Exploratory IND
The Problem

- Less than 10% of INDs for new molecular entities progress beyond the investigational agent stage to NDA
- 90% of INDs FAIL.
  - reduce time and resources expended on candidate products that are unlikely to succeed.
- New tools needed to distinguish promising candidates from those that have a low probability of success.
FDA Guidance – April 06

• Existing regulations (21CFR 312) allow flexibility in the amount of data required for an IND depending on the:
  – Goal of the investigation
  – Specific human testing proposed
  – Expected risks

• Sponsors have not taken full advantage of this flexibility and often provide more information than required

• Purpose of the April 06 guidance is to clarify approaches for consideration in planning limited, early exploratory IND studies in humans:
  – Preclinical
  – Clinical
  – Chemistry, manufacturing and controls information
  – Previous human experience with the investigational drug or related compounds
Exploratory IND Study
Limited subjects, limited dose, for limited time

An exploratory IND study is:

• Conducted early in Phase 1, prior to traditional dose escalation/safety studies
• Intended to assess feasibility for further development
• Involves very limited human exposure
• No therapeutic/diagnostic intent/no MTD
  – (eg. Screening studies, microdose studies)
• Involves limited duration of dosing (e.g. < 7 days)
Objectives of Exploratory IND Studies

- Determine whether MOA defined in nonclinical studies is also observed in humans (e.g. binding property or inhibition of an enzyme)
- Provide PK information
- Select the most promising lead product from a group of candidates
- Explore biodistribution characteristics using various imaging techniques
Traditional vs Exploratory Approach

Traditional

- Broad objectives
- Only 1 compound
- Extended duration of dosing
- Toxicology is extensive—rodents/nonrodents
- Allows selection of a **safe** starting dose (1/10 HED based on NOAEL)
  - Target organ toxicity—estimate margin of safety between clinical and toxic dose
- Resource intensive — more subjects, more API needed

Exploratory

- Exploratory objective
- Multiple compounds
- Limited duration of dosing (<7 days)
- Smaller tox program
- Limited exposure/dose range (1/50 – ¼ NOAEL)
- Less resource intensive — less API, less subjects
- Earlier into humans

*Does not replace traditional IND*
  - Exploratory IND to be withdrawn upon completion of planned studies
  - Exploratory IND can be referenced
Types of Clinical Studies

• Single-dose: sub-pharmacologic or pharmacologic dose given to a limited number of subjects (HV or patients)
  – e.g. microdose study involving single small dose
  – Collect PK data and/or perform imaging studies
  – Not designed to induce pharmacologic effects

• Multiple-dose: PD endpoints
  – <7 days
  – Dose escalate to evaluate PD endpoints not tolerability
Content of traditional vs exploratory

IND
• Clinical development plan
• MTD
• CMC (graded information)
• Batch to batch information
• Extensive toxicology
• Certified GLP

Exploratory
• Rationale only
• <7 days, no MTD
• CMC Summary report—not all impurities need to be characterized
• Limited toxicology—fewer animals 4 non-rodent/group,
• Limit species/single sex if no gender differences
• Consistent with GLP—exemptions allowed
Exploratory IND - CMC Information

• General information – similar to traditional IND
  – Description of product, method of manufacture, excipients, dosage form, test methods, stability

• Analytical characterization – 2 scenarios
  • Same batch used in toxicology studies and clinical trial(s)
    – Impurities are “qualified” in tox studies
    – Establish impurity profile to extent possible but not all impurities must be characterized at this stage.
  • Clinical batch different from tox batch
    – By analytical testing, show that clinical batch is representative of tox batch – identity, structure, purity, impurities, potency, physical and microbiological characteristics as appropriate.
Exploratory IND - Safety Program Examples

Microdose studies

- Single dose study designed to evaluate PK or imaging of specific targets
- Not intended to induce pharmacologic effects
- Microdose is
  - <1/100 of dose calculated (based on animal data) to yield a pharmacologic effect
  - maximum dose ≤100 µg or ≤ 30 nanomoles for a biologic
- Single dose toxicity study by clinical route with 14 day observation period
  - Establish a dose causing minimal toxic effect or establish large safety margin (eg 100 X)
- Single mammalian species OK if justified by in vitro metabolism data and data on in vitro PD effects
- Additional studies in nonrodents (dogs) to confirm the rat as the sensitive species
- Genetic toxicity and safety pharmacology studies not needed.
Exploratory IND - Safety Program Examples
Studies at Pharmacologically Relevant Doses

- Study of pharmacologic effects, no MTD, dosing up to 7 days
- Starting clinical dose <1/50 NOAEL
- Maximum dose – lowest of (1) ¼ NOAEL, or (2) ½ AUC in rat or AUC in dog or (3) dose with pharmacological effect
- Further dose escalation after consulting FDA
- 2 week at toxicity study by clinical route in sensitive species + TK
  - Goal of study is to select safe starting and maximum doses for clinical trial
  - Single dose level approximating the NOAEL
- Additional studies in nonrodent (dog) can confirm that rat is the sensitive species
  - Dose escalation culminating in repeated doses equivalent to rat NOAEL
  - If rodent not more sensitive species, 2-wk study in nonrodent is needed
- Safety pharmacology and genetic toxicity studies needed
Exploratory IND - Safety Program Examples
Studies of MOA Related to Efficacy

• Alternative pharm/tox studies can establish clinical starting dose and escalation scheme
• Short term studies in 2 species with dosing strategy to achieve clinical PD endpoint can serve as basis for selecting safe starting dose
• Animal studies would incorporate endpoints based on the pharmacology of the drug that are believed to be important to effectiveness
• Single species can be used if established as the more relevant species
• Safety endpoints considered important to evaluate in clinical study should also be assessed in the toxicity studies
Advantages

- Test multiple compounds under 1 IND
- Toxicology program is abbreviated
- Smaller quantity of drug
- Shorter timelines (~8 months to FIM)
- Eliminates non-promising drug candidates early
Disadvantages

• Study objectives must be exploratory
• No MTD
• Dose range tested is limited, esp. with low NOAEL
• Dosing duration limited (< 7 days)
• After completion of exploratory IND objectives, it should be closed and a traditional IND should be opened to further develop the drug
• Start of Phase 2 may be delayed