Preclinical Studies: What are the FDA's Expectations

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Disclaimer

I have no disclosures related to the content of this presentation

Learning Objectives

- Assess and be familiar with early stage (eIND) nonclinical requirements for low dose diagnostic agents
- Share Common Regulatory Challenges
- Share through Q & A commonly asked questions by Academic Researchers and Product Developers on this topic

Focus

Exploratory INDs:

Screening, Microdose and Feasibility Studies

Concept Based On

FDA: Guidance for Industry, Investigators and Reviewers: Exploratory IND Studies (2005)

ICH: Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmacueticals;ICH-M3(R2) (Jan 2010 Revision)*

*expanded the scope of eINDs and supersedes the FDA guidance in areas in which they differ.

A Guidance is just that: Guidance!

"FDA guidance documents do not establish legally enforceable responsibilities. Instead a guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited"

Ideas and Concepts (1)

"Exploratory IND study is intended to describe a clinical trial that occurs very early in phase 1, involves limited human exposure, and has no diagnostic intent"

For example, screening, microdose and feasibility studies

Ideas and Concepts (2)

- Evaluate mechanism of action
- Explore product characteristics through imaging technologies
- Identify lead candidate
- Obtain P/K and biodistribution info
- Characterize new diagnostic targets

Examples Of Studies

- Clinical studies of pharmacokinetics or imaging
- Clinical trials to study pharmacological effects
- Clinical studies of MOAs related to efficacy

Exceptions (FDA eIND)

- Pediatric patients, pregnant or lactating women.
- Does not apply to human cell or tissue products, blood and blood proteins, vaccines, or to products regulated by FDA Center for Devices.

Not addressed by ICH M3 (R2)

Microdose IND DMIP(06/13)

230 eIND focusing on imaging

- PET/SPECT Imaging in Alzheimer and Parkinson's disease
- Receptors Imaging (CNS, Vascular and tumor)

ICH M3 (R2)

- Is a revision of ICH guidance “M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals:
- a new section on microdose/exploratory studies
- Applies to situations usually encountered in small molecules drug development
- Says very little about biotechnology-derived products other than to recommend appropriate strategies
- Recommends approaches appropriate scientifically and ethically

M3 Exploratory Studies: What's New

"Exploratory clinical studies are those intended to be conducted early in Phase I, involve limited exposure, have no therapeutic intent, and are not intended to examine clinical tolerability"

Similar objectives to US FDA Guidance on eINDs

M3 Exploratory/Microdose Studies: What's New

Two different microdose approaches:

No more than a total dose of 100 µg administered as a single dose or divided doses. No inter-dose interval limitations.

Involves ≤ 5 administrations of a maximum of 100 µg per administration (total of 500 µg per subject).

Washout between doses (six or more actual or predicted half lives).

Approach 1 Requirements

- Maximum and starting dose can be the same; but not exceed 100 µg
- In vitro target receptor profiling
- Primary pharmacology characterization
- Extended single dose toxicity study in one species, usually a rodent
- Dosimetry as appropriate
- Genotoxicity or local tolerance studies not recommended

Approach 2 Requirements

- ≤ 5 administrations of a maximum of 100 μg per administration (total of 500 μg per subject)
- In vitro target receptor profiling
- Primary pharmacology characterization
- 7-day repeated-dose toxicity study in one species usually a rodent.
- Dosimetry
- Genotoxicity or local tolerance studies not recommended

Regulatory Challenges

Challenges: Process 1

- Microdose concept broadens the stakeholder base (Great!) that may not be familiar with drug development process (We are here to help)
- Data quality/lack of data
- Uncertainty in terms of number of subjects (Perhaps Regular IND)

Challenges: Process 2

- Species selection
- The robustness of the science behind lead candidate selection when multiple candidates fail
- Is failure due to backup candidates being presented for quick yes or no answer?

Challenges: Technical

- Timing/closing of eINDs
  - Not withdrawn expeditiously
  - Standard INDs not submitted expeditiously
- Interpretation of guidance
  - Multiple trials OK
  - Should all trials be described in original submission?
    - No

Challenges: Technical

- Tracking limitations and difficulties
  - Communication within FDA and with industry
- Maximum clinical dose issues (sometimes):
  - Designed to exceed PD effect
  - Designed to assess tolerability
  - AE criteria narrowly defined to maximize dose escalation
  - Subsequent trials with proposed max. dose higher than original trial

Challenges: Global

- Slow adaptation of a new paradigm (it works!) and we encourage its use
- Lack of awareness of guidance availability especially amongst the academic community
- Microdose studies may not be predictive
- Protracts the time line
- Designed to kill drugs early that are likely to fail.

Remember!

- Microdose/eIND should be a developmental tool NOT the only tool
- The goal should be to provide early go/no go decision and provide feedback to discovery
- Potential to save on time and cost
- Some candidates are bound to fail
- Consideration should be given to whether to utilize the pathway or not

Commonly Asked Questions (1)

Q: How or why did FDA determined that a microdose study would use ≤100 µg of product

A: Historical FDA data base. The microdose guidance was issued in 2006. DMIP has decades of experience regulating these products In addition, ancillary experience from mass doses used in RDRC studies. The 100 µg is an outlier; in our experience, most microdose studies utilize less than 20 µg .

Commonly Asked Questions (2)

Q: Is there an FDA document that allows up to five "closely related" compounds to be studied under eIND based on animal toxicology of only one of the compounds

A: No. There are no current FDA document that allows this developmental paradigm. The nonclinical studies needed to support eIND application are as stated in eIND guidance and ICH M3 document. While multiple compounds can be studied under the same IND, the toxicology data support is expected to be adequate for each analog

Commonly Asked Questions (3)

Q: Can you comment on why the nonclinical requirements are different for eIND, ICH M3 and Medical Imaging Guidance

A: The nonclinical requirements for the 3 pathways are different because the development goals may be different. Both the ICH M3 and eIND guidance focus on microdose study in a limited number of subjects. Sponsors are free to cite either guidance. Medical Imaging Guidance provides recommendations for studies needed for product approval with no limitation on number of subjects

Commonly Asked Questions (4)

Q: Can the Agency concur to request to use a NonGLP-complaint Lab/Process for eIND-enabling Toxicology study

A: We prefer you to use a GLP-complaint facility. The ICH M3 (R2) recommends that general toxicity studies supporting the safety of an eIND be conducted according to GLP regulations (21 CFR Part 58) to ensure data quality and integrity. However, if scientifically justified, deviations that would not have significant impact on the quality and integrity of studies may be acceptable on a case-by-case basis.

Commonly Asked Questions (5)

Q: What constitutes “Very limited human exposure” ?

A: The Guidances are silent on this point.

- In general, very limited human exposure refers to approximately 40 subjects
- Some objectives have been completed with fewer than 10 subjects

Commonly Asked Questions (6)

Q: I want to increase the number of subjects in my current eIND study; do I need to close the eIND and open a traditional IND?

A: It depends.

- A sponsor may be allowed to increase the number of subjects in the current eIND
- Request should be submitted/discussed with DMIP
- Determination made on a case by case basis

Commonly Asked Questions (7)

Q: I want to close my eIND and open a traditional IND; do I need to conduct new animal studies and follow the Medical Imaging Guidance with respect to preclinical requirements?

A: It Depends

- Flexibility in interpretation (eIND, full IND)
- Available information must be adequate to support further human studies.
- Case-by-case science-driven decisions
- Nonclinical studies may be waived per justified request [21 CFR 312.10]

Commonly Asked Questions (8)

Q: I want to close my eIND. Can I continue collecting (safety) data in subjects enrolled in the eIND study after I close it?

A: No

- Once the IND is closed, the clinical study is considered closed as well.

Conclusions

- Utilize the microdose/eIND mechanism when applicable
- Communicate as early and as frequently as possible with the Review Division
- We are committed to a more flexible approach that allows innovative products to move safely and quickly through pre-clinical development