Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- Provide an overview of the regulations for Bio-INDs*
- Review best practices for planning and submitting Bio-INDs
- Discuss frequently asked questions related to Bio-INDs

* The term Bio-IND distinguishes these submissions from INDs for investigational new drug products submitted to the Office of New Drugs (OND).

21 CFR 320.31(a)

- **21 CFR 320.31(a) -** any person planning to conduct an in vivo bioavailability (BA) or bioequivalence (BE) study in humans must submit a Bio-IND if the study involves a:
    1) Radioactively labeled drug product
    2) Cytotoxic drug
- Check the Product-Specific Guidance (PSG) website* for the Reference Listed Drug (RLD) product, if available, to see if a Bio-IND is required under the regulations

* See https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development for more information.

21 CFR 320.31(b)

- **21 CFR 320.31(b) -** any person planning to conduct a BA or BE study in humans using a drug product that contains an already approved, non-new chemical entity must submit a Bio-IND if the study is one of the following types:
    1) A single-dose study in normal subjects or patients where either the **maximum single or total daily dose exceeds** what is specified in the labeling of the drug product that is the subject of an approved new drug application (NDA) or an ANDA
    2) A multiple-dose study in normal subjects or patients where either the **single or total daily dose exceeds** what is specified in the labeling of the drug product that is the subject of an approved NDA or ANDA
    3) A multiple-dose study on an extended-release drug product on which no single-dose study has been conducted

Content of a Bio-IND - 21 CFR 312.23

- **21 CFR 312.23 –** contains requirements for all IND content and format
- Recommend to follow **Attachment 1 - "IND Checklist for Completeness and Acceptability"** in CDER Manual of Policies and Procedures (MAPP) 5210.5 "Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs"
- "IND Checklist for Completeness and Acceptability" in MAPP 5210.5 can be found at: https://www.fda.gov/files/about%20fda/published/Review-of-Investigational-New-Drug-Applications-%28Bio-INDs%29-by-the-Office-of-Generic-Drugs.pdf

Responsibilities for Bio-IND Review

- **Division of Filing Review**
  - Reviews new Bio-INDs for completeness and acceptability
  - Schedules teleconferences (if needed) with Sponsor
  - Prepares clinical hold letters
- **Division of Clinical Safety and Surveillance**
  - Evaluates study protocol and additional information such as Informed Consent Form, Investigator Brochure, Investigator Qualifications from a ***clinical safety perspective***
- **Office of Pharmaceutical Quality**
  - Evaluates information related to drug product, drug substance, manufacturing, and inactive ingredients
- **Division of Bioequivalence**
  - Evaluates study protocol to assess adequacy of the study design for ***demonstrating bioequivalence***

Clinical Hold and Non-Hold Comments

- **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: 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 Clinical Hold - 21 CFR 312.42(b)

- Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury
- Clinical investigators are not qualified by reason of their scientific training and experience to conduct the investigation described in the Bio-IND
- Investigator brochure is misleading, erroneous, or materially incomplete
- Bio-IND does not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies

Timeline for Bio-IND Review

- **By Day 30**
  - Teleconference with the Sponsor and FDA to notify if any clinical hold has been identified by FDA
  - If no clinical hold deficiency is identified by Day 30, the study will be allowed to proceed per 21 CFR 312.40
- **By Day 60**
  - The clinical hold letter will be issued no later than 30 days after the imposition of the clinical hold - 21 CFR 312.42(d)

- Non-hold comments and recommendations from the Division of Bioequivalence regarding the adequacy of the study design for demonstrating bioequivalence are not confined to the dates listed above and may be sent *after Day 60*

Recommendations for Planning and Submitting Bio-INDs

General Recommendations

- Be familiar with **MAPP 5210.5 "Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs"**
- Complete **Attachment 1 – "IND Checklist for Completeness and Acceptability"** in MAPP 5210.5 prior to submitting Bio-IND
- Incorporate recommendations from Product Specific Guidance into study design
- Use controlled correspondence or pre-ANDA meeting to discuss complex issues (example: different study population) related to study design with FDA

General Recommendations (2)

- Incorporate safety information from Reference Listed Drug (RLD) label into study design
  - Indications and Usage (Section 1)
  - Dosage and Administration (Section 2)
  - Contraindications (Section 4)
  - Warnings and Precautions (Section 5)
    - Boxed warnings
  - Adverse Reactions (Section 6)

General Recommendations (3)

- Incorporate safety information from Reference Listed Drug (RLD) label into study design
  - Drug Interactions (Section 7)
    - Prohibited concomitant medications
  - Use in Specific Populations (Section 8)
    - Pregnancy
    - Females and males of reproductive potential
    - Renal and hepatic impairment
  - Clinical Pharmacology (Section 12)
  - How Supplied/Storage and Handling (Section 16)

General Recommendations (4)

- Provide specific details in study protocol
  - Acceptable lab values and vital signs, duration of stable dose
- Remember to include Investigator Brochure, Form 1572, and Curricula Vitae for all investigators
- Use language that subjects will understand in Informed Consent Documents (21 CFR 50.20)

Frequently Asked Questions about Bio-INDs

Safety Reporting

Question: What are the requirements for safety reporting for a bioequivalence study conducted under a Bio-IND?

Answer:

- Refer to 21 CFR 312.32 and Draft Guidance for Industry "Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies (June 2021)" for details (https://www.fda.gov/media/150356/download)
- For Bio-INDs, **serious**, **unexpected**, and **causally related** adverse events must be reported to FDA via a Bio-IND Safety Report
  - Within **7 calendar days** for unexpected fatal or life-threatening
  - Within **15 calendar days** for non-fatal or non-life-threatening

Non-U.S. BE Studies

Question: Does a Bio-IND have to be submitted for a bioequivalence (BE) study that will be conducted entirely at non-U.S. study sites?

Answer:

- 21 CFR 320.31 describes the applicability of requirements for the submission of INDs submitted for bioavailability or bioequivalence studies
- 21 CFR 312.120 describes the conditions under which FDA will accept foreign clinical studies not conducted under an IND as support for an application for marketing approval including ANDAs
- FDA will assess during the review of the ANDA whether the conditions of the regulations have been met

Bio-IND Amendment

Question: A BE study that was previously submitted under a Bio-IND needs to be performed again with minor changes (add new investigator) to the study protocol. Is a Bio-IND amendment required?

Answer:

- Yes, a Bio-IND amendment should be submitted
- Refer to 21 CFR 312.30 and https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-protocol-amendments for details
- Bio-IND amendment is required for
  - New study protocol
  - Changes to existing study protocol affecting the safety of subjects, scope of investigation, or scientific quality of study
  - New investigator is added

Challenge Question #1

All serious adverse events for a BE study under a Bio-IND must be reported to the FDA:

A. True

B. False

For Bio-INDs, adverse events that are **serious, unexpected, and causally related** must be reported to FDA via a Bio-IND Safety Report. Requirements for safety reporting for Bio-INDs are *different* than those for IND-exempt BA/BE studies.

Challenge Question #2

Which of the following statements are best practices that Sponsors should follow when planning and submitting a Bio-IND?

A. Use “IND Checklist for Completeness and Acceptability” (Attachment 1) in MAPP 5210.5 to ensure Bio-IND submission is complete

B. Incorporate recommendations from Product Specific Guidance into study design

C. Incorporate safety information from Reference Listed Drug (RLD) label into study design

D. Utilize a controlled correspondence or pre-ANDA meeting to discuss complex issues related to study design

E. All of the above

Summary

- Be familiar with applicable regulations and guidances related to Bio-INDs
- Refer to MAPP 5210.5 “Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs” for detailed information
- Submit complete and accurate Bio-IND application
- Ensure safety reporting requirements for Bio-INDs are followed


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