CDER's Clinical Consideration for First-in-Human Trials

Caitlin Tydings, MD

Pediatric Hematologist/Oncologist
Medical Officer, Division of Oncology 3
OOD | OND | CDER

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Overview

- General good practices for FIH studies
- IND overview
- Common pitfalls
- Helpful resources

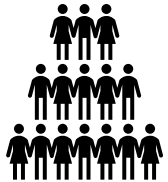
General Good Practice

- Engage trialist(s) with expertise
  - Disease indication
  - FIH trial experience
- Pre-IND meetings
- Drug activity vs. clinical benefit

IND Overview

Chemistry, Manufacturing, and Controls (CMC): Information pertaining to chemical composition, manufacturer, stability, and controls used for manufacturing the drug

Preclinical data and analysis to permit an assessment as to whether the product is reasonably safe for initial testing in humans



Protocol(s) describing Sponsor's plans for initial clinical trial(s)

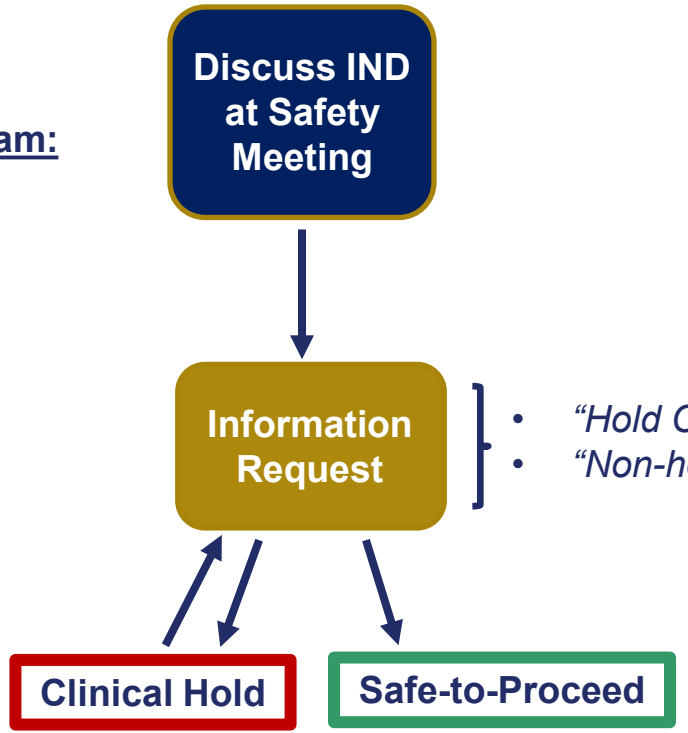
Reference: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

IND Overview

Multidisciplinary Review Team:

- Manufacturing
- Clinical pharmacology
- Statistics
- Pharmacology/toxicology
- Clinical

FDA has 30 days to review a new IND



- *"Hold Comments": **must*** address
- *"Non-hold Comments":* think about

- Partial Hold/Full Hold
- Sponsor withdraws

IND Overview

1. **SAFETY of patients**
2. **Can the trial proceed? Yes or No.**
   - If yes, with contingencies or not?
     - Example of contingency: trial can proceed after formal submission of agreed upon documents (e.g., revised protocol, ICD, IB)
   - If no, partial hold or complete hold from the trial proceeding?
     - Partial hold – trial can proceed up to a certain portion of the trial, but then the Sponsor must discuss with FDA again to address FDA's concerns to be removed from partial hold
     - Complete hold – trial cannot proceed at all until all potential hold issues are addressed

fda.gov/cdersbia

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-clinical-hold;
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.42

IND Overview

- Trial design
- Eligibility criteria
- Dose selection
- Dose-limiting toxicities (DLTs)
- Dose modification
- Safety monitoring
- Trial stopping criteria

IND Overview – Trial Design

- Dose escalation:

Design	Define	Can consider
Rule-based Model-based	RP2D MTD MAD	• staggered dosing of patients • intrapatient dose escalation

Highly encourage finding the optimal dose – consider target saturation, randomized dose trials

- Dose expansion: testing the RP2D, sometimes in all-comers, sometimes in defined populations

IND Overview – Trial Design

Traditional Approach

- Phase 2 trial: activity estimation (proof of concept)
  - Single arm
  - Randomized
- A trial for each disease
- Second dose finding study for combinations may be needed

Newer Strategies

- Multiple dose finding combination cohorts
- Expansion cohorts
- Master protocols
  - Basket trials
  - Umbrella trials
  - Platform trials
- Adaptive designs
- Tissue-agnostic

IND Overview – Eligibility Criteria

	Type of cancer	Stage of cancer	Line of therapy[1]	Contraception
EXAMPLES	• all-comers • histology-defined • biomarker-defined (e.g., protein-expression, genetics)	• advanced • metastatic	• no standard options • previously treated • no curable options	• Risk of genotoxicity • Consistent with label if marketed drugs

[1] FDA guidance - Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings: https://www.fda.gov/media/150244/download

IND Overview – Dose Selection

Dose range[1]:

- guided by nonclinical toxicology data (C_{max}, AUC, $t_{1/2}$, etc.) are used to determine dose selection, schedule, and escalation in Phase 1 trials, and
- further PK/PD studies in animals can be done in parallel with clinical development

Dose escalation:

- Linear
- Logarithmic
  - Half-log (more aggressive)
  - Modified logarithmic: e.g., modified Fibonacci (less aggressive)

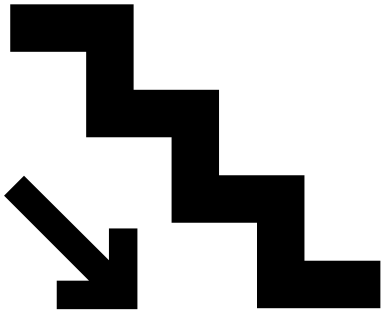
Abbreviations: C_{max} = peak serum/plasma level, AUC = area under the curve, $t_{1/2}$ = half-life, PK/PD = pharmacokinetics/ pharmacodynamics

[1] FDA Guidance - S9 Nonclinical Evaluation for Anticancer Pharmaceuticals: https://www.fda.gov/media/73161/download

IND Overview - DLTs

- **Define the DLT observation period**
  - Generally, at least 1 treatment cycle or at least 1 month
  - Duration depends on the drug's safety profile and potential for long-term toxicities and tolerability
- **Define the DLT-evaluable patient**
  - Patients who receive X% of planned dose
  - Includes patients who discontinued trial drug for adverse events at least possibly related to trial drug if received <X% of planned doses
- **List the DLT criteria**

IND Overview – Dose Modification



- Base dose modification on anticipated toxicities and/or DLTs
- Can consider dose reducing to the previously tested levels in the trial

IND Overview – Safety Monitoring

- **Monitor and collect all adverse events during FIH trials for:**
  - 30 days from last dose of drug(s) if not immunotherapeutic(s)
  - 90 days from last dose of drug(s) if has immunotherapeutic effects and if delayed onset of adverse event is possible

- **Examples of parameters to monitor:**
  - CBC and CMP at least (particularly electrolytes if drug may affect QTc)
  - ECG if drug may affect QTc
  - TTE or MUGA if drug may affect LVEF (e.g., trastuzumab, anthracyclines)
  - Urine analysis (e.g., bevacizumab and proteinuria)

Abbreviations: CBC = complete blood count, CMP = complete metabolic panel, ECG = electrocardiogram, TTE = transthoracic echocardiogram, MUGA = multigated acquisition scan

IND Overview – Stopping Criteria

- **Terminating trial for safety**
  - Decision point is part of the dose-escalation design
    - May not reach the MTD depending on the toxicity/tolerability of the drug
  - If dose-escalation is not part of trial, should have list of safety criteria for terminating trial
    - E.g., One Grade 5 event or 2 Grade 4 events should halt study
- **Terminating trial for futility in efficacy (i.e., go/no-go decision)**
  - Usually applied in dose-expansion portion of the trial where preliminary efficacy is assessed
  - In single-arm trials, go/no-go decision can really only be based on historical data so risk of failure in future trials is high
  - Thus, can consider randomized dose expansion trials
    - Balance larger sample size, cost, trial complexity

Common Pitfalls

- Related vs unrelated AEs
- Aggressive dose escalation
- Not considering toxicities from patients who are not considered DLT-evaluable
- Not starting at least dose -1 for combination regimens
- Not providing dose modifications based on anticipated toxicities
- Not stating discontinuation plan for all drugs in a combination regimen if there is a toxicity
- Lack of study stopping criteria
- ICF – alternative therapies

Helpful Resources

- FDA website: https://www.fda.gov/
  - https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
  - https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-clinical-hold
  - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.42
  - Project Optimus | FDA
- Guidances: https://www.fda.gov/regulatoryinformation/guidances/
  - S9 Nonclinical Evaluation for Anticancer Pharmaceuticals: https://www.fda.gov/media/73161/download
  - Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings: https://www.fda.gov/media/150244/download
- Templates: Protocol Templates and Guidelines | Protocol Development | CTEP (cancer.gov)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