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May 31, 2002

Lawrence J. Lesko, PhD
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Dr Lesko:

Enclosed are our comments on the "Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications" draft guidance which was published at <http://www.fda.gov/cder/guidances/index.htm>.

Please contact us if you have any questions.

Sincerely,



Chetan D. Lathia, PhD
Deputy Director
Clinical Pharmacology

Sincerely,



Prabhu Rajagopalan, PhD
Associate Director
Clinical Pharmacology

Cc:

Allen Heller
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02D-0095

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This document provides guidance on principles of exposure-response. This guidance does not offer any specific recommendations. It discusses the utility of exposure-response data across the spectrum of clinical drug development. It is a very well-written guidance document which provides the agency's current thinking on this topic. 19:33

In the background section of the document, reference is made in line 45 to considering a drug to be safe and effective only when the relationships between exposure-beneficial effects and between exposure-adverse effects are known. It is worthwhile to point out that in some drug development programs, pharmaceutical companies may evaluate a range of doses in Phase 1. Once a Phase 2 dose (or dose-range) is selected, however, for therapeutic areas with high medical need, the company may in certain instances choose to evaluate only one or two dose-levels for Phase 2 and 3 studies. In such a situation, the relationship between exposure (dose or plasma exposure) and efficacy is not characterized as extensively as that alluded to in this section. It would be useful to add such a caveat in this section.

In the sub-section titled "Contributing to Primary Evidence of Effectiveness and/or Safety," it is mentioned that an adequately designed dose-response study could allow reliance on a single study as evidence of effectiveness. This concept has been mentioned in other scientific forum as well. It would be very useful if examples, with references, could be provided where the FDA has allowed such dose-response studies to allow reliance on a single study as evidence of effectiveness.

In the sub-section titled "Providing Support for Primary Efficacy Studies," in lines 174-177, it is mentioned that systemic concentration-response data may allow explanation of marginal results and could ideally support approval. This concept makes scientific sense. However, it would be very useful if examples, with references, could be provided where the FDA has allowed such data to support approval.

In the sub-section titled "New dose regimens, dosage forms, and formulations, routes of administration, and minor product changes," reference is made in lines 255-257 about approving a new dose or dosing schedule if the exposure-response relationship is known. This, again, appears to be a very sound scientific concept. However, there are no well-publicized examples on this. It would be very useful to the pharmaceutical drug-development community to have examples, with references, stated in this document. Further in this sub-section, on lines 301-305, there is a mention that exposure-response information could be used to support a change in the route of administration by using known exposure-response relationships. Again, this concept makes a lot of scientific sense. However, without adequate examples, with references, it may be difficult for a pharmaceutical company to apply these principles.

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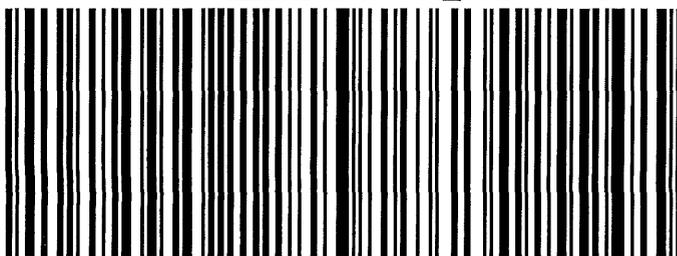
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