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June 22, 2005

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

Dear Dockets Management:

Re: **Draft Guidance for Industry, Investigators, and Reviewers:  
Exploratory IND Studies**  
[Docket No. 2005D-0122, 70 *Federal Register*, 19764, April 14, 2005]

Pfizer appreciates the opportunity to provide comments on this draft guidance and commends the Pharmacology/Toxicology Committee for developing guidance on this topic.

Additionally, we would invite direct dialog with the Agency if you would consider the opportunity valuable.

Sincerely,

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Senior Director, Toxicology III

2005D-0122

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**General Comments:**

This draft guidance is reasonable and welcomed, and it appropriately reflects recommendations from the CHMP microdose guideline and the PhRMA Exploratory IND proposal. In particular we appreciate the emphasis on flexibility for program design and desire on the part of the agency to engage in dialogue about planned approaches. There are some new concepts introduced as well, and for those, some additional clarity is requested. In the Introductory Statement and General Investigational Plan, the guidance states that the Sponsor should indicate their plans with regard to withdrawal of the exploratory IND or the intent to supplement the exploratory IND with appropriate nonclinical data to support expanded clinical testing. We would suggest clarification in the guidance on whether Sponsors may provide additional data and conduct standard Phase I single and multiple dose tolerance studies under the experimental IND, or whether the additional investigations would be limited to investigating PK/PD endpoints. Would an experimental IND only have to be withdrawn if it were submitted to support a screening study involving more than one drug candidate?

The CMC expectations are reasonable, and are nearly identical to those described in "Content and Format of Investigational New Drug Applications for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products." However, the terminology used is not always ideal. Use of terminology such as 'candidate product' makes it difficult to tell if the reference is to a drug substance or a drug product. There is also a reference to a type of solid dosage form as "pills." Our recommendation is that the document be edited for consistency with standard CMC terminology.

**Specific Comments:**

The following editorial suggestions are intended to help distinguish exploratory clinical studies (also referred to as Phase 0 studies) from traditional Phase I clinical tolerance trials.

Line 33: Delete "very early in phase 1,"

Line 35: Add "conducted prior to the traditional phase 1 dose escalation..."

Line 37: Delete "phase 1"

Line 53: Modify "This guidance describes some early ~~phase 1~~ exploratory clinical approaches...."

Line 128: Delete "phase 1"

Line 91: Please clarify what the Agency considers "closely related drugs or therapeutic biological targets."

Line 137: We suggest for clarity to modify the sentence to read "...to treat serious diseases or affect novel pharmacologic targets."

Line 272: In the sentence referring to impurity characterization, please specify which guidance is referred to, or delete the sentence entirely.

Line 273: This line and its reference to Footnote 13 are confusing as they refer to expectations in the guideline entitled "INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing and Controls Information" with regard to "if and when a sponsor files a traditional IND for further clinical studies." This may not be appropriate since a sponsor could file a traditional IND to conduct Phase I studies, in which case this guidance would not apply.

Line 311: Although we understand a precedent has been established in the CHMP position paper, we question the setting of a microdose limit of not greater than 100 mcg. Pharmacologic potency varies from drug candidate to candidate, and the choice of the nonpharmacologic dose to be used should be set based on evaluation of available data. For example, this Sponsor has conducted a microdose study using a single 500 microgram dose for one candidate which was determined to be 1/100 or less than the predicted human therapeutic dose, but sufficient for pharmacokinetic characterization. Data from broad receptor screens (eg, CEREP panel), activity at HERG or other ion channels, or data from behavioral models may be useful in supporting the safety of the clinical dose.

Line 317: The acceptance of single-dose toxicity studies in support of single-dose clinical trials applies to all types of studies. Therefore, we recommend moving this statement up from under the microdose heading.

Line 318: We suggest that, as for trials to study pharmacological effects (lines 348-349), for microdose study support the single species toxicology study may be conducted in one gender only if the clinical trial is to involve one gender.

Line 325: We suggest that the acceptable multiple could be stated as a range (e.g., 30 to 100X) to capture the intent of establishing a margin of safety for a particular drug.

Line 330: We support the concept that FDA does not require genetic toxicology testing for single-dose microdose studies because exposures are comparable to routine environmental exposures. In further justification for this approach, as a routine aspect of drug development, compounds reaching this stage of development have generally successfully passed early genotox screens.

Line 382: We suggest for clarification the following addition: "(1) 1/4 of the 2-week NOAEL on a mg/m2 basis;"

Line 383: We suggest the following editorial change for clarification: "(2) 1/2 of the AUC at the NOAEL in the 2-week rodent study, or up to the AUC in the dog at the rat NOAEL, whichever is lower;"

Lines 381-384: A fourth stopping criterion, the occurrence of adverse effects in the clinical trials, should be added.

Line 391: We appreciate the statement of flexibility in considering alternative or modified toxicology programs in support of mechanism of action studies. We would welcome a similar statement at the end of the Conclusion section, to further emphasize the Agency's willingness to discuss alternative proposals for nonclinical programs designed to support exploratory clinical studies.

Line 393: Would the Agency consider a day-for-day dosing approach for the nonclinical studies used to support mechanism of action or other exploratory clinical studies?

Line 405: The statement "many informative endpoints (eg, hematology and histopathology) typically incorporated into toxicity studies should be investigated at all doses" is broad and vague. Alternative wording could be "appropriate toxicity endpoints selected to support the clinical safety evaluation (eg, hematology and histopathology) should be investigated at all doses."

Line 421: We respectfully disagree with the comment that "for some special studies, certain of the GLP provisions may compromise proper science." There are times when some aspects of GLP provisions may not apply to some studies and/or situations and the Study Director has the authority to document any deviations from GLP with explanations as to cause and effect. Additionally, at times it may not be feasible to adhere to GLP provisions (e.g., full test article characterization for radiochemical work to support microdose studies). However, the GLPs are designed to support and not compromise science. Inclusion of this statement, especially without detailed context, sends a mixed message to sponsors and their responsible scientists. This statement should be removed.

Line 425: We request clarification on whether unaudited draft toxicology study data may be submitted to support an exploratory IND, falling within the 120-day submission framework of the "Content and Format of Investigational New Drug Applications" guidance.