products (in addition to payment reforms for other products), pending the results of a Government Accountability Office (GAO) study on hospital acquisition costs and a MedPAC study of pharmacy overhead that CMS is to use in establishing reimbursement rates for certain drugs and biologicals in 2006 and beyond.

We believe that this solution is crafted to establish adequate reimbursement for many innovative medicines for which reimbursement had been inadequate. BIO hopes that CMS will review the results of these studies carefully and set payment rates that fully reflect hospital acquisition and overhead costs for delivering complex pharmaceutical therapies.

B. Hospital Inpatient Prospective Payment System

Similar to the outpatient setting, Congress also recognized that certain new products delivered to hospital inpatients under Medicare may also be reimbursed inadequately when they first come to market. This is because the data used to set payment rates for inpatient hospitals are slow to account for the costs of new technologies. In response to this problem, Congress created a program to provide add-on payments to hospitals for certain new technologies for 2 to 3 years from the issuance of an appropriate code.

BIO has been disappointed by CMS' implementation of this program. Even after Congress enacted modifications to the program to clarify the scope and purpose of these new technology payments, CMS continues to make overly restrictive determinations undermining Congressional intent.

For example, CMS continued its restrictive reading of the statute in its recent final rule for the inpatient prospective payment system. BIO believes that patient access to new technologies in the hospital setting will be delayed because of CMS policies in this area. In particular, we continue to be concerned with the CMS decision to narrowly define those products that qualify as "new" based on the two to three year period from FDA approval, despite the clear intent of Congress that this period begins from the date the product receives its code.

Over the longer term, this policy choice will have a detrimental effect on investment decisions and on future innovation. We urge you to require CMS to revisit this decision.

C. Physician Fee Schedule

In addition to establishing a new drug benefit under Part D of Medicare, the MMA reformed payments for those products covered in the physician office setting. BIO is concerned that these reforms, which limit physician reimbursement to 106% of "Average Sales Price," (ASP) may inhibit patient access to important therapies. Without a corresponding update to drug administration codes to offset drug payment decreases, BIO is concerned that patients will be caught between the physician's office and the outpatient setting. BIO is concerned that this "ping-pong" effect will cause reimbursement confusion and hamper innovation. Therefore, we continue to urge CMS and HHS to monitor patient access carefully to identify and assess issues that may arise as a result of this reform.

Medicare Needs Clear and Foreseeable Reimbursement Rules

In addition to the need for adequate reimbursement, another essential component of favorable reimbursement policy is the adoption of reimbursement rules with sufficient advance notice and full opportunity for public comment.

We have been pleased in several instances with CMS actions on this front. For instance, in 2002, CMS released a streamlined version of hospital claims underlying the HOPPS. This file, and subsequent updates, has allowed BIO and its members to analyze many of the coverage and payment policies under that system and provide meaningful comments. Using these data, some of our members were able to discover problems with the way they were being reimbursed and they successfully sought changes. In other cases, more systematic problems were revealed, and BIO and others advocated for some of the changes to the HOPPS in the MMA.

In some cases, however, CMS has provided little or no guidance about substantive policy changes until final rules or interim final rules. In some cases, policies have been described only generally or presented as a series of "options," preventing the public from analyzing a proposal or its potential impact in time to comment meaningfully. For

example, without the intervention of the MMA, reforms to physician payments for drugs and biologicals were slated to be adopted in this manner.

While we are still reviewing the proposed regulations for Titles I and II of the MMA, we have been pleased generally by the open and collaborative process. We are hopeful that CMS will provide opportunities for formal comment concerning any major policy pronouncements that are in the final regulations but were not contemplated in the proposed rules.

We are also pleased by recent advances at CMS to provide further transparency to its decision-making process. The "Open Door Forums" recently established by CMS have provided valuable opportunities for the public to receive clarification on new rules and to get advance notice of major policy changes. BIO believes that this sort of communication is vital to the continued development of clear and foreseeable reimbursement rules.

We hope that CMS will continue to be open to input from BIO and its members as we seek to ensure that Medicare patients have access to innovative technologies.

Medicare Coverage for the Costs of Clinical Trials

BIO appreciates HHS efforts to provide coverage for the routine costs of clinical trials. We understand that the interagency work group established to identify criteria for trials that are not "deemed" to have met the desirable characteristics required under the national coverage decision proposed some criteria for this purpose. However, these criteria have not been issued by CMS. The lack of such criteria is restricting the scope of trials that could have their routine costs covered. BIO urges CMS to clarify the process by which trials that are not "deemed" covered under the national coverage decision may seek to have their routine costs covered by Medicare.

Medicaid Issues

We believe a number of state proposals seeking to control costs will, if implemented, limit access to biotechnology products. Some of these proposals would place all biotechnology products in "prior authorization" categories, often seeking to subject these products to extremely limited reimbursement. These proposals have the effect of encouraging the use and, thus, the development of lowest common denominator products rather than innovative breakthroughs. We urge HHS to work with the states to encourage cost control mechanisms that will not have such a chilling effect on innovation.

II. Government Support for Research and Facilitation of the Approval of New Technologies

As we indicated in the earlier discussion, the key for BIO is the thoughtful development of policy with a view toward the long-term impact on patients, and the biotechnology industry's ability to continue innovation. Reimbursement policy, discussed above, has taken a rather shorter term view, focusing principally on immediate expenditure and budget considerations. We have explained that this short-term approach can be

exceedingly harmful to innovation and, consequently, to the patients innovation can benefit. Similarly, development of policies and implementation of practices in the regulatory arena absent consideration of potential long-term implications can have a detrimental impact on investment in biotechnology as well as on the expeditious availability of new technology to patients.

We believe, as we have stated in earlier comments to the Food and Drug Administration (FDA) regarding its "Critical Path" initiative, that the agency holds the keys to future innovation and to patient access to new technology. How it turns those keys is a crucial determinant not only of whether and when a particular new product reaches the market but also of whether the biotechnology industry can succeed in delivering the promise of the 21st century biological revolution. Several specific examples, some of which we have noted in prior comments, respond to the following question:

<u>"What strategies and approaches could HHS implement to accelerate the development and application of new medical technologies?"</u>

Strategy/approach: Early and Productive Communication with Product Sponsors

It is critically important to sponsors in early product development to have the best handle possible on the data and other requirements FDA believes will be necessary for an adequate demonstration of effectiveness. The availability of "tools of the trade," outlined in FDA's Critical Path document, may help in earlier identification of more or less promising avenues of developmental research. In addition, however, and certainly in the interim, FDA can provide important advice and early signals of what approach is more or less likely to succeed in the review process. Effective communication between FDA and product sponsors is among the goals of the Prescription Drug User Fee Act (PDUFA) that, when accomplished optimally, absolutely spurs innovation. The earlier a sponsor can recognize what is needed, what is missing, and what needs to be done differently, the less time and fewer resources are wasted and the more quickly and easily a safe and effective breakthrough product reaches patients.

At the "other end" of the review spectrum, FDA's recent announcement that it will replace previous "approvable/not approvable" letters with "complete response" letters – to which the biotechnology industry has been accustomed – is a step in the right direction, to the extent that the communications accomplish the goal of specificity in describing and finalizing what issues remain to achieve approval of an application. While we applaud FDA's intention to try, through this mechanism, to provide sponsors with the "bottom line" on their applications, there is still the need to explicate problems earlier in the process. Last-minute notification that there are multiple outstanding issues simply serves to re-start a 6- or 12-month clock, sometimes for the second or even third time, delaying the availability of a safe and promising product. Such late notification, even if detailed, not only is an obstacle for the product in question but also sends a signal of unpredictability and unreliability of the process that has implications for future innovation and investment in biotechnology.

Strategy/Approach: More Effective Utilization of Surrogate Markers or Other "Non-traditional" Effectiveness Measures

Often, the demonstration of effectiveness is especially difficult and challenging for biotechnology products, many of which are intended to treat unusual conditions, disease states that have great inherent variability, or diseases that affect small populations. Traditional endpoints are frequently neither appropriate nor possible, requiring more creative approaches to measuring effectiveness, such as responder analysis and surrogate endpoints. To ensure that the measurement of effectiveness for biotechnology products does not become itself a barrier, FDA must ensure that its reviewers take a reasonable approach to alternative effectiveness assessment, regardless of their disease specialty or review division but particularly in areas where there is an urgent medical need and/or no current treatments exist. When used appropriately, a surrogate is an endpoint that is appropriately though perhaps not fully validated and is reasonably likely to predict effectiveness, not an absolute predictor. The suitable use of surrogate endpoints, appropriately defined, is a spur to innovation. Unfortunately, the approach to this matter has varied within FDA. Such variability and unpredictability is an obstacle to innovation and to investment, which deplores ambiguity.

The Orphan Division at FDA is a division that is particularly dependent on the development of creative approaches to the demonstration of effectiveness. BIO strongly supports the Orphan Division, and the important role it does and can play in drug development. The Division's grants and other support can be crucial not only for academic research (which often partners with companies), but also for small biotechnology companies as well. We would urge that FDA continue to support the efforts and objectives of the Orphan Division and increase cooperation between the Orphan Division and other parts of FDA.

Strategy/Approach: More Appropriate Use of Post-Market Commitments

In recent years, FDA has made increased use of post-market commitments, often notifying sponsors of the need to conduct post-market studies at the very end of the review process. At this point, sponsors, especially those in economically fragile situations (as is often the case for small biotechnology companies), are in no position to take exception or debate the point. They simply must agree to FDA's conditions, whether they believe them appropriate or not, because failure to agree will result in a delay in their application approval. So that the use of post-market commitments does not become an obstacle to innovation, BIO recommends several steps. First, if the agency believes post-market studies will be needed, every attempt should be made to communicate this to the sponsor earlier, rather than later in the review process. This will provide an opportunity for the sponsor to have input not only into whether the studies are, in fact, necessary but also into the decision about the nature and number of any such studies. Second, we believe the agency needs to establish, with input from the industry, clearer criteria for when and why post-market studies would be required. Third, a process should be developed and clearly delineated by which proposed post-market studies may be negotiated between FDA and the applicant. During the course of any such negotiation, the purpose and anticipated outcome of studies should be established so any required studies will provide answers to essential questions regarding the safe and

effective use of the product. The use of post-market studies as academic exercises serves as a barrier, not a spur to innovation.

Strategy/Approach: Pursue FDA's Goal of Efficient Risk Management

In its 2003 Strategic Action Plan, FDA noted that "a key element … is 'efficient risk management' … seeking to use the best risk management science … to achieve our health policy goals as efficiently as possible." BIO agrees that the use of the best science is critical to every activity FDA undertakes and is crucial to the evolving FDA activities related to risk management. We recommend that, in the interest of establishing policies and practices that spur innovation rather than discouraging it, the agency ensure that each new regulatory requirement truly addresses a clear and identifiable need and that an appropriate cost-benefit analysis has been undertaken. Companies developing innovative therapies and emerging technologies depend on the development of regulatory requirements that are clear, value-added, and flexible enough to accommodate the fast-moving science of biotechnology. Because much of the expertise in biotechnology resides in the industry, FDA should take advantage of opportunities to develop policies and regulations in concert with the industry, so that it can access the best science. BIO urges that FDA establish additional opportunities and processes for interaction with the biotechnology industry and its scientific and technical experts.

"Which HHS policies and programs effectively spur innovation? Which policies and programs at NIH (and its grantees), CMS, FDA, and CDC should be expanded to help spur innovation? Do any policies and programs pose obstacles to innovation?"

"How can HHS help its agencies … to work together more effectively to eliminate obstacles to development?"

While carefully constructed regulatory policies can spur innovation from the "end product" point on the continuum, it is essential that the biotechnology industry have access to a cadre of appropriately trained clinical researchers who can take the original concept and translate it into that end product. The government has an important role to play in building and sustaining that research capacity, through support, especially from the National Institutes of Health (NIH), of clinical research training. BIO urges NIH not only to maintain its investment in that area, but to increase it. NIH has an exemplary record and leads the world in supporting basic biomedical research. BIO believes this support should continue and increase, as the fruits of this research often are translated into breakthrough therapies through subsequent and additional research and development by the biotechnology industry. In our view, NIH has not placed similarly sufficient emphasis on the development of clinical research expertise. This should be remedied; greater NIH support for clinical research training will serve to spur innovation, generating the additional expertise and motivation need to increase studies that will lead to new therapies.

Recently, NIH and FDA announced the formation of a joint program directed toward the discovery, development, and availability of new therapies for cancer. BIO applauds this effort as an excellent example of an innovative program that can spur innovation. We strongly recommend that this program continue and that its policies and activities be

developed further in concert with the industry. Moreover, we recommend that HHS evaluate opportunities of a similar nature in other disease areas, where greater input from FDA into NIH research priorities and greater input from NIH into FDA regulatory policies can spur innovation in these areas as well.

We encourage NIH and CDC to pay particular attention to the development of surrogate markers in their research programs. If each agency asks grantees to collect consistent information, it could result in the development of surrogate markers much more quickly. In addition, when NIH and CDC conduct long-term trials (some lasting 10 or more years), it would be helpful if they included in those trials the kinds of long-term outcomes that might help the FDA understand certain risk-related parameters. We also suggest that before any agency undertakes a large trial that it consider whether the results will be useful to the entire Department and the broader development community. Small design changes can result in significantly better understanding of regulatory concerns.

This kind of more productive communication and cooperative activity should be encouraged by HHS so all of the agencies can take advantage of the expertise and skills of the others and so agencies are not operating at cross-purposes. HHS should look closely at where agency efforts already overlap or are tangential, to ensure that there are not "turf" issues or unnecessary disagreements regarding policies and procedures that are serving as obstacles to development of new technologies, and to ensure that collaboration among agencies does not inappropriately dilute the agencies' focus on their own individual missions.

"What forums should HHS use to survey constituents about obstacles to innovation?"

BIO believes that the best methods of communication are face-to-face opportunities to exchange ideas. FDA has established a number of such opportunities, but more are needed. Such opportunities would be, for example, meetings between key FDA officials and industry representatives, devoted to a circumscribed set of topics and providing an opportunity not only for an update on agency thoughts and actions but also for industry representatives to raise concerns and make suggestions. BIO recommends that agency-industry meetings be scheduled on a regular basis, no fewer than four times per year. These meetings are far preferable to a draft written policy on which there is opportunity for comment, as the agency already has a stake in moving any such draft forward. Any significant policy change should be discussed with the industry well in advance of having a written description. This can be done without compromising in any way the ability of the FDA to make decisions that are in the best interests of consumers, but it will serve to ensure that draft policies do not serve as an obstacle to innovation. We would also like to see more regular interaction between industry representatives and CDC, CMS, and NIH.

It is important to keep in mind that regardless of the word "draft" on a document issued by FDA or its sister agencies; the investment community reads a potentially adverse policy as a signal that biotechnology is not an industry in which to invest. Because of the economic fragility of the industry, anything stated officially by HHS, and certainly by FDA, but also occasionally by CDC, CMS, and NIH, has the potential to affect the financial markets. Effects on the financial markets are felt especially acutely by companies that are smaller and more reliant on venture capital. The vast majority of

companies in the biotechnology industry fall into this category. An official statement that investors believe may bode poorly for biotechnology or for pharmaceutical products in general is likely to have a huge impact on companies that have no financial cushion – namely, small start-up biotechnology companies with a wonderful idea that has yet to be developed into a viable product. Since this is where innovation in biotechnology begins, adverse impacts here will have the downstream effect of stifling or slowing development of new technologies. This kind of impact can be avoided by earlier consultation with industry, even if on the general parameters and not the detailed specifics of a new policy.

The recent announcement by CMS that it will hold a public meeting to discuss development of standards for drug classes and categories under the new Medicare prescription drug benefit is an example of the kind of communication that appropriately considers the importance of input from industry and others in the public. The agency appears not to have made its decisions on this crucially important issue yet, and thus can meaningfully consider outside views. This is an example of both an appropriate forum for surveying constituents and appropriate timing, both of which are critical to prevent creating obstacles to innovation. By contrast, BIO remains concerned about the approach being taken by the U.S. Pharmacopeia (USP), which to date has appeared disinclined to seek or consider public input. BIO urges HHS to ensure that prior to adoption of any of the guidelines developed by the USP, CMS weigh carefully the input received at its public meeting and through other means, which will include considerations of the long-term impact on these decisions on the biotechnology industry.

Conclusion

BIO appreciates the opportunity to comment on the important questions of how HHS and its agencies can work with our industry more effectively to ensure that its policies, programs, and practices serve as incentives, not obstacles to innovation. We look forward to a continuing dialogue with HHS in this regard.

Sincerely,

/s/

Michael Werner
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Biotechnology Industry Organization