

**Alice E. Till, Ph.D.**  
VICE PRESIDENT  
SCIENCE POLICY AND TECHNICAL AFFAIRS



June 3, 2002

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

Re: Draft guidance for Industry on Exposure-Response relationships: Study Design, Data Analysis, and Regulatory Applications [Docket No. 02D-0095, 67 *Federal Register*, 15576, April 2, 2002]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier and more productive lives. Investing more than \$30 billion in 2001 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA, therefore, appreciates the opportunity to provide the attached comments on the Draft Guidance for Industry on Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications.

We hope that you will give careful consideration to the attached comments as you work to finalize the guidance. Please contact me if there are any questions.

Sincerely,

A handwritten signature in cursive script that reads "Alice E. Till".

Alice E. Till, Ph.D.

CC L. Lesko

Att.

02D-0095

C 11

*Pharmaceutical Research and Manufacturers of America*

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3564 • FAX: 202-835-3597 • E-Mail: [atill@phrma.org](mailto:atill@phrma.org)

# **Comments on Draft FDA Guidance: Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications**

## **1. General**

Overall, the guidance is of a high standard and represents a translation into guidance form of ideas previously put forward in general terms in FDA-sponsored publications and in the FDA Modernization Act, 1997. From a scientific perspective this is an invaluable step forward in using modern methods to study and regulate drugs. Two different drafts of the guidance were posted and the line numbering differed slightly between them. The comments and line numbering in this document refer to the draft guidance dated 4/1/02. Major comments are listed first followed by minor (e.g. editorial, phraseology) comments.

## **2. Major Comments and Recommendations**

- 1. More Clarity and Examples.** The use of exposure-response information for regulatory decision-making is a key aspect of this guidance. In order to provide more clarity and guidance around this issue, the agency should give more specific examples of the successful use of exposure-response information to support registration. For example, the term "well-understood" is used for different statements pertaining to exposure-response relationships on **lines 201-202, lines 268-9 and lines 298-9** but without offering any specific information as to what the agency means by the term. While it may be difficult to give simple definitions that will apply in all cases, the use of examples could go a long way to clarify the intent of the various statements.

**Recommendation.** FDA should provide clear examples of when knowledge of the exposure-response relationship facilitated the approval process (e.g. contributing to primary evidence of effectiveness/safety or providing support for primary efficacy studies, etc.) and/or obviated the need for two well-controlled clinical trials. Guidelines should also be provided about the minimum requirements for accepting that a relationship between concentration and biomarker/surrogate/clinical endpoint has been established.

2. **Consistency.** The FDA should consider instituting a procedure to encourage consistent and balanced interpretation of the guidance between different divisions of the agency and between individual reviewers. Differences between reviewers and divisions occur frequently and a clear guidance with specific examples could help prevent these occurrences. A reasonable goal would be to seek consistency across divisions and reviewers about what constitutes a valid exposure-response relationship to help support drug registration (e.g. contributing to primary evidence of effectiveness/safety or providing support for primary efficacy studies, etc.).
3. **Lines 123-125.** Replace the sentence "In general.....endpoints are studied" with the following text.

*"In 1997 the FDA Modernization Act (FDAMA) changed the requirements for demonstrating efficacy from at least two well-controlled clinical trials to "one adequate and well-controlled investigation and confirmatory evidence" (FDAMA, Section 115a). This change in law makes it possible for a sponsor to submit one well-controlled trial (e.g. a Phase III trial) along with one well-controlled exposure-response study, where the endpoint of the exposure-response study is the actual clinical endpoint or an accepted surrogate endpoint. In order for exposure-response information to be considered "confirmatory evidence" it must be derived from an adequate and well-controlled study (see 21 CFR 314.126)."*

Alternatively, the guidance should clearly state (e.g. use examples) under what conditions could exposure-response information provide "confirmatory" evidence of effectiveness along with one adequate and well-controlled trial.

**Rationale.** This is a key issue to foster the use of properly designed dose/exposure-response studies and should be emphasised in the guidance. Better dose/exposure-response information will be generated as sponsors recognize the benefits in terms of potentially fewer studies needed to establish effectiveness.

4. **Lines 137-147.** In order to be clear and consistent with the ICH-E4 guidance on dose-response (part III B 1.), the following text should be added after line 147.

*"A statistically significant dose-response relationship from an adequate and well controlled study constitutes primary clinical evidence of effectiveness.*

*Statistically significant differences in pair-wise comparisons between doses are not necessary if a statistically significant relationship (e.g. upward trend or slope) across doses can be established.”*

**Rationale.** This issue continues to be misunderstood by many individuals in the industry and the FDA. A clear statement on this matter (even if it largely repeats some of the E4 guidance) will help generate better dose-response information in future submissions by encouraging sponsors to perform studies with a wider range of doses. The mistaken need to show pair-wise statistical significance in dose-response trials limits the number of doses that are studied because larger numbers of patients are then required in each dose group.

5. **Lines 149-56.** This paragraph is confusing because it introduces a new issue, namely how it may be possible to rely on a single dose-response study as evidence of effectiveness. Is the intent of this paragraph to describe attributes of a study that could be used as the single trial supporting effectiveness or dose-response trials in general? The key issue again is about the need for statistically significant differences between doses versus a statistically significant relationship (upward trend or slope). For example, the comment concerning the “consistent ordering of responses (most persuasive when, for example, several doses are significantly different from placebo and in addition, show an increasing response with dose)” is not consistent with the ICH-E4 guidance (part III B 1; see above comment). A study could show a statistically significant dose-response but not consistent ordering if the top doses are approaching a plateau (e.g. Emax type pattern where the highest dose could produce a slightly lower observed response than the second highest dose because of variability).

**Recommendation.** Our recommendation is to clarify whether or not this paragraph pertains only to the case of a single dose-response study as evidence of effectiveness as well as the issue of significant pair-wise differences versus significant dose-response relationship.

6. **Concentration-controlled and other trials, lines 351-376 and lines 406-424.** The use of concentration-controlled trials to define the exposure-response relationship is emphasised in this document, despite the inherent difficulties and relative lack of use in drug development. The rationale for this design versus the dose-controlled trial appears biased, and there is literature to substantiate the value of alternate study designs.<sup>1,2,3</sup> **Lines 360-5.** The example listed is interesting but how often has it been clearly demonstrated to

occur (i.e. higher plasma concentrations truly do not lead to higher response but we are fooled into thinking so by another unknown factor that causes both increased absorption/plasma concentrations and response)? While the *potential* for the confounding described exists, it is essential to recognize that valid, unbiased concentration-response relationships can be described using a variety of study designs and mathematical/statistical methods, provided the investigator is aware of the potential confounding.

**Recommendation.** FDA should consider including a description of and balanced assessment of all relevant study designs, or clearly define that these are examples. The guidance should also elaborate on the phrase “prospectively designed” (**line 423**) in the context of building exposure-response models. What aspects of the exposure-response model building process need to be prospectively defined in the protocol? For example, does one need to specify that response increases as a straight line function of dose or just that it increases with dose (monotonic increasing); a subtle but potentially important distinction that could lead to different statistical conclusions.

7. **Line 611.** Regulatory guidance on what constitutes a “rigorous statistical evaluation” of a biomarker to become a validated surrogate endpoint would be very helpful.

## 2. Minor Comments

8. A comment is needed regarding instances in which it may be unethical to give low doses to establish the lower portion of the exposure-response relationship for efficacy (e.g. in infectious diseases where pharmacodynamically-linked parameters are known and dose can be selected based on pharmacokinetics in healthy volunteers) or to give high doses to establish the upper portion of the exposure-response relationship for safety reasons.
9. **Lines 45-46.** “That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known.” This statement oversimplifies understanding of the exposure-response relationship, particularly when a direct relationship is not evident, but an indirect response may be hypothesized. In addition, this sentence

seems to confuse efficacy and toxicity when discussing response; it needs rephrasing so as to distinguish between these two different aspects of response. The word "known" is likely too strong, and should be changed to "characterized". Finally, considerations of inter-individual variability in these relationships, and the associated risk that some fraction of the population will invariably have non-optimal exposure should be recognized.

**Recommendation.** FDA should consider rewording this sentence to include comments about how useful understanding the exposure-response relationship can be in the assessment of the benefit-risk ratio for changes in exposure, and the impact that interindividual variability may have on exposure optimization.

10. **Line 64.** Should add reference(s) for this statement.

11. **Line 78.** Change the title to "Regulatory and Drug Development Applications".

**Rationale.** Parts of this section pertain to drug development decisions that are not part of regulatory decisions.

12. **Lines 91-93.** This sentence could be clarified by making more explicit reference to prior PK/PD work in animals e.g. ".....can also (1) validate prior PK/PD extrapolations from animal data and demonstrate/explore the degree of continuity in PK/PD relationships between animals and man ..". The value of these data in selecting doses for first time in human studies should be mentioned. This is a long sentence and it might be better to split out each point as a bullet on a new line.

13. **Line 161.**

**Recommendation.** The phrase "*when an assigned dose is poorly correlated to plasma levels, obscuring an existing concentration-response*" should be changed to "when a concentration-response relationship exists, but a poor correlation of assigned dose to plasma concentration (e.g. nonlinear relationship between dose and plasma concentration, interindividual pharmacokinetic variability) prevents the recovery of a dose-response relationship"

14. **Line 287.** re: "a sponsor may be able to support the view that the wider confidence interval or difference in bioavailability or exposure would not lead to a therapeutic difference."

Does this mean that the Agency will accept a justification to widen the 80 – 125% equivalence interval if the exposure-response relationship is well understood? Or, will the definition of bioequivalence (90% CI within 80-125%) remain unchanged, yet the study can be used to justify the product switch because the lack of bioequivalence will not impact safety or efficacy. It is a subtle difference, but one with potential impact on generic entries - the innovator will likely have the data to justify proceeding despite a failure to achieve bioequivalence (through their safety and efficacy databases), but widening the equivalence interval creates the potential that an inequivalent product is approved without the corresponding supporting clinical trial evidence.

15. **Line 347.**

**Recommendation.** *The phrase “individual PK variability” should be changed to “inter-individual PK variability”*

16. **Line 368.** The reference to “the second kind of study” is not clear. It should be clarified that this statement refers to the study that titrates nonresponders to higher doses (in the proceeding sentence) and not to the second kind of study introduced earlier in the same paragraph (lines 351-5).

17. **Line 370.** The reference to “these studies” is also not clear. Please clarify that you are now referring to randomised dose studies and not to studies that titrate nonresponders to higher doses (if that is the intent of the statement).

18. **Table 1.** Under “Parallel, fixed dose,” the second bullet appropriately mentions that individual dose-response is not possible with this study design. However, an additional point should be made stating that individual concentration-response may be possible if “concentration-response relationships in the same individual are observed over time.” (as previously discussed on lines 375-376).

19. **Table 1.** Third bullet under “Parallel, fixed dose”.

Change “Should have a relatively large number of subjects” to *“May require a larger number of subjects relative to other study designs”*

20. **Line 448.** Change “...parent drug and its metabolites.” Measurement of all active moieties....” to *“parent drug and its important active metabolites. Measurement of all important active moieties....”*

**Rationale.** Measurement of all active moieties may not be possible for compounds with a multitude of very minor active metabolites but measurement of important active moieties is reasonable (as per recent attempts by PhRMA/FDA to define major metabolites for toxicology studies).

21. **Lines 509-512.** This first paragraph needs rephrasing to state that the appropriate measure of exposure is dependent on the nature of the relationship between exposure and response.

**Recommendation.** *"The most appropriate representation of exposure will depend on the relationship between exposure and response. If both exposure and response vary dynamically with time within a dosage interval, then the maximum information will normally be retrieved by a PK/PD analysis that relates response to concentration within an individual subject, taking account of sequential measurements of both concentration and response. In some cases, when, for example, a single categorical pharmacodynamic response is obtained on a given sampling day, it may be more appropriate to represent the exposure by more simplified metrics such as  $C_{avg}$ ,  $C_{max}$ ,  $C_{min}$  or AUC."*

22. **Line 553.** Insert the following statement before the sentence that starts with "This approach . . ."

*"Depending on the sample scheme and drug, empirical Bayes predictions of certain individual PK parameters (e.g. volume of distribution, absorption rate, lag time) may suffer from poor precision and bias (shrinkage to the mean). However, fairly accurate estimates of individual clearance and AUC may still be obtained with appropriate sparse sampling."*

23. **Line 580.** "In many cases, multiple response endpoints are more informative than single endpoints for establishing exposure-response relationships."

Construction of a weighted or combined response that weighs each endpoint relative to biomarker, surrogate and/or clinical benefit may be helpful when interpreting such data.

**Recommendation:** *FDA should consider including a statement on how to weight the relative importance of multiple (possibly conflicting) endpoints.*

24. **Lines 685 – 701.** For clarity, it may help to structure the various assumptions under headings related to different components of the model e.g. structural model, statistical model, and disease model.

25. **Line 681.** Change to read “should be clearly identified prospectively”
26. **Line 692.** Add “and placebo response model” after “Disease state progression”
27. **Line 709.** “The model selected should be based on the assumption made and the intended use of the model in decision making”. It should be added that model selection should be governed by the mechanism of action of the drug, which will lead to the use of, e.g., direct, indirect or irreversible response models. A tabular format, such as that used for study designs would be very useful way to organize this perspective. Such a table could also help clarify what is required for a 'well-understood' relationship. It would be helpful if the Agency would expand this section to provide some examples of models that would be viewed as generally acceptable, their strengths and weaknesses, and the type of conclusions that could be reached on the basis of a particular modeling approach.

**Recommendation.** FDA should consider including a statement that “model selection should be governed by the mechanism of action of the drug, which will lead to the use of, e.g., direct, indirect or irreversible response models as well as the assumptions made and the intended use of the model in decision making.”

28. **Lines 721 – 742.** It should be noted that validation of the predictive performance of the exposure-response model is dependent on the use of the model and that under certain circumstances may not be necessary. For example, in an exposure-response study with an active comparator, the primary objective may be to estimate relative potency. In this setting, accurate population estimates of the relative potency (e.g. EC50 and perhaps other PK/PD parameters) and inference about these estimates may be of interest and not the predictive performance of this model. It should also be noted that when exposure-response models are developed from pooled studies, if the model fit is adequate and robust to various design conditions and populations with differing inclusion/exclusion criteria (i.e., when study-specific parameter estimates are not required), then there may be a greater degree of confidence in the inference from the exposure-response model. To this end, the guidance should acknowledge the importance of assessing the appropriateness of pooling data from various studies.

The described approach to model validation only strictly applies to large data-sets such as obtained in Population PK/PD studies. It should be made clear that alternative approaches related to goodness of fit and the principle of parsimony may be more relevant for conventional PK/PD analysis of data-sets in a small number of individuals, when there are insufficient data to set aside a significant proportion for validation of the model. In addition, consideration should be given to the possibility that the parsimony principle should be relaxed if features of the model are considered important, but unsupported by well-controlled data. Examples might include age-related changes that are well documented in early trials, but less well supported in late phase trials due to sparseness of data in that population.

29. **Lines 735-738.** “The common method for estimating [model] predictability is to split the data set into two parts, build the model based on one set of data, and test the predictability of the resulting model on the second set of data.” This approach to model validation only strictly applies to large data sets such as obtained in Population PK/PD studies.

**Recommendation.** FDA should provide guidance regarding model validation/evaluation based on smaller populations of subjects that have undergone intense PK/PD sampling. Examples include the relationship to mechanism of action and measures of goodness of fit. Change “The common method” to “A common method”

**Rationale:** It is possible/likely that other methods (e.g., posterior predictive check) will largely replace data splitting for demonstrating the predictive power of a model.

#### 4. References

---

<sup>1</sup> Levy G, Ebling WF, Forrest A. Concentration- or Effect-controlled Clinical Trials with Sparse Data. *Clin Pharmacol Therap* 1994; 56(1): 1-8.

<sup>2</sup> Ebling WF, Levy G. Population Pharmacodynamics: Strategies for Concentration- and Effect-Controlled Clinical Trials. *Ann Pharmacother* 1996; 30(1): 12-19.

<sup>3</sup> Ebling WF, Matsumoto, Levy G. Feasibility of effect-controlled clinical trials of drugs with pharmacodynamic hysteresis using sparse data. *Pharm Res* 1996; 13: 1804-1810.

PhRMA  
1100 15TH NW 9TH FLR  
Washington DC 20005  
(202)835-3400

SHIP DATE: 04JUN02  
ACC# 146640001

ACTUAL WGT: 1-LBS SCALE

TO: DOCKET MANAGEMENT BRANCH (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061

Rockville MD 20852

4257 2813 8600



REF: COUNTS

PRIORITY OVERNIGHT WED

CAD# 0057147 04JUN02

TRK# 4257 2813 8600 Form 0201

Deliver by:  
05 JUN 02

IAD

AA

20852 -MD-US

19 GAIA

153077 RIT 11/01

