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VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS



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July 12, 2005

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

Re: Draft Guidance for industry on Exploratory Investigational New Drugs Studies
[Docket 2005D-0122, 70 *Federal Register*, 19674 (April 14, 2005)]

Dear Sir/Madam:

The following comments on the subject draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members invested an estimated \$38.8 billion in 2004 in discovering and developing new medicines. PhRMA companies are leading the way in the search for new cures.

For the industry, an exploratory Investigational New Drug (expIND) process offers an opportunity to select compounds for development or test proof of concept with human data in about half the time that it takes for a standard IND. We recognize that this approach does not guarantee a successful evaluation of a drug candidate, in that the paradigm may not allow us to achieve a pharmacologic dose or the non-rodent may prove to be more sensitive than the rodent. Nevertheless, it is our belief that the benefits far outweigh the risks associated with failing to fully achieve the testing objectives. PhRMA is very appreciative of the FDA's staff's understanding of the value and minimal safety risk this new approach poses. We also appreciate the very productive, scientific interactions that facilitated the development of this guidance. The implementation of the guidance and the experiences that we collectively have will, in the end, judge its success.

With few exceptions, the guidance incorporates what industry believes to be the appropriate parameters of an effective exploratory IND process. If not adequately addressed, however, these exceptions have the potential to significantly impede implementation of the proposed expIND.

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Pharmaceutical Research and Manufacturers of America

1. **Assessment of the Sensitivity of the Non-rodent**

The inclusion of the non-rodent in the testing scheme was to qualify the rodent as adequately sensitive to the test article. The limited non-rodent study was never intended to provide target organ information or any precise assessment of toxicity. We firmly believe that this can be accomplished with three or four animals in the treatment group. The guidance leaves open to variable interpretation the appropriate size of the non-rodent study. This will no doubt lead to variable interpretation of the intent of the guidance by different Agency Divisions and could undermine the utility of the approach proposed making it difficult for the industry to anticipate regulatory expectations.

2. **Assessment of the Non-rodent Sensitivity By Gender**

The guidance suggests that the observation of a gender difference in the rodent would require both genders to be assessed in the non-rodent. If differences are observed in gender-specific organs in the rodent, and if humans of the both genders (or the targeted gender) are planned for inclusion in the clinical trials, then it may be appropriate to construct the non-rodent study to include both genders (or the targeted gender). If this is not the clinical circumstance, or the effects are on gender-specific organs, there is no basis to include both genders in the non-rodent study. There is no evidence that for general toxicity, gender differences in susceptibility in animals translates to similar gender differences in susceptibility in humans. Thus, such data has no relevance to the decision process. We would ask that the language be changed to indicate that either gender of non-rodents is acceptable, and that gender based differences in susceptibility as a factor in preclinical and clinical study design only apply to gender-specific organ toxicities.

3. **Stop Dose Criteria**

The text on line 383 is very clear in terms of the stop dose criteria for the non-rodent AUC – the criteria is the AUC observed in the non-rodent at a dose approximating the rodent NOAEL calculated on a mg/m² basis. However, the wording in the flow chart attachment is ambiguous. It reads “clinical equivalent of ½ of rat or non-rodent AUC – which ever is lower”. We suggest the following text for the attachment:

“Clinical equivalent of ½ the AUC in the rodent or the AUC in the non-rodent – whichever is lower.”

4. **Reference to Animal Species**

In several places throughout the guidance, reference is made to the rat or dog. Since the rodent could be a mouse and the non-rodent could be a non-human primate we would suggest that reference should in all cases be to a rodent or non-rodent.

5. **3rd Example starting on line 388**

The 3rd example of an Exp IND approach is inadequately presented to allow a reader generally informed about drug development to understand the recommendation. Please clarify what is the recommended approach and how it differs from the other 2 approaches. Please revise the description or delete it as it is not informative in its current form and will lead to significant confusion.

6. **Reference to Phase of Development**

In several cases reference to expINDs is to Phase I studies. Although typical first in man studies are referred to as Phase I studies, for expINDs it might be less confusing if these studies are referred to as Phase 0 studies.

7. **Line 63**

We would suggest the following change: "...or closely related active moieties in terms of their pharmacology or target protein. Promising candidates"

8. **Patent Issues**

Under Title II of the Drug Price Competition and Patent Term Restoration Act patent life can be extended to compensate patent holders for marketing time lost while developing a product and awaiting government approval. Extension is based on the "regulatory review period" which consists of two parts: a testing phase, and an approval phase. The testing phase for a human drug product is the period between the effective date of an IND and the initial submission of the marketing application (New Drug Application). We recommend including some discussion in the final guidance of the effect, if any, of an exploratory IND on the determination of the length of the testing phase for the purposes of patent extension.

9. **Section I: Introduction (Line 37):**

"The duration of dosing in an exploratory IND study is expected to be limited (e.g., 7 days)."

In the example provided (7 days), it is unclear whether the intent is to refer to consecutive calendar days or dosing days. For example, can several "every-2-weeks" or "once-monthly" doses be administered under an exploratory IND, if the same number of doses and dosing interval was included in the pre-clinical tests? At Lines 357 – 358 in the discussion of "*Clinical trials to study pharmacological effects*" the draft states, "*The number of repeat administrations at the rat NOAEL should, at minimum, be equal to the number of administrations, given with the same schedule, intended clinically.*" In addition, at lines 400-401 under discussion of "*Clinical studies of MOAs related to efficacy*" it states, "*The dose and dosing regimen determined in the animal study would*

be extrapolated for use in the clinical investigation.” These examples suggest a case-by-case determination of the human regimen under an exploratory IND. It would, however, be helpful if this were addressed.

10. **Section II (B) – Exploratory IND Approach** (Lines 135-142): *“Although exploratory IND studies may be used during development of products intended for any indication, it is particularly important for manufacturers to consider this approach when developing products to treat serious diseases. Because the approach can help identify promising candidates more quickly and precisely, exploratory IND studies could become an important part of the armamentarium when developing drug and biological products to treat serious or life-threatening illness.”*

While we assume that all subjects (healthy, minimal disease, extensive disease) may be enrolled under an exploratory IND with the appropriate rationale, we recommend that this be explicitly stated.

11. **Section III(C) (2) – Content of IND Submissions; Safety Program Designs – Examples; Clinical trials to study pharmacological effects:**

a. (Lines 361-363) – *“If the data from the confirmatory study suggests that the rodent is not the most sensitive species, a 2-week repeated dose toxicity study should be performed in the second species to select doses for human trials.”* And – (Lines 380-381) – *“The starting dose is anticipated to be no greater than 1/50 of the NOAEL from the 2-week toxicology study in the sensitive species on a mg/m² basis.”*

This text does not seem consistent with the Attachment (Line 448), which perhaps needs an arrow between “2-week tox study in nonrodent” and “Calculation of clinical start dose, 1/50 of rat NOEL” with the latter modified to replace “rat” with “most sensitive.”

b. (Lines 366-367): *“If an exploratory IND study is designed to elicit pharmacological effects, each candidate product to be tested should be evaluated for safety pharmacology.”* It would be helpful to directly address for all the example scenarios (micro-dose, pharmacologic effect, MOA studies) in what cases, if any, the pharmacological and/or toxicological studies can be completed for a subset of a series of related compounds.

12. **Line 23**

We would suggest the following change: “...including studies of drugs or therapeutic biological products having similar pharmacology or directed to the same target protein, under an...”

13. **Line 33**

We would suggest the following change: “...clinical trial or trials that occurs very early...”

14. **Line 73**

We would suggest the following change: "...performed in a rodent (usually rats) and non-rodent (usually dogs)..."

15. **Line 231**

We would suggest the following change: "...by the same route of administration and amount (12) or tested through appropriate animal studies."

16. **Footnote 13**

We suggest the following: "See footnote 10 and guidelines for industry for standard IND studies, Chemistry..."

17. **Line 190**

We suggest the following insertion: "... the limits of tolerability. If studies are to be conducted in which the same cohort of subjects receive more than one test article the doses should follow appropriate wash out periods and dosing should be limited to a maximum of 10 daily doses."

18. **Line 63**

We suggest the following insertion: "... might be selected. In this study the selection of the high dose should normally be the maximum tolerated dose; however, for compounds of low toxicity a maximum dose of 1000 mg/kg could be used. If a rodent species..."

19. **Paragraph starting with line 308**

We propose to modify this approach to allow for up to 5 sequential micro-doses with appropriate washout periods with a total limited dose of 250 micrograms with no single dose being larger than 100 micrograms. The route of administration should be the same as the expected route for humans including the iv route and concomitant substances should be allowed. A rationale for these points follows:

Imaging of tissue function and anatomy is increasingly important in our understanding of normal physiological processes and responses to pharmacological agents. Single radiotracer administrations are most useful in exploring pharmacokinetics with very low drug mass and establishing anatomical relationships such as tissue distribution of a drug. For dynamic responses to a pharmacologic agent, only when the baseline state can be largely anticipated and a baseline assessment is not need can a single micro-dose radiotracer administration be used successfully.

In many circumstances the baseline assessment (e.g., ^{18}F -glucose uptake by a tumor) is required and a subsequent evaluation using the same probe is needed to assess the response to a potential therapeutic agent. PET probes are increasingly being developed for the most nettlesome areas of drug development (e.g., neurosciences, oncology) in which the understanding of the pharmacology and local receptor occupancy levels have been both inaccessible and unassessable in humans and problematic in translating from other experimental animals. For novel molecular targets, PET probes are being developed in parallel with pharmacological agents to explore receptor occupancy as well the pharmacological response to establish the correct dose for later phase clinical trials in the hope of avoiding unnecessary dose groups and equivocal study results. To use many of these agents, a baseline assessment of receptor-probe interaction is required in each individual before determining the effect of the pharmacological agent on probe tissue distribution and radiointensity and thereafter deriving the critical results (e.g., receptor occupancy, changes in cellular function, expression of apoptotic signals). The limitations of imaging micro-dose studies to a single administration will significantly diminish the value of the exploratory IND in this critical emerging area.

Most PET imaging studies use doses that are usually limited by the radiation exposure rather than mass of material administered. Radionuclides used in PET scanning are typically isotopes with short half lives such as ^{11}C , ^{13}N , ^{15}O , and ^{18}F (half-lives of 20 min, 10 min, 2 min, and 110 min respectively). As a consequence of the very short radioactive half-life, body residence time of the intact radiotracer (i.e., pharmacological active agent) is very transient and is far less than that associated with unlabeled drug. The net result is far greater toxicological safety from a pharmacological perspective. As the radiotracer doses are very small, the overall toxicological safety from xenobiotic perspective should be minimal. It is proposed that for PET imaging tracers that 5 exposures with the radiotracer should be feasible under the exploratory IND, so long as the net exposure is a large multiple (100x) of the anticipated human exposure and do not cause adverse event in experimental animals.

20. **CMC Language**

The document needs extensive editing for consistency with standard CMC terminology.

21. **Draft Toxicology Study Data**

We request clarification on whether unaudited draft toxicology data may be submitted to support an exploratory IND, falling within the 120-day submission framework of the Phase I IND Content and Format Guidance

22. **Line 123-126**

The Guidance has not addressed the issue of women of childbearing potential in exploratory studies

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23. **Line 137**

We suggest the following insertion: "...to treat serious diseases or affect novel pharmacologic targets."

24. **Line 318**

We request clarification that for micro-dose study support, the single species toxicology study may be conducted in male animals only if the clinical trial is to involve male subjects only consistent with the CHMP position paper.

25. **Line 384**

There is no mention of a forth stopping criterion, that is, the occurrence of adverse effects in the clinical trials.

26. **Combination of Approaches**

We would ask that the guidance allows co-administration of a micro dose with a dose by the same or different route at a higher dose. An example could be a micro iv dose in combination with an oral dose (at a higher dose level). Such an approach could for example allow for very efficient assessments of absolute bioavailability in the same subject, using AMS technology.

27. **Line 322**

Please replace "sacrifice" with "necropsy".

28. **Line 405**

The statement "many informative endpoints (e.g., hematology and histopathology) typically incorporated into toxicity studies should be investigated at all doses" is broad and vague. Alternative wording could be "relevant informative endpoints (e.g., hematology and histopathology) selected as important for clinical safety evaluation should be investigated at all doses."

29. **Lines 257-258**

The sponsor is required to provide information showing the stability of the test article during the toxicology studies, but no specific duration of stability testing is mentioned. Applicants are referred to earlier FDA guidance¹ that also does not mandate any set period of stability testing, but has the following statement (Section III F): *For example,*

¹ *Guidance for Industry: Content and Format of Investigational New Drug Applications for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products.*

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although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly very limited. We would assume, therefore, that it will be generally acceptable for investigational material that is used in toxicology studies to have no pre-existing stability data, if the batch used is found to be within specifications immediately before and immediately after the dosing period. If this is the case, we suggest that it would be helpful if this were explicitly indicated in the guidance. If this is not the case, and a longer duration of stability must be shown, then we suggest that this, too, should be indicated in the guidance, together with an explanation of the need for the longer duration.

30. **Lines 417-424**

We note that FDA indicates in the draft guidance that it will be prepared to be, to some degree, flexible with regard to the requirement for all data presented in an exploratory IND to have been generated under full Good Laboratory Practices (GLPs). In the spirit of making the exploratory IND as powerful a source of time and resource efficiency as possible, we suggest that many of these pre-development studies, if conducted in the "spirit of the GLPs" (i.e., not in compliance with GLPs in every detail, but in compliance with the major provisions of GLPs) could be used to support early human trials. Therefore, we would recommend that the Agency should remove the general requirement for studies submitted in an exploratory IND to have been conducted under GLP's, provided that they have been well designed and conducted, and the data are sufficiently robust to support the proposed trials. We believe that the removal of this restriction is justified because it would allow significant working efficiencies and because all compounds that progress to full clinical development will be supported, in any case, by a full IND application. As a corollary to lifting the general requirement for data to have been generated under GLPs, we would suggest that FDA should indicate more specifically those types of studies for which formal compliance with GLP will be essential.

We appreciate the opportunity to provide these comments on the draft guidance on exploratory Investigational New Drugs studies and thank you in advance for your consideration of these comments as you finalize the guidance.

Sincerely,


Alice E. Till, Ph.D.

CC D. Jacobson-Kram