

July 8, 2005

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0122: Draft Guidance on Exploratory Investigational New Drugs

Dear Sir or Madam:

Introduction

We welcome FDA's initiative to publish recommendations related to exploratory IND studies. It is appreciated that the guidance is overall very generic and flexible, and covers both small molecules and biologics. Nevertheless, as it relates to a new approach in the IND process, clarification of several areas of the current draft, both technical and procedural, would be useful.

FDA indicates that Sponsors often provide more information in their INDs than required. As a Sponsor, we are usually very concerned about submitting the appropriate information to support the use of an investigational compound in humans and to avoid a clinical hold. We recommend that FDA provide examples of where Sponsors are submitting more than required. We also propose that the requirements for traditional INDs be better clarified.

General comments

IND data requirements

To better illustrate differences in pre-clinical data requirements, we suggest adding tables showing requirements for exploratory INDs versus traditional INDs.

The content of the IND should be clarified, as it may have significant impact on the timelines of the program. For instance, would summary information be sufficient for non-clinical sections of the IND? Would final reports be needed e.g. within 120 days of receipt of the IND by the FDA as for traditional INDs?

Possible applications

It seems that exploratory INDs could have value in a limited number of applications:

To make a selection based on human data in rare cases, when several closely related clinical drug candidates with insufficient preclinical differentiation are available.

To further evaluate a compound that has shown issues (e.g. PK or bioavailability) in preclinical development. In this case, a microdose study may have value for decision making on continued development.

For many other situations though, it seems unclear how to use it in a meaningful way.

When several closely related clinical drug candidates with sufficient preclinical differentiation are available, it is likely that a more comprehensive clinical data set (e.g. including PD endpoints) would be preferred for further decision making. This would force the program in the direction of a traditional IND.

If a pharmacologically active dose is used in the exploratory IND study, more extensive preclinical studies would be needed. In addition, in case of promising results, preclinical studies would need to be repeated to support a standard phase 1 study. In this example, an additional layer seems to be added to the process.

The interruption of the usual workflow and planning of early drug development for the implementation of an exploratory IND approach will need to be taken into account.

For above mentioned reasons we strongly recommend that FDA provides specific examples of meaningful exploratory studies with guidance on study design and methods.

Exploratory INDs for studies in serious and life threatening disease

The exploratory IND is particularly important in treatments for serious and life-threatening disease. This raises the question about the acceptability to patients and IRBs of studies with single or sub-therapeutic doses when no benefit of receiving the drug can be expected. Considerations on the ethical aspects of exploratory IND studies in patients would be useful.

We recommend also that advantages offered by the Accelerated Approval and Fast Track provisions in the context of exploratory INDs be better clarified.

Human exposure

The guidance states that exploratory INDs usually involve very limited human exposure. We recommend that FDA provides an estimated number of patients to be included in exploratory studies.

Specific comments

Microdose and imaging studies

We recommend that FDA clarifies the preclinical requirements for closely related drugs.

Screening studies are mentioned as an example of exploratory IND studies. This is a very general term, covering a multitude of study designs. We recommend that the Agency provides more details on the type of studies this refers to.

Considerable investment may be needed to detect a PK or PD effect at very low exposures. A discussion of relevant analytical techniques may be helpful. A clarification is also needed on whether radioactive labeling would be allowed for an exploratory IND study, if first in humans.

The incremental value of microdosing studies in the development program over commonly used non-clinical in vivo/in vitro models is currently not well understood. Information sharing among FDA and industry for both microdosing and non-clinical models in this respect may be useful.

Convincing examples of the usefulness of data from microdose studies in predicting PK and PD parameters at higher doses may be helpful.

Trials to study pharmacological effects

Time and animals could be saved in a pre-clinical program intended to support a repeat dose clinical study, if the rodent is the most sensitive species. A significant drawback is that the required repeated dose study in the second species will need to be repeated if the rodent appears not to be the most sensitive species.

The calculations of the clinical starting and maximum doses seem very restrictive. This may be too restrictive to reach a pharmacological effect and/or restrict exploring the dose-response curve of drugs with a narrow therapeutic index.

The calculation of the maximum clinical dose seems inconsistent with the attachment to the guideline. It appears that $\frac{1}{4}$ of the rat NOAEL would always be the maximum clinical dose if the rat is the most sensitive species.

It is stated that the numbers of animals used in the confirmatory study can be fewer than normally used to reach statistically meaningful comparisons. Further clarification, such as providing an example, would be helpful.

The process and timelines to obtain FDA's concurrence on escalation from the proposed stopping dose should be explained.

It is understood that less API may be required if the preclinical evaluation can be less extensive. However, sufficient API to fully test the non-rodent would be needed up front in order to avoid delays if the non-rodent appears to be the more sensitive species.

Clinical studies of MOAs related to efficacy

The requirement for histopathology at all doses (line 404-406) should be clarified.

CMC

Flexibility regarding GMP requirements could be very resource sparing. We wait for FDA's new guidance document on this topic in order to understand the requirements for clinical batches used in exploratory INDs.

We suggest replacing line 239 by "method of manufacture and packaging, as appropriate for the drug product". Providing the packaging procedure should not be needed for solid oral dosage forms.

For lines 251-256, we suggest to clarify if acceptance criteria should be provided.

Additional guidance should be provided regarding impurity requirements. One would expect that more flexibility would be allowed in terms of impurity profiles which deviate from the tox batch (than for classical INDs) since sub-therapeutic doses are used.

Process related comments

FDA indicates that flexibility will be allowed regarding the type of applications and the preclinical programs in support of the exploratory IND. This implies a need for interaction and agreement with FDA. We recommend that the process and timelines be described.

FDA indicates that the necessity of exemptions from GLP provisions should be discussed prior to conducting preclinical safety studies. We recommend that the process be clarified.

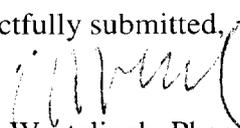
Would the clinical hold concept be applicable?

Would other aspects of traditional IND maintenance such as preparation of annual reports apply?

Details, including timelines, on the conversion of exploratory IND to full IND would be helpful.

In conclusion, Hoffmann-La Roche Inc. appreciates the opportunity to provide comments on the draft new guidance and is confident that collaboration and information sharing will be beneficial for its implementation and for improving the efficiency of the drug development process.

Respectfully submitted,



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