BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

1225 Eye Street NW, Ste. 400
Washington, DC 20005

August 2, 2004

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

Re: Critical Path Initiative [Docket No. 2004-N-0181, 69 *Federal Register*, 21839 (April 22, 2004)]

Dear Madam/Sir:

The Biotechnology Industry Organization (BIO) represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial, and environmental biotechnology products. We appreciate the opportunity to comment on the Food and Drug Administration's (FDA's) proposed initiative, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products."

BIO agrees with FDA's assessment of its twofold responsibilities to protect and promote the public health and, in the latter regard, to do what it can to facilitate and promote new medical technology and patient access to innovative therapies. We also concur with several areas highlighted in FDA's analysis including: the importance of promoting clinical research as an essential component of future medical advances; the need for a greater and more targeted federal role in supporting clinical research training; the need for earlier and more meaningful

interaction between FDA and product sponsors to design the clinical components of the development program; and the need to use federal resources to provide the expertise needed for better evaluation of emerging science and technology. BIO recognizes that FDA can play a significant role in stimulating the science of drug development, for example by evaluating research and development tools and translating that evaluation to improved development programs, more appropriate science-based regulation, and, ultimately faster market entry for new products. We also believe that FDA has an important role to play streamlining the drug development process, for example by helping to improve efficiency of the process and decrease its time and cost.

General Comments

BIO sees FDA's role in traversing this "critical path" as complementary to, but not a replacement for, its essential responsibility as the gateway to the market for new drugs and biological products. We urge FDA to place the highest priority on meeting its obligations under the Prescription Drug User Fee Act and the Food and Drug Administration Modernization Act. In meeting these regulatory responsibilities – expediting and facilitating market entry for safe and effective products – FDA must continually evaluate itself and its reviewers concerning consistency, fairness, efficiency, and creative approaches to problem-solving. This means, for example, that FDA must work productively and creatively with sponsors, especially in cases where effectiveness demonstration is particularly difficult, to find scientifically and medically acceptable approaches, including surrogate endpoints, reasonable and appropriate post-marketing studies, and other methods, to assure effectiveness. With respect to such surrogates, the intention of the law is that a surrogate must reasonably predict effectiveness; not, as has been the case sometimes and for some reviewers and divisions at FDA, that the surrogate must be fully validated and an absolute predictor. Where a marker or endpoint has been applied successfully or even, in some cases, validated and promoted by some in the FDA, we urge the Agency to ensure that this marker or endpoint is accepted as appropriate, regardless of which division is reviewing an application. New approaches intended to make drug development more efficient cannot be successful if some FDA reviewers continue to reject the approaches.

BIO sees the Critical Path initiative as proposing activities and expenditure of FDA resources for a second prong of FDA's two-pronged regulatory responsibility. That is, to provide assistance to sponsors and developers through identification, validation, and dissemination of new techniques and approaches that will eliminate costly duplication of unsuccessful approaches, and to provide help in identifying projects and approaches that are more likely to succeed than to fail. These activities, should they be undertaken by FDA, are not a replacement for the Agency's responsibility to review and approve products in the most efficient way, nor are they more important. BIO believes that FDA's

fulfillment of its User Fee goals is crucial in the short-term, to ensure access to new products that are being developed now. We see activities discussed as part of the Critical Path as being valuable over the longer term, as they are designed to ensure that drug development continues and improves as science and technology allow.

It is of critical importance that where opportunities are identified and new tools are developed, these replace, not add to existing ones. The identification and accomplishment of the priorities of the Critical Path will not advance development and market entry if the main result is an increase in regulatory burden that is not justified by a realistic and science-based risk-benefit analysis.

Specific Comments

BIO surveyed a number of its member companies with respect to three questions we viewed as being important to understanding the biotechnology industry's views. The questions and summary responses are given below.

1. Which Critical Path opportunities are most important, in light of the eight questions posed by FDA in its Critical Path Federal Register notice?

Effectiveness Standards. One key goal is to place more emphasis on developing, reforming and modernizing efficacy standards. Frequently, well-accepted effectiveness standards do not exist for particular conditions or therapeutic candidates. This is most likely to be true for the very kinds of breakthrough therapies on which the biotechnology industry focuses, such as cellular therapies and other newly emerging treatment modalities. In addition, effectiveness standards often do not exist for conditions for which there are no existing therapies, because there has been no reason to develop standards. It is a heavy burden on sponsors to develop, validate, and gain acceptance for such standards. It is crucial in such cases that FDA regulate creatively, with less emphasis on fully demonstrated effectiveness, provided safety is established. In cases where available tools of clinical assessment are commonly used by clinicians to monitor their patients' status, these should be accepted by FDA, however imperfect they may be. If these tools are standard in clinical practice, this should be prima facie evidence of their suitability as clinical trial outcome measures. The unacceptable alternative would be to wait until new tools can be fully validated and accepted. This would result in a delay of at least several years; in worst cases, it could result in cancellation of the development program. In that vein, BIO strongly supports the suggestion, included in the Critical Path document, of accepting interim measures, while new tools are being developed. BIO also urges FDA to communicate early, clearly, and often with sponsors about how the Agency will assess the risk/benefit balance for a given clinical development program.

Pharmacogenetics and Personalized Medicine. The challenge of diversity of responses among different populations is a crucial hurdle and is often at the core of defining effectiveness. Current regulatory criteria appear to be focussed on ensuring that every product is safe and effective for the general population. Such an approach makes failures likely for certain products that otherwise might actually be safe and effective for use by specific subpopulations or on an individualized basis. The challenge is to develop regulatory approaches that allow for a realistic movement to a new era of personalized medicine by determining, when appropriate, how to assess the personalized effectiveness and safety of a healthcare product. Currently, the infrastructure for personalized dispensing and use of products does not exist; its development is also a hurdle on the Critical Path.

Biomarkers, Surrogate Endpoints, and Imaging. In both the area of effectiveness standards and diverse product responses, there is a need for a process to facilitate regulatory evaluation and acceptance of novel biomarkers, surrogate endpoints, and imaging technologies. Similarly, the expanded use of predictive modeling techniques should be prioritized. This covers a wide range of diseases but with respect to development efficiency, is particularly important in chronic, long-term disease conditions (such as Alzheimer's and diabetes). One approach may be to target diseases or conditions where there are unmet medical needs and to focus efforts on identifying markers for these. The commitment to accept the use of new surrogates/biomarkers will require agreement on validation processes and a willingness for these new approaches to replace current assessment endpoints/tools rather than being additions to development programs.

Another key issue related to new evaluation tools is: who will develop them? If they are developed by industry alone, will FDA view them apprehensively, as has been the case in the past? If so, the goal of facilitating their use will not be achieved readily. Some platform technologies are beyond the ability of an individual organization to develop; the use of consortia should be encouraged and funded. Industry and FDA could also develop markers in collaboration; this would allow appropriate use of FDA's and industry's respective knowledge and expertise. The use of clinicians' experience to define endpoints that are used in the clinical setting would also be valuable.

Post-marketing Commitments. As noted above, it is of key importance that where opportunities are identified and new tools are developed, these replace, not add to existing ones. One area in which FDA currently seems to be trading positive movement with negative change is in the area of the increasing level and number of required post-marketing commitments. For every post-marketing commitment a sponsor takes on, there will be a commensurate reduction in the number of early-development projects that can be undertaken. We ask FDA to look closely, from a science-based and risk-based perspective, at these kinds of trade-offs, otherwise no amount of translational research will accomplish the goal

of shortening and reducing the cost of the development path. In addition, there is a clear need to establish a better process for determining when post-marketing studies are needed, and how and when the FDA's proposals for such commitments are communicated to and discussed with sponsors.

QT Prolongation. One example of emerging science that does not appear to be making the appropriate regulatory impact is in the area of QT prolongation, which has been of great interest at FDA. This area exemplifies the importance of achieving consistency between FDA's goals and its practices. The potential risk associated with QT prolongation is an important safety consideration that should be evaluated during drug development. However, the current draft guidance in this area raises the regulatory bar by making a "thorough" QT study a *de facto* requirement. Although this approach may lead to early discontinuation of development programs for certain products that are shown to have an unacceptable QT risk, it will also *increase* the development costs and possibly development time for products that are ultimately proven to be safe and effective. This does not seem to be consistent with the stated objectives to speed innovation and improve efficiency of the drug development process. An alternative, more efficient and practical approach needs to be identified for evaluating the risk of QT prolongation without unduly prolonging the development time for innovative new therapies. FDA's acceptance of emerging science in this area could lead to progress in a number of product areas, such as the broad area of oral drug development.

Data Mining. Data mining is mentioned several times in the Critical Path document. Development of validation processes (to include both algorithms and data quality) is a necessary first step, particularly for applications such as adverse event data mining. Decisions made without considering methods validation will be counter-productive.

Incentive Programs. Finally, the document alludes to expanding incentive programs such as those for orphan drugs, to foster development in other areas. BIO believes that an incentive that would have an enormously favorable impact would be expanded terms of market exclusivity (similar to Europe).

2. One Critical Path premise is that "the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences." Is the Critical Path initiative a key part of the solution to this problem?

It is true that the applied aspects of the new science – the research that must occur after the basic and translational research at the National Institutes of Health (NIH) and academia reach their limit – need more attention and funding. Unfortunately, although the NIH budget has increased dramatically on an annual basis, this is not true for the budget of FDA or other agencies that might be expected to play an appropriate role in funding such research. However, we

think that FDA can drive substantial change without significant additional resources, by harnessing the experience and expertise of FDA reviewers, and by clarifying for academia/industry what tools (e.g., surrogate markers, new toxicology tests) would be accepted by FDA if developed by others. BIO also believes that more must be done in the area of re-structuring, to prepare FDA for a new role as a driver of innovation in addition to its existing regulatory role.

Although lagging applied science may be one cause of declining new drug and biological product applications and approvals, it is not the only cause. As the pharmacopoeia has expanded and epidemiology and toxicology detection methods have improved, the benefit-risk hurdle for new therapies has elevated. Continued re-assessment and improvement in regulatory decision-making processes and paradigms is equally, if not more, important.

3. What pitfalls or problems, if any, are posed by the Critical Path initiative?

One key concern is added regulatory burden without advances in the review process. While there are many good ideas in the initiative, these activities require endorsement and support at all levels both inside FDA and within the Department of Health and Human Services. To embark on the project without such support could lead to inappropriate use of resources and to decisions that are counter to the objectives of the proposal. One key requirement is that any new activities in this area not siphon resources from PDUFA, Quality Systems, GMP, or other priority regulatory efficiency improvement efforts. Another key requirement is that any Critical Path program result in a diminution, not an increase in regulatory burdens.

In addition, the Critical Path Initiative may complicate drug development rather than stimulate or streamline it, in the absence of international regulatory harmonization. BIO urges FDA to work with sister regulatory agencies globally to encourage acceptance of any new development tools that emerge from the Critical Path Initiative.

Conclusion

BIO recognizes the considerable creative thought that has gone into this document and looks forward to working with FDA toward the goals that the Critical Path initiative is designed to achieve. We are very supportive of the renewed emphasis the Department of Health and Human Services has recently placed on the importance of public/private partnerships (for example through FDA's Critical Path initiative and the NIH's "Roadmap" document). We hope that FDA will continue, as it has done with this thoughtful publication, to seek and consider input from its broad base of stakeholders.

However we ask FDA to ensure that Critical Path activities can be fully supported without detracting from FDA's other goals. We also ask that there be real accountability involved as FDA moves into this uncharted, albeit important, area: metrics should be developed by which to measure the initiative's success, and cost-benefit analyses must be conducted on a continuing basis to ensure that priorities and goals are appropriate. We note that the "best science" does not necessarily ensure a "better" clinical outcome. FDA and industry need to "share the risk" of the development and adoption of new technologies, new biomarkers, and clinical trials simulation and modeling.

BIO and its member companies in the biotechnology industry appreciate that FDA has involved us in the process of developing the framework and details of this initiative. We hope dialogue about these issues will continue productively, whether each and every aspect of the initiative proceeds forward or not. The potential of a rich pipeline, more efficient and less costly clinical trials, and earlier identification of more or less promising products cannot be overstated as benefits for our industry and the patients for whom we develop products. To the extent that the activities of the Critical Path contribute to these goals without compromising FDA's critical mission to review and approve new products in the most efficient way, everyone wins.

Sincerely,

Sara Radcliffe
Managing Director, Scientific and Regulatory Affairs
Biotechnology Industry Organization