Draft Guidance for Review and Comment

Draft Guidance for Industry
Exploratory IND studies

Docket No. 2005D-0122

Issued for Comment 1-Apr-05
Comments due 13-Jul-05

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GENERAL COMMENTS

The following comments are provided by Genentech, Inc. on Docket No. 2005D-0122, “Draft Guidance for Industry: Exploratory IND Studies”. We welcome FDA’s efforts to clarify preclinical and clinical approaches when planning exploratory IND studies.

- It may be advisable to change the term "small molecule therapeutics" to "chemical therapeutics" throughout the guidance since not all therapeutics(e.g., heparins, long chain fatty acids) are small molecules.

- It would be useful if preclinical toxicity studies should be specified for chemical therapeutics vs. biologics

- The term “limited human exposure” is used throughout the document. A definition of what the upper limit or acceptable range is which qualifies a study as an exploratory IND would be useful.

- A separate discussion on chemical therapeutics vs. biological products should be provided in every section where appropriate.

- There is not much relief in the amount of CMC data needed for exploratory vs. traditional phase 1 IND. Emphasis should be on safety (sterility, pyrogens, freedom from adventitious agents) with enough characterization to assure acceptable batch to batch consistency.

- At several points in the guidance scaling based on body surface area is referred to. Depending on the program `in question scaling based on mg/kg or pharmacokinetic/pharmacodynamic modeling maybe more appropriate. A discussion on general principles that would help guide the determination if surface area or other endpoints are appropriate would be useful.

- Within the toxicology portion (section III. C.) we found the organization to be difficult to follow and generalize to situations not specifically described by the examples provided. Rather than focusing on the examples, we suggest starting with a General Principals section outlining specifically and clearly what information is expected from toxicology studies to support short term studies and then describe the types of clinical trials that could be supported. This would include at least a clear definition and listing of:

  1) Clinical trial duration supported
  2) Clinical endpoints
  3) Toxicology study duration
  4) The need for a recovery period
  5) TK/metabolism expectations
  6) What multiples above the clinical dose are necessary to support the clinical trial if toxicity is not observed in the exploratory studies (e.g., studies on pharmacodynamic effects or MOA where the guidance notes that MTD is not necessarily an endpoint of the toxicology study)
  7) Need for safety pharmacology
  8) Need for GMP material in clinic (either explicitly stated in this document or the upcoming GMP Guidance for clinical trial materials)

  This approach would facilitate the understanding of how to design exploratory INDs that do not necessarily conform to the proposed examples and also enable sponsors to determine what additional information they might need due to special properties of their test material. In keeping with this reorganization, the examples 1 and 2 under section C should be re-titled: 1) Exploratory Clinical Trials Using a Single Microdose in Humans and 2) Exploratory Clinical Trials with Dosing up to 2 Weeks in Humans.

Further to these general comments, specific comments on the various sections of the Guidance are included in the following table.

Table1-1

Specific Comments for Draft Guidance
"Exploratory IND Studies"

Section	Line Reference	Genentech Comment
II. B.	114-115	Please provide further information on what 'limited' refers to as in "a limited number of subjects", "a limited dose range" and "a limited period of time".
III. A. 1.	175-177	If results from an exploratory IND warrant additional studies under traditional IND, the IND should be amended with new protocol and supporting preclinical studies to support further clinical studies. If the sponsor has no interest in pursuing development of the product then the exploratory IND should be withdrawn or inactivated.
III. B.	210-213	Reference is made to a guidance being developed on cGMP; however, it is not clear whether the material used in the clinic in the exploratory studies has to be made under GMP conditions. Will the upcoming GMP guidance for clinical trial materials cover exploratory INDs?
III. B. 1.	232-234	Reference is made to excipients needing to be GRAS or to have been used in approved products. Using new excipients should be allowed. Clarification on whether the new excipients should be studied in accordance with the FDA Guidance for Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients? Or a reduced requirement can be acceptable
III. B. 2.	264-289	Not much relief in amount of CMC data needed for exploratory vs. traditional phase 1 IND. For biological products, emphasis should be on safety (sterility, pyrogens, freedom from adventitious agents). When clinical batch is different from the nonclinical batch, there should be enough characterization to assure acceptable batch to batch consistency.
III. C.	299-300	Delete the last sentence. The paragraph talks about more limited toxicity studies based on "reduced scope of an exploratory IND study". Obviously scope of clinical study will dictate level of preclinical studies needed

Table1-1

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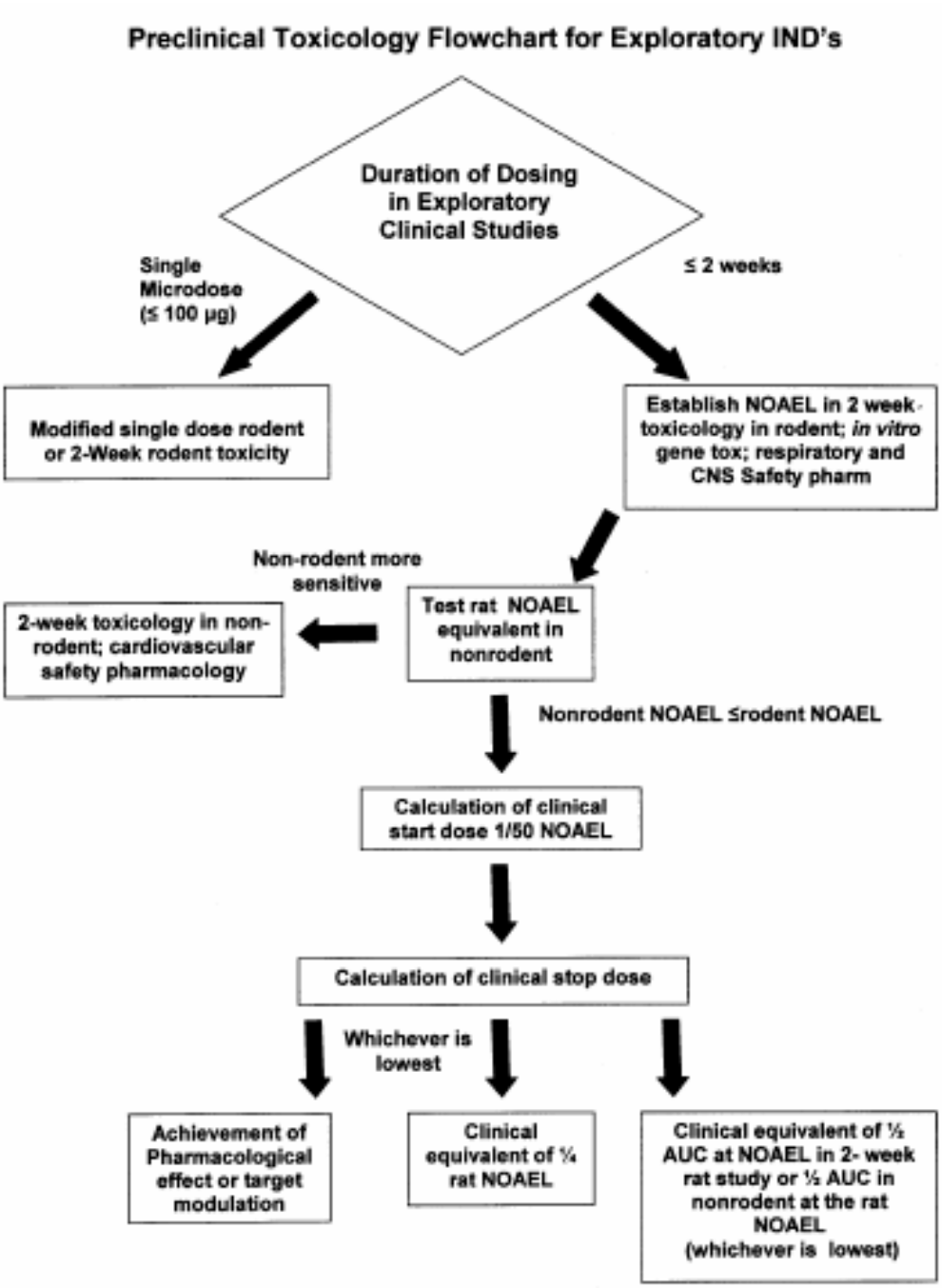
Section	Line Reference	Genentech Comment
III. C.	305	Validating a clinical model in healthy volunteers is referred to. Since the prior section referred to the use of Exploratory INDs in serious diseases can we assume that in life threatening diseases such as neoplasm's that patients could be substituted in exploratory IND trials. This would be especially important for Pharmacokinetic and Imaging studies where pathways may be altered in diseased patients.
III. C. 1.	310	Microdosing with biological therapies such as monoclonal antibodies may not fall in this definition. 1/100th of a pharmacological dose may be greater than 100 micrograms. A higher dose should be acceptable for biological products with low activity. It may be more applicable to measure protein concentrations/exposures in studies such as radio-imaging studies
III. C. 1.	317-328	This guidance should cite the previously existing FDA guidance: "Single Dose Acute Toxicity Testing for Pharmaceuticals" (http://www.fda.gov/cder/guidance/pt1.pdf) which was an earlier attempt at offering flexibility in toxicology support for clinical trials
Attachment	445-449	The flow chart does not reflect the overall process, but instead a particular example of a small molecule. If redesigned to take into account the general principles to cover exploratory INDs, this could be made much clearer. The Appendix contains an example of a more generalized flowchart approach based on our understanding of the current draft of the guidance.

Appendix


Preclinical Toxicology Flowchart for Exploratory IND's
Duration of Dosing in Exploratory Clinical Studies
Single Microdose (≤ 100 µg)
≤ 2 weeks
Modified single dose rodent or 2-Week rodent toxicity
Establish NOAEL in 2 week toxicology in rodent; in vitro gene tox; respiratory and CNS Safety pharm
Non-rodent more sensitive
2-week toxicology in non-rodent; cardiovascular safety pharmacology
Test rat NOAEL equivalent in nonrodent
Nonrodent NOAEL ≤rodent NOAEL
Calculation of clinical start dose 1/50 NOAEL
Calculation of clinical stop dose
Whichever is lowest
Achievement of Pharmacological effect or target modulation
Clinical equivalent of ¼ rat NOAEL
Clinical equivalent of ½ AUC at NOAEL in 2- week rat study or ½ AUC in nonrodent at the rat NOAEL (whichever is lowest)