



Date: JUL 11 2005

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

Re: Docket Number 2005D-0122
Response to FDA Call for Comments
Draft Guidance for Industry on Exploratory Investigational New Drug Studies

Dear Sir or Madam:

Reference is made to the April 14, 2005 Federal Register notice announcing the request for comments on Draft Guidance for Industry on Exploratory Investigational New Drug Studies.

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Greg Taylor, Regulatory Project Manager, at (302) 886-1216.

Sincerely,



Barry Sickels, Executive Director
Regulatory Affairs
Telephone: (302) 886-5895
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Enclosure

2005D-0122

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US Regulatory Affairs
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**Docket No. 2005D-0122, CDER 200497. Draft Guidance for Industry on
Exploratory Investigational New Drug Studies**

General Comments

- We support this initiative and believe that this guidance should help increase the efficiency of drug development by allowing for the early testing of pharmacological activity of candidate drugs and for quickly dropping those that do not have the properties in man to progress. Also, it should help when selecting compounds to develop if we have more than one candidate with the same pharmacological activity. We also encourage future dialogue between global Regulatory Agencies that takes into account other examples of approaches that may be useful in this context.
- The draft guidance is calling for individual approaches depending on desired clinical results. It is understood that sponsors need to discuss proposals with the FDA prior to initiating in-house activities. How is this initial contact and discussion of proposals best achieved and will the FDA be resourced to deliver on these activities?
- The draft guidance comments on the relationship between the duration of clinical studies and the treatment period in pre-clinical safety studies. Please clarify the minimum treatment period to support single-dose studies at dose levels up to pharmacological activity but not MTD, and the maximum duration of an explorative clinical study?
- Please clarify if exploratory IND studies allow for the investigation of reversible side effects that are directly related to pharmacological target modulation (i.e. blood pressure/heart rate changes, changes of laboratory markers etc.)?
- In section III.B the guidance mentions that CMC information in support of the exploratory IND can be "provided in a summary report." Does this statement imply that individual CMC technical reports are not provided with the IND? And if so, can nonclinical data be presented using "summary reports" obviating the need to submit individual study reports/individual animal data in the IND? Please clarify.
- In short-term toxicology studies the preparation and reading of the histological slides often is the longest duration of the study. The amount of histological data that is required is not discussed. Will it be possible to decrease the amount of information that is required, especially in the non-rodent study in the case in which the rodent (usually the rat) is the most sensitive species? Suggest that the histological information be limited to the organs/tissues that are grossly abnormal, the tissue that is the target organs for toxicological effects based on the rodent, and critical tissues such as the liver, cardiovascular, pulmonary and kidney systems.

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- In section III.C.3, an example is provided for clinical studies of MOAs related to efficacy. However, very few details are discussed. More detailed guidance for this example would be beneficial. For example, the guidance for what “alternative, or modified” studies will be accepted by FDA is not very clear in this section. Does “...based on a dosing strategy...” mean demonstrating a margin rather than identifying target organ toxicity by using the MTD approach? In addition, requirements for Genetic Toxicology, Safety Pharmacology, and human starting and maximum doses should be clarified in more detail.
- Under manufacturing it states that GMP material should be utilized, and the FDA will be producing a guideline outlining the step-wise approach to GMP. As the amount of required compound is decreased, the amount of material required for the studies may be able to be manufactured in facilities utilized to produce research material. Usually the same lot of material will be utilized for the toxicology studies and the exploratory studies. It will be useful if the step-wise GMP approach will allow for material from such facilities to meet the GMP requirements.

Specific Comments

Section	Page or Line Number	Comment or proposed replacement text
II.B	102	Suggest adding the bolded text, “treatment of a disease or side effect. ”
II.B	114	Please clarify if “subjects” include patients as well as healthy volunteers.
II.B	123-126	Here and elsewhere, the guidance does not address the issue of women of childbearing potential (WOCBP). Please address.
III.B	210	The guideline for CGMPs that will be issued at a later date (line 210) is critical to this whole effort to be successful. If CGMPs will be followed for exploratory IND work, then stating that intent as was done for the GLPs later in the document (line 417) would be helpful.
III.C.1	322	Please use “necropsy” in place of “sacrifice”
III.C.2	350-351	This statement appears to be in conflict with statements regarding determination of group sizes in the Animal Welfare Act. Please ensure that no regulatory conflict exists.
III.C.3	393	Why are “two” animal species specified for this example?