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

Subject: Docket 02D-0095 - Draft *Guidance for Industry Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*

Dear Sir/Madam,

Thank you for this opportunity to review the draft *Guidance for Industry Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*.

General comments:

It is encouraging that this topic is being addressed by the FDA and that the Agency is recognizing characterization of exposure-response relationships as a powerful and widely applicable approach in registration strategies. However, the guidance lacks specific examples and recommendations on acceptable study designs, content, and format for exposure-response analyses. As such, it falls short in terms of a guidance since implementation of the approach in the development process is not adequately addressed.

The guidance document has "Study Design, Data Analysis, and Regulatory Applications" as part of its title. However, the discussion is extremely general. The document reads more like a "Points to Consider" type of document than one specifically addressing study design, data analysis, and regulatory applications.

Specific comments are as follows:

02D-0095

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1. Lines 66-69 *For the purposes of this guidance, we are using the broad term exposure to refer to dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (e.g., Cmax, Cmin, C_{ss}, AUC). Similarly, response refers to a direct measure of the pharmacologic effect of the drug.*

It may be confusing to include “dose” as a type “exposure.” In fact, later in the document it seems that a distinction is being made between “dose” and “exposure” which is more consistent with general understanding and usage, for example in the following text on lines 158-162:

In some cases, measurement of systemic exposure levels (e.g., plasma drug concentrations) as part of dose-response studies can provide additional useful information. Systemic exposure data are especially useful when an assigned dose is poorly correlated with plasma levels, obscuring an existing concentration-response relationship.

Should “response” not also refer to an “indirect” measure of the pharmacologic effect of the drug as, for example, many biomarkers may be indirect measures?

2. Lines 88-90 *Many drugs thought to be of potential value in treating human disease are introduced into development based on knowledge of in vitro receptor binding properties and identified pharmacodynamic effects in animals.*

As a clarification, suggest add “receptor” to distinguish from non-specific binding, etc.

3. Lines 162-168 *This can occur when there is a large degree of interindividual variability in pharmacokinetics and/or there is a nonlinear relationship between dose and blood drug levels concentrations and/or time-dependent changes in blood drug concentrations occur. Blood concentrations levels can also be helpful when (1) both parent drug and metabolites are active, (2) different exposure measures (e.g., C_{max}, AUC) provide different relationships between exposure and efficacy or safety, (3) the number of fixed doses in the dose-response studies is limited, and (4) responses are highly variable and it is helpful to explore the underlying causes of variability of response.*

Suggest use “blood” rather than “plasma” throughout the document to allow for more matrices (plasma, serum, whole blood). Suggest use “concentration” rather than “levels.” The above point (4) is already covered in the previous sentence.

4. Lines 176-178 *Ideally, in such cases the explanation would be further tested, but in close cases this information could support approval.*

Explain what is meant by “close cases.”

5. Lines 187-193 *Exposure-response data using short-term biomarkers or surrogate endpoints can sometimes make further exposure-response data from clinical endpoint exposure-response studies unnecessary. For example, if it can be shown that the short-term effect does not increase past a particular dose or concentration, there may be no reason to explore higher doses or concentrations in the clinical trials. Similarly, short-term exposure response studies with biomarkers might be used to evaluate early (e.g., first dose) responses seen in clinical trials.*

Explain what is meant by “short-term biomarkers.”

Also, if a biomarker has not been validated as a surrogate for the clinical endpoint, it is possible that one cannot predict an individual's response on the clinical endpoint based on that biomarker.

6. Lines 199-202 *Exposure-response information can sometimes be used to support use, without further clinical data, of a drug in a new target population by showing similar (or altered in a defined way) concentration-response relationships for a well-understood short-term clinical or pharmacodynamic endpoint.*

It would be useful to provide more specific guidelines on what one needs to do to show "similar concentration-response relationship" between a new target population and an existing one. This will be useful to sponsors who plan to employ the bridging strategy to gain approval in a separate geographic region.

7. Lines 314-317 *Where effectiveness is readily measured repeatedly in the course of a dosing interval (e.g., analgesia, blood pressure, blood glucose), it is possible to relate clinical response to blood concentrations over time, which can be provide critical information for choosing a dose and dosing interval.*

Above has been revised to improve semantics.

8. Lines 365-367 *Also, a study that titrated only nonresponders to higher doses might show a lower response with higher concentrations (i.e., an umbrella-shaped concentration-response (or dose-response) curve, a misleading result).*

If one can assume that an individual responding at lower concentration will also respond at the higher concentration level, then the estimated concentration-response curve will be monotone as long as the appropriate estimation method is used.

9. Lines 472-475 *In this circumstance, measurement of ~~only one or more moieties can be appropriate as markers~~ said in understanding exposure-response relationships and can even be used to identify the major active moieties.*

The above has been revised because the moieties are really exposure parameters and referring to them as "markers" gives the impression that they constitute response elements.

10. Lines 494-496 *Renal or hepatic diseases can alter the binding of drugs to plasma proteins. These changes can influence the understanding of PK and PK-PD relationships.*

The changes (alterations to the plasma protein binding) do not influence our understanding but necessitate the measure of free drug to better define the PK-PD relationships.

11. Lines 671-675 *This can suggest ways to optimize dosage regimens and to individualize treatment in specific patient subsets for which there are limited data. Creating a theory or rationale to explain exposure-response relationships through modeling and simulation allows interpolation and extrapolation to better doses and responses in the general population and to subpopulations defined by certain intrinsic and extrinsic factors.*

Should also consider the application to individualize treatment not only in specific patient subsets but also in "individuals," which is actually what the verb, "individualize," means.

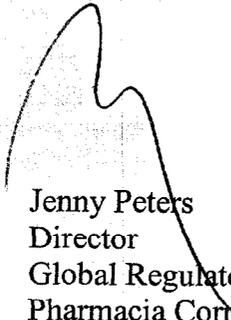
12. Other

The writing could be more concise and less repetitive. It might be useful to define certain terms from the outset in a listing to increase consistency and to reduce repetition in the text, e.g exposure, response.

It might be useful to discuss quality of response measurements relative to their value and credibility. Measurements of exposure are already covered in that respect by bioanalysis guidelines.

Should any clarification of our input be required, please don't hesitate to contact me at (616)-833-8141.

Sincerely,



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Pharmacia Corporation

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