



August 23, 2004

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, rm.1061
Rockville, MD 20852

Re: Docket No. 2004S-0233 Solicitation of Comments on Stimulating Innovation in Medical Technologies; Establishment of Docket

Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck commends the Department of Health and Human Services (HHS) in its efforts to promote innovation in medical technologies and welcomes the opportunity to provide comment on this important initiative. As a leading pharmaceutical company, Merck has extensive experience in successful product development. Therefore, we are well qualified to provide comment to the Innovation Initiative as described by HHS on May 24, 2004¹. Herein, we are providing comment to the HHS docket: *Solicitation of Comments on Stimulating Innovation in Medical Technologies*.

We have detailed below our ideas related to certain aspects of the innovation initiative, focusing on the Food and Drug Administration's Critical Path document issued for comment on March 16, 2004². We will use our responses to the Critical Path document as the basis for our comments herein, both in terms of the scientific and regulatory structure needed to facilitate the research, development and approval of safe and effective pharmaceutical products. We believe these ideas will improve our ability to work together to ensure that safe and effective products reach the market more efficiently.

General Comments

There have been and continue to be huge successes not only in discovering treatments for many diseases but also in the development of products that prevent some diseases from occurring. These successes indicate that the current system for discovering, developing

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69 FR 21839, Docket No. 2004N-0181

and licensing drugs, biologics and devices is working. But, with any system, improvements can be made based on the march of science and the resulting increased knowledge base. As FDA notes in their Critical Path document, it appears that the number of new drug and biologic applications are falling while research efforts are increasing dramatically. Although it takes time for research efforts to reach fruition, this apparent slowdown may be attributed to a need for innovation in drug discovery, pre-clinical and clinical study designs and innovative regulatory approaches. As such, the HHS efforts to investigate areas where innovation is warranted and to address the identified needs are critical. Additionally, with the oversight of HHS, the various constituent agencies can pool their efforts toward progressing in a coordinated manner without costly duplication of efforts.

The announcement on May 19, 2004 outlining the formation of a taskforce on medical technology innovation, chaired by Dr. Lester Crawford, Acting FDA Commissioner, is a commendable effort to support cross-communication between the HHS agencies. Important outreach efforts of the taskforce are to include public round tables and should also provide for meetings with the pharmaceutical industry to hear their thoughts in a real time manner on the proposed innovation initiatives and possibly design collaborative models for appropriate topics. We welcome the opportunity to actively participate in the discussions.

Specific Comments

We are focusing our specific comments in six key areas: FDA Critical Path, Biomarkers, Disease Prevention, Clinical Development, Consortia and Training.

FDA Critical Path

We believe the most important innovation goal for HHS is to foster the development and implementation of the initiatives described in the FDA Critical Path report. HHS is well-positioned to ensure that other similar initiatives, such as the National Institutes of Health (NIH) Roadmap for Medical Research, are coordinated and integrated with FDA's Critical Path initiative. Providing adequate funding to accomplish the goals outlined in the Critical Path will be a critical component of the innovation initiative. The FDA must be granted adequate resources to explore innovative approaches along with continuing to meet the expectations and timing goals of the essential, ongoing workload. Without adequate support and recognition, noble goals and initiatives sometimes fail.

Biomarkers

Research into the identification of biomarkers that may predict efficacy or safety must be promoted. We believe that HHS, through the FDA and NIH, can play an important role in encouraging the development of biomarkers. HHS should foster an information exchange between its agencies concerning the development and acceptance of biomarkers. We believe it is important for the FDA to clarify that the use of validated biomarkers is acceptable as an alternative to traditional approaches to dose selection and

determination of proof of concept, as well as ensure that a consistent process is used to make these determinations. We encourage HHS transparency in the path forward in developing and validating biomarkers to surrogate endpoints. This will allow industry to determine acceptable development strategies earlier, which will decrease overall drug development times.

Collaboration between FDA and NIH would be valuable to advance the use of toxicogenomics as an early indicator of development success. The goal of toxicogenomics is to allow researchers to associate a safety outcome with an expression signature, enabling sponsors to identify adverse events earlier in the development process. This will ultimately result in a decrease in the amount of time necessary to develop pharmaceuticals as unsuccessful drug candidates may be identified earlier. While this area remains scientifically complex, both the FDA and the NIH (through the NIH Roadmap) identified genomics as one area in which further research and study is necessary. To that end, the NIH is committed to providing resources and expertise to this area, which would complement the efforts of the FDA and industry. We recommend that the HHS use the Critical Path Initiative as the framework for collaboration in this important research area.

Primary Prevention of Disease

As we noted in our comments to FDA's Critical Path Initiative, we recommend that the agency create a joint task force with industry and other HHS agencies, as appropriate, to enhance the development of medicines for use in the primary prevention of disease. This effort may decrease the traditionally long review period for new drugs intended for prevention rather than treatment. The joint task force could consider such issues as regulatory barriers that impede the development of new medicines for the primary prevention of disease, policies that accelerate the development of new prevention-oriented drugs, or parameters that define an accelerated review process for disease prevention drug candidates based on biomarker data. This endeavor must include vaccines and encompass creative approaches to the developmental life-cycle of safe and effective vaccines that foster the use of validated surrogate immunogenicity endpoints for approval prior to the completion of long-term efficacy trials. Additionally, we encourage HHS to develop programs to continue public education on the importance of disease prevention, and the value of vaccines and other medicines toward this end.

Innovative Clinical Trial Designs

We are requesting that HHS promote, through the FDA and NIH, exploration of innovation in the design of clinical studies. We have identified three areas of focus: adaptive trial designs, multiple end point standards and harmonization, and combination product development.

Adaptive Trial Design: HHS agencies should advance the use and acceptance of flexible or adaptive trial designs prospectively, especially trials that occur in early development. Clinical development would benefit if interim analyses were accepted throughout the trial which may drive the current trial design to encompass more or less patients (which impacts time to completion). Of course, the analyses must be conducted in a manner that will not introduce bias nor put the overall study design at risk. Being more creative and allowing a flexible trial design based on the rollout of data will move Phase III trials forward more quickly. We recognize that FDA is sponsoring a workshop on adaptive designs for clinical trials in October of this year to continue to explore the topic.

Multiple Endpoint Standards: Clinical studies for some diseases, for example, in studies for Alzheimer's and obesity, may stimulate regulatory requirements specifying that several endpoints be met. This increases the study size as, to achieve an overall positive outcome, companies must power the study so that the endpoint that is the most difficult to prove is successful. Promoting collaboration and consistency between HHS agencies and industry on the need and design of multiple endpoint trials would be valuable. Additionally, we support collaboration with the various foreign review agencies through the ICH to ensure that multiple endpoint requirements are consistent internationally. By including stakeholders in these discussions, the setting of multiple-endpoint standards will become more consistent, which will make the drug development process more efficient.

Combination Products: While we commend the FDA for evaluating means to develop good review management practices for combination products, we believe a more innovative approach can be developed for clinical development programs for combination products. The requirements for demonstrating the safety and efficacy of combination products should consider the following scenarios and how the company's prior clinical experience may be used to support that same company's development of the combination product: 1) 2 or more marketed drugs are combined; 2) when a novel product is combined with a marketed product; and 3) when 2 novel products are combined.

Consortia

A novel approach to enhance clinical development in support of treatments for historically refractory diseases may be the accumulation of knowledge about past failures. Obtaining and collating clinical data from multiple sources may be one way to overcome failures in drug development by preventing the repeat of past mistakes. In principle, we would be interested to explore creative ways, with appropriate safeguards for data confidentiality, to pool data with other companies and HHS agencies to benefit the treatment of these refractory diseases. This type of model has been used in the validation of RNA copy number as a surrogate endpoint for the efficacy of drugs to treat

AIDS/HIV. We encourage HHS to continue to support NIH basic research into the underpinnings of refractory diseases.

Training and Development

HHS should fully support efforts to increase collaboration between the FDA, NIH, CDC, academia, and industry to focus on new technologies or emerging areas of science that may make the drug development process more efficient. For instance, HHS could support the development of academic curricula for training students at various educational levels (undergraduate to graduate) that will provide, upon graduation, a cadre of applicants for the agencies, academic institutions, and the industry to choose from for entry level positions up to senior science advisors. In particular, FDA may also consider supporting a personnel exchange for agency staff to experience first hand what is involved in drug development from an industry perspective (from clinical decisions to analytical development) and for industry staff to experience the agency perspective. Allowing these personnel exchanges in a non-competitive, non-inspectional manner will foster a better understanding of the different perspectives, hopefully leading to a more streamlined drug development process.

We appreciate the opportunity to share our comments with respect to the HHS solicitation Stimulating Innovation in Medical Technologies. Please do not hesitate to contact me, should you have any questions.

Sincerely,



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Vice President
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