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June 3, 2002



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

**RE: [Docket No. 02D-0095] *Draft Guidance For Industry on Exposure-Response Relationships: Study Design, Data Analysis and Regulatory Applications***

Merck & Co., Inc., is a leading worldwide, human health product company that has produced many of the most important pharmaceutical products on the market, today. Merck's multidisciplinary Research and Development (R & D) is a highly risk-intensive process that depends upon a predictable regulatory environment.

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. MRL's research scientists ensure that our Research process identifies cutting-edge product candidates from thousands of chemical and molecular entities screened, each year. Only one in ten of these exceptional research product candidates is selected to enter the most rigorous Development testing programs in the pharmaceutical industry. The medicines that Merck ultimately presents to worldwide health authorities for marketing approval are those that have met the highest technical standards available and those that are able to withstand the most critical regulatory review.

In the course of bringing our product candidates through developmental testing and clinical trials, Merck scientists regularly address issues affected by this *Draft Guidance, Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*, hereafter referred to as *The Draft Guidance*. Therefore, we are unusually well qualified to comment on *The Draft Guidance*.

General Comment

We commend the FDA for this well-written Draft Guidance for Industry, which is generally sound scientifically. However, we have the following specific comments, which, if considered, might add clarity to some issues.

Specific Comments

**Lines 164 -165 and 448 - 455:** These sections should refer specifically to major active metabolites whenever metabolites are mentioned. Measurement of inactive or minor active metabolites is not warranted.

In addition in these sections, *The Draft Guidance* should note that it can be substantially more

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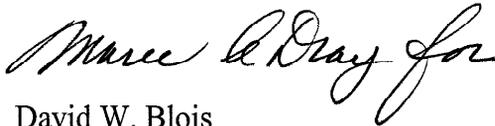
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complex to characterize the overall exposure response relationship in the presence of major active metabolites. An assessment of the contribution of each active moiety to response based on plasma concentrations must take into account likely differences in potency and pharmacokinetics (including distribution to the site of action).

**Lines 285 - 286** in *The Draft Guidance* state: ‘... or can demonstrate a difference in exposure that falls within the standard interval but is nonetheless real.’ This is in conflict with other FDA bioequivalence (BE) guidances where it is recognised that such a difference does not result in a failed BE study.

**Lines 351 - 376:** *The Draft Guidance* should present a more balanced view of concentration-controlled *versus* dose-controlled trial designs. The confounding of dose and concentration, described in this section, is a potential issue for dose-controlled trial designs. However, the importance of this issue may be overstated in *The Draft Guidance* because it does not seem likely to occur very often and can be handled by approaches other than a concentration-controlled trial. Conversely, *The Draft Guidance* does not acknowledge that there are serious practical difficulties involved in conducting a concentration-controlled trial, which is one of the principal reasons that they are rarely conducted. This section should provide a brief description of each trial design along with the *pros* and *cons* of each. One approach would be to expand upon the information in Table II.

We appreciate your consideration of these comments.



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