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April 22, 2002



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

**RE: Docket No. 02D-0003
Draft Guidance for Industry on Exercise-induced Bronchospasm (EIB)—
Development of Drugs to Prevent EIB**

Merck & Co., Inc. is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds or potential drug candidates at one time through comprehensive, state-of-the-art R & D programs.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. In the course of bringing pulmonary product candidates through developmental testing and clinical trials, Merck scientists confront issues affected by this draft guidance. Therefore, we are very interested in and well qualified to comment on FDA's draft guidance on the development of drugs for exercise-induced bronchospasm.

We commend the FDA for its efforts to facilitate the development of drug products for EIB by describing its current thinking on the issue and encouraging dialogue with interested parties through the comment process under its good guidance practices regulations.

We have reviewed the draft guidance and we have the following comments for your consideration in finalizing this important guidance:

1) In measuring efficacy, it is important to quantitate the time to recovery of FEV₁ in addition to the maximum fall, since efficacy may be measured by a shorter time spent at low FEV₁. These two measures may be integrated by the AUC_{0-60 min} endpoint that has been utilized widely in the exercise literature.

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2) If a “threshold” level of response is used as a critical criterion of efficacy, it is important to recognize that the baseline level of exercise severity can impact the number of patients who achieve proposed thresholds. For example, if the maximum fall in FEV₁ is 40% and improves to 25%, the patient would not qualify as achieving efficacy under the draft guidance, whereas a patient with a maximum fall of 24% who improves to 19% would. This discrepancy can be addressed by determining the Percent Protection Statistic in addition to the efficacy measures described. It can be further enhanced by identifying and validating the level of protection that is meaningful to patients.

3) For a drug that can be used chronically to control asthma as well as acutely for the prevention of EIB, it is essential to assess whether the efficacy observed with true intermittent (i.e., acute) use persists in patients who use the drug chronically. Based upon results of short term studies sufficient to attain an indication, practitioners may extrapolate this short term effect to the long term; this relationship does not hold in every circumstance and may be critically important for patients.

We welcome the opportunity to comment on this draft guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,



for Bonnie J. Goldmann, MD
Sr. Vice President
Global Strategic Regulatory Development