Bio-IND Best Practices: An Analysis of Common Clinical Safety Hold and Non-hold Issues

Comparative Analyses Update

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Part 1: Bio-IND Best Practices:
An Analysis of Common Clinical Safety Hold and Non-hold Issues

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Learning Objectives

- Identify FDA resources to assist with the Bio-IND process
- Learn time-saving tips for Bio-IND submissions

21 CFR 320.31

(a) Any person planning to conduct an in vivo bioavailability or bioequivalence study in humans shall submit an "Investigational New Drug Application" (IND) if:

The study involves a radioactively labeled drug product; or

The study involves a cytotoxic drug product.

(b) Any person planning to conduct a bioavailability or bioequivalence study in humans using a drug product that contains an already approved, non-new chemical entity shall submit an IND if the … daily dose exceeds that specified in the labeling of the drug product.

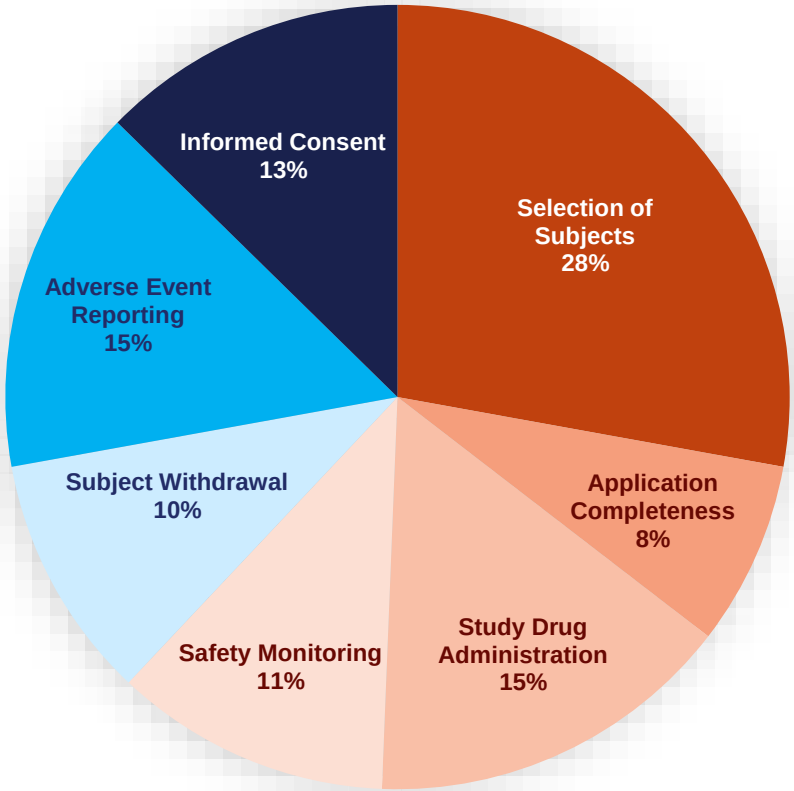
Clinical Safety Review

- Performed by the Division of Clinical Safety and Surveillance
- Clinical hold: 21 CFR 312.42
  - Delays a proposed clinical investigation or suspends an ongoing investigation
  - Subjects may not be given the investigational drug when a proposed study is placed on clinical hold
- Non-hold Comments: 21 CFR 312.41(c)
  - Recommendations that Sponsor may consider to improve the safety and study design
  - Submitting responses to FDA for non-hold comments via Bio-IND amendments are recommended but not required

Reasons for a Clinical Hold

- 21 CFR 312.42(b)
  - Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury
  - **Submit clinical investigators CVs**
  - **Submit an Investigator's Brochure**
  - **Submit Study Protocol**

DCSS Information Requests and Comments for Bio-INDs



Study Design and Protocol Tips

- Recommend following the Product-Specific Guidances (PSG) for Generic Drug Development
  - Note: Can use an alternative approach with adequate justification

- Should refer to the Reference Listed Drug (RLD) Label

Tips for Subject Selection

- Follow PSG Recommendations
- Align with RLD labeling
  - Indications and Usage
    - Special populations
    - Dosage reduction
  - Contraindications
  - Warnings and Precautions
  - Drug Interactions
- Define acceptable vital signs ranges
- Define acceptable laboratory ranges

Examples

- If a drug is contraindicated in patients with disease X – list it as an inclusion/exclusion criteria
- If enrolling healthy subjects with “normal vital signs” - list what range is considered “normal”.
  - Note: A heart rate of 40 bpm or a systolic blood pressure of 90 mmHg is not “normal”.
- If a subject needs to have “normal liver enzymes” - list specific range of values that is considered “normal”.
  - Note: Do not allow that value to be “within 5% of the normal range.”

Tips for Study Drug Administration

- PSG recommendations
- RLD labeling
  - Dosage and Administration
  - How Supplied/Storage and Handling
- Include description of monitoring and safety equipment for possible medication reactions
- Include details on drug preparation
- Include procedures for safe drug handling

Examples

- If subjects are to receive **pre-medications** - List the medications and dosages they are to receive. Make sure these medications are available in the U.S., and that they are not contraindicated.
- If **enrolling patients** - Do not alter the timing of their drug dosage "for administrative reasons."
- If a drug can cause **anaphylaxis** – Describe how subjects will be monitored and the emergency equipment and personnel that will be available.

Tips for Safety Monitoring

- PSG recommendations
- RLD labeling
  - Warnings and Precautions
  - Adverse Reactions
- Define acceptable vital signs ranges
- Define acceptable laboratory ranges
- Consider the timing and frequency of laboratory testing

Examples

- If a drug can cause **neutropenia** 1 week after study drug dosage - Check laboratory values (CBC) 1-week post-dose for each period.
- If a drug can cause **liver injury** – Check liver enzymes laboratory tests prior to administering the next dose.
- If a drug can cause **electrolyte changes** – Check electrolytes shortly before drug dosage (within 3 days).
- If labs need to be “normal” – list what range is considered “normal.”
  - Note: A sodium of 160 mmol/L is not “normal”
- If concern for embryo-fetal toxicity - Test for pregnancy at end of the study and discuss follow up for potential pregnancy.

Tips for Subject Withdrawal

- RLD labeling
  - Warnings and Precautions
  - Adverse Reactions
  - Contraindications

Examples

- If a subject develops a **contraindication** to the study drug (e.g., allergic reaction to the study drug, elevated liver enzymes, etc.) – They should not receive further doses of study medication and followed until the adverse event resolves.

Tips for Adverse Event Reporting

- Per 21 CFR 312.32(a) - The sponsor must notify FDA of potential serious risks, from clinical trials or any other source, as soon as possible.
  - No later than 15 calendar days in the case of:
    - Serious and unexpected suspected adverse reactions
    - Findings from other studies that suggest a significant risk to humans exposed to the drug
    - Increased rate of occurrence of serious suspected adverse reactions.
  - No later than 7 calendar days if unexpected fatal or life-threatening suspected adverse reactions
- Guidance for Industry - Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for INDs and BA/BE Studies
  https://www.fda.gov/media/150356/download

Tips for Informed Consent

- Resources
  - 21 CFR 50
  - Informed Consent: Guidance for IRBs, Clinical Investigators and Sponsors
    https://www.fda.gov/media/88915/download
- Make Informed Consent Form (ICF) clear and understandable
- Fully inform subjects about study risks
- Fully inform subjects about study events
- Include specific study restrictions

Examples

- If a study has ongoing **study restrictions** (e.g., contraception) – List that in the informed consent.
- If the RLD label includes a **Medication Guide** – Consider including this document with your informed consent.
- Consider including a **study event table** can help inform subjects about study events.

Tips for Bio-IND Amendments

- Include “tracked changes” of protocol
- List of changes between previous submitted and current study protocol

Details	Already Conducted BE Study Study No. BE XXX version 1.0	Repeat BE Study Study No. BE XXX version 2.0	Remarks
Serum electrolytes at Screening and prior to check-in in each study period.	Serum electrolytes (Sodium, Potassium, Chloride and Magnesium)	Serum electrolytes (Sodium, Potassium, Chloride, Calcium and Magnesium)	One Additional Serum electrolyte parameter added
Washout Period	At least 28 days	At least 42 days	As per Previous study Experience
Inclusion Criteria	No minimum weight criteria for Inclusion	Required minimum weight of 50 kg for enrollment	Weight criteria updated
Section 5.0: Check-in Activities and Section 9.8.2: Check-in Activities and Housing Period	Not available	medical and medication history	As per revision in current protocol template.
Section 9.8.1: Screening Activities	Not available	Urine Examination for Alcohol Test.	Revised as per current protocol template.

Resources

- Manual of Policies and Procedures: Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs
  https://www.fda.gov/media/72562/download
- Product-Specific Guidances for Generic Drug Development
  https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development
- Guidance for Clinical Investigators, Sponsors, and IRBs. Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND
  https://www.fda.gov/media/79386/download
- Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted under an IND Frequently Asked Questions
  https://www.fda.gov/media/83209/download
- Guidance for Industry: Sponsor Responsibilities - Safety Reporting Requirements for INDs and BA/BE Studies
  https://www.fda.gov/media/150356/download
- Informed Consent: Guidance for IRBs, Clinical Investigators and Sponsors
  https://www.fda.gov/media/88915/download
- 2022 SBIA: Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs
  https://www.fda.gov/media/165546/download?attachment

Challenge Question #1

Which of the following statements about Bio-INDS is NOT true?

A. A required part of a Bio-IND submission is an Investigator's Brochure.

B. A bioequivalence study in healthy subjects does not need to consider the RLD label's Warnings and Precautions.

C. Study investigators must inform the FDA of serious and unexpected suspected adverse reactions within 15 days after becoming aware of its occurrence

D. FDA provides guidances regarding best practices for safety reporting and informed consent.

Summary

- FDA has provided multiple resources to help guide Bio-IND submissions
- Refer to the RLD label and PSG when designing Bio-IND studies

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