
POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

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

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PURPOSE

- This MAPP describes the Office of Generic Drugs’ (OGD) policy and procedures for review of investigational new drug applications (INDs) for proposed generic drugs submitted for bioavailability (BA) or bioequivalence (BE) studies under 21 CFR 320.31 (also known as Bio-INDs).
- The term Bio-IND distinguishes these submissions from INDs for investigational new drug products submitted to the Office of New Drugs (OND). The Bio-IND is required by regulations in specific instances to ensure that proposed drug products that contain already approved, non-new chemical entities are safe for use in human test subjects and do not expose the subjects to undue risk.

BACKGROUND

- The requirements for the submission of a Bio-IND in support of an abbreviated new drug application (ANDA) were revised when FDA published the Title I regulations¹ in April of 1992. The revisions made the

¹ 57 FR 18000, Apr. 28, 1992.

requirements for the submission of a Bio-IND consistent with the generic drug program's practice at that time. The regulations state specifically when a Bio-IND must be submitted for an in vivo BA or BE study in humans² and the required content of the IND.³

- As stated in 21 CFR 320.31(a), any person planning to conduct an in vivo BA or BE study in humans must submit a Bio-IND⁴ if:
 - (1) The study involves a radioactively labeled drug product, or
 - (2) The study involves a cytotoxic drug.

- As stated in 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.

POLICY

- In addition to the general requirements for an IND submission⁵ including a BE study protocol,⁶ sufficient information should be available in a Bio-IND for OGD and Office of Pharmaceutical Quality (OPQ) to determine the safety of the formulation to be used in the proposed BE study. For example, a qualitative and quantitative listing of all active and inactive ingredients

² 21 CFR 320.31.

³ 21 CFR 312.23.

⁴ 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> and <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm> for more information.

⁵ Per 21 CFR 312.23.

⁶ Consistent with 21 CFR 320.31(c) and (d), Part 50 (Protection of Human Subjects-Informed Consent) and Part 56 (Institutional Review Boards) are applicable to any BE study in humans conducted under an IND as well as any BE study in humans that is exempt from the requirements to submit a Bio-IND.

- should be provided. If an inactive ingredient exceeds the amount found in the Agency's Inactive Ingredient Database (IID) (<http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm>), or has not previously been used in a drug product intended for the same context of use (i.e., route of administration, patient population, duration of use), OGD or OPQ may request additional safety information from the person who takes responsibility for and initiates the study (referred to as "sponsor" in this MAPP) and/or may place the Bio-IND on clinical hold (21 CFR 312.42(d)).
- OPQ will determine whether complete information on chemistry, manufacturing, and controls has been included in a Bio-IND so that the safety of the planned study can be adequately evaluated. This material will need to be resubmitted with the ANDA.
 - OGD will perform a clinical review of the Bio-IND and determine whether the study is safe to proceed.
 - When OPQ or OGD concludes that there may be grounds for imposing a clinical hold, consistent with 21 CFR 312.42(c), the Agency will attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.
 - The Director of OGD's Division of Clinical Safety and Surveillance (DCSS) in the Office of Safety and Clinical Evaluation (OSCE) will convene a meeting with the appropriate subject matter experts (SMEs) within the Agency and the sponsor to discuss any clinical hold deficiencies identified in the proposed protocol and suggest modifications to resolve safety concerns or place the Bio-IND on clinical hold (21 CFR 312.42).
 - For all due dates within this MAPP, if the due date falls on a weekend or holiday, the due date will be the closest prior business day.
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RESPONSIBILITIES

- IND Coordinator in OGD's Division of Filing Review (DFR)
 - Reviews new Bio-INDs for completeness and acceptability,
 - Issues acknowledgement letters.
 - Notifies the appropriate offices of the receipt of Bio-IND submissions.
 - Schedules teleconferences.
 - Prepares clinical hold letters.
 - Discipline Reviewers
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- Conduct the primary review of a Bio-IND.
 - Identify potential clinical hold and non-hold issues.
 - Recommend whether a clinical hold is necessary.
- Discipline Team Leaders (TLs) and Secondary Assessors (SAs)
 - Conduct the secondary review of a Bio-IND.
 - Coordinate discussions with their respective discipline review teams.
 - Resolve potential clinical hold issues within their respective disciplines.
- Discipline Project Managers (PMs)
 - Inform Discipline TLs and SAs of Bio-IND submissions.
 - Assign discipline Reviewers to each Bio-IND.
 - Track project progress.
 - Report on project status.
- Director of OGD's DCSS (DCSS Director)
 - Evaluates the Bio-IND review team's recommendation(s) for clinical hold.
 - Makes the final decision regarding clinical hold.
 - Serves as the signatory for the clinical hold letter.
- Director or designee thereof of the assigned OGD Division of Bioequivalence (DB) within the Office of Bioequivalence (OB)
 - Reviews the DB assessment team's recommendation(s) for the study protocol(s)
 - Signs-off on DB's review
 - Serves as the signatory for communications conveying non-hold comments or recommendations, when sent separately from any clinical hold letter.
- Document Room Staff
 - Receives and identifies Bio-INDs.
 - Assigns an IND application number (or, if applicable, validates pre-assigned application information).
 - Uploads electronic data into the appropriate electronic filing system and processes incoming and outgoing communications with sponsors and other relevant offices.

PROCEDURES

1. The Document Room Staff will:
 - a. Receive and identify a Bio-IND based on the cover letter and Form FDA 1571.
 - b. Determine if the sponsor had previously requested a pre-assigned application number for the Bio-IND submission. If so, the Document Room Staff will validate that the pre-assigned application information is accurate and enter the data into the appropriate electronic filing system.
 - c. Link the file location to the electronic record and, if applicable, upload electronic data onto the Electronic Document Room (EDR).
 - d. Process incoming amendments, new correspondence, and periodic reports and forward them to the IND Coordinator.
 - e. Process any outgoing clinical hold(s), as well as other necessary letters, and issue them to the sponsor.

2. The IND Coordinator will:
 - a. Review new Bio-INDs for completeness and acceptability using the IND checklist (See Attachment 1 and see 21 CFR 312.23, *IND content and format*).
 - b. Issue an acknowledgement letter by email to the sponsor, within 7 calendar days of the receipt of the Bio-IND.
 - c. Notify the appropriate Discipline PMs in OGD's OSCE, OB, and OPQ's Office of Program and Regulatory Operations (OPRO) of the receipt of the Bio-IND. The notification should include relevant details such as the assigned IND application number, the sponsor's name, the identity of the drug product, the reason a Bio-IND is required, the date of receipt, and the requested deadline for clinical hold determinations and finalized discipline reviews. It will also indicate if any information is missing from the Bio-IND.
 - d. Send the acknowledgement letter, including the 30-day clinical hold determination date, to the sponsor.

3. Each Discipline PM will notify their discipline TL or SA of the Bio-

- IND and assign a Discipline Reviewer to the Bio-IND within 7 calendar days of the notification.
4. Each Discipline Reviewer will perform the primary review of the portion of the Bio-IND pertinent to their discipline (quality, BE, and clinical, in addition to pharmacology/toxicology, microbiological or statistical, as appropriate) and identify potential clinical hold issues.
 - a. Each Discipline TL or SA will conduct a secondary review and either concur or not concur with the recommendation of their discipline's Reviewer. The recommendation will be reviewed through the discipline's management chain, and documented and archived in the appropriate system of record.
 - b. The discipline review team, through the discipline TL or SA, will notify DFR of any discipline clinical hold issues identified no later than Day 28.
 5. If a Discipline Reviewer has identified a potential reason for a clinical hold they will:
 - a. Communicate the potential for a clinical hold and the means to address the clinical hold issue to both their Discipline TL or SA and their discipline review team.
 - i. Each relevant Discipline's TL or SA will then coordinate discussion within their own discipline and facilitate the resolution of these potential clinical hold issues within their own discipline review teams.
 - ii. When possible, each relevant discipline review team will attempt to resolve potential clinical hold issues internally before it considers recommending a clinical hold order.
 - iii. If time is available, each relevant discipline review team may send an information request to the sponsor to identify and resolve easily addressed potential clinical hold issues.
 - b. Identify all clinical hold issues by Day 30 after the initial IND receipt. If the recommendation is to impose a clinical hold, the Discipline PM will notify the DCSS Director of the discipline recommendation.
 6. The DCSS Director provides an assessment and makes the final decision.
 7. When the need for a clinical hold is identified and approved by the DCSS Director, the IND Coordinator will:

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- a. Schedule a teleconference with the sponsor and the DCSS Director no later than Day 30 or the closest prior business day to impose a clinical hold. If Day 30 falls on a weekend or holiday, then the teleconference should be scheduled no later than the closed prior business day. The DCSS Director will notify the sponsor's representative during the meeting of the need for a clinical hold and the supporting reasons. The IND Coordinator will document the telephone notification in the appropriate electronic filing system.
 - b. Prepare a clinical hold letter for the signature of the DCSS Director, documenting the reasons for the clinical hold. Consistent with 21 CFR 312.42(d), the clinical hold letter will be issued no later than 30 days after the imposition of the clinical hold. Other recommendations identified that are not reasons for a clinical hold will be communicated as well. Such recommendations should be distinguished clearly from clinical hold deficiencies in the letter. These non-hold comments will be limited to appropriate and reasonable measures that the sponsor may consider to improve their protocol but are non-binding.
 - c. Obtain the DCSS Director's signature for the clinical hold letter in the appropriate electronic filing system and then send the signed letter to the Document Room Staff. (The Document Room Staff will mail the letter within 2 business days of its appearance in the processing queue.)
8. If there are no clinical hold deficiencies identified, the study will be allowed to proceed per 21 CFR 312.40. In this case, the sponsor will receive an email that explains: "This is in reference to IND XXXXXX, after our initial 30-day safety review, there have been no clinical hold deficiencies identified at this time pursuant to 21 CFR 312.42 and the study may proceed. Additional non-hold comments or recommendations may be communicated at a later date, if applicable."
 9. A clinical hold will be lifted after the relevant discipline Reviewers have determined that the sponsor has submitted a satisfactory response to all clinical hold items communicated in the clinical hold letter, 30 days after receipt of a sponsor's response to the clinical hold. The IND Coordinator will prepare a remove hold letter for the signature of the DCSS Director.
 10. If the discipline review team determines that the clinical hold cannot be lifted, the IND Coordinator will schedule a teleconference with the sponsor and the DCSS Director and other discipline staff as appropriate. The DCSS Director will notify the sponsor of the reason(s) for the maintained clinical hold by telephone. The IND Coordinator will appropriately document the call, prepare a letter, obtain the DCSS Director's signature for the letter, and issue the letter to the sponsor.

11. If, during the conduct of the Bio-IND study, clinical safety reports or other communication(s) from the sponsor indicate a potential safety signal, the discipline Reviewers will discuss the ongoing Bio-IND study with the DCSS Director to determine whether the study should be placed on clinical hold. This will be based on a risk assessment of the available data.
 12. Modification(s) of the study protocol or other documents due to non-hold comments and/or the sponsor's response(s) to non-hold comments will be reviewed at the discretion of the discipline that issued the non-hold comments. The timeline(s) for reviewing responses to non-hold comments will be determined by the discipline team(s) that issued the non-hold comments.
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REFERENCES

- Draft Guidance for Industry *Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators* (May 2015), available at: <https://www.fda.gov/media/92604/download>
 - Draft Guidance for Industry *Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021), available at: <https://www.fda.gov/media/150356/download>
 - Guidance for Industry *Submitting and Reviewing Complete Responses to Clinical Holds* (October 2000), available at: <https://www.fda.gov/media/72548/download>
 - 21 CFR 320.31 *Applicability of requirements regarding an "Investigational New Drug Application."*
 - 21 CFR 312.23 *IND content and format.*
 - 21 CFR 312.40 *General requirements for use of an investigational new drug in a clinical investigation.*
 - 21 CFR 312.42 *Clinical holds and requests for modification.*
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DEFINITIONS

- Clinical Hold: An order issued by FDA to the sponsor of an IND to delay or to suspend a clinical investigation for reasons described in 21 CFR 312.42. A clinical hold may be either a complete clinical hold or a partial clinical hold. A clinical hold (including a partial clinical hold) involves the Agency (1) requiring additional information and/or data, (2) reviewing the additional

information and/or data to determine whether the hold can be lifted, and (3) after the review, informing the sponsor whether they can proceed. The Agency will not impose a clinical hold if it requests additional information and/or data from the sponsor, but the sponsor does not have to wait for FDA review of that additional information and/or data and authorization to proceed before initiating a new protocol.

- Complete Clinical Hold: A delay or suspension of all clinical work requested under an IND.
- Partial Clinical Hold: A delay or suspension of only part of the clinical work requested under the IND (e.g., a specific protocol or part of a protocol is not allowed to proceed; however, other protocols or parts of the protocol are allowed to proceed under the IND).

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
5/10/2004	N/A	Initial
7/7/2006	1	Updating the MAPP to reflect changes in procedures.
10/25/2016	2	Updating the MAPP to reflect current OGD policy and procedures and the changes from a recent office reorganization
4/14/2022	3	Procedures updated

ATTACHMENT – IND Checklist for Completeness and Acceptability

	Revised June 2021
IND:	IND Number
SPONSOR:	Sponsor
DRUG PRODUCT NAME:	Drug Product Name
STRENGTH(S):	Strength(s)
RLD NAME:	RLD name
RLD NUMBER:	RLD number
LETTER (1571) DATE:	Letter date
RECEIVED DATE:	Received date
30-DAY CLINICAL HOLD DETERMINATION DATE:	30 Days from Date of Receipt

<p>Completion Signature</p> <hr/> <p>X</p> <hr/> <p>Filing Reviewer</p>	<p>Recommendation:</p>
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CORRESPONDENCES/GENERAL COMMENTS:

Select Type of IND (Basis) per 21 CFR 320.31(a)(3): Select Type

Select Signed and completed FDA Form 1571

 Cover Letter

Comments	
Select	Table of Contents <ul style="list-style-type: none">• For Protocol
Select	Introductory Statement
Select	General Investigational Plan
Select	Protocol(s) for conducting an in vivo bioequivalence study in humans <ul style="list-style-type: none">• For each planned study
Select	Environmental Assessment or Claim for Exclusion
Select	Compliance Statement
Comments	
<u>Drug Substance (Active Ingredient)</u>	
Select	Manufacturing Controls for Active Ingredient Drug Master File
Select	Specification and Tests for Active Ingredient
Select	Source of Active Ingredient
Select	Certificate of Analysis from Drug Substance Manufacturer
Select	Certificate of Analysis from Drug Product Manufacturer
<u>Drug Product</u>	
Components and Composition	
Select	<ul style="list-style-type: none">• A qualitative and quantitative statement of the components and composition of the generic drug to be used in the bioequivalence study, including the amounts of the active ingredients and all excipients
Select	<ul style="list-style-type: none">• Provided acceptable IID justification table

Select	Certificate of Analysis for Finished Dosage Form
	<u>Inactive Ingredients</u>
	Specification and Tests for Inactive Ingredients <ul style="list-style-type: none"> • With information for any allowable differences in excipients, impurities, container closure systems, etc. in comparison to the RLD
Select	Source of Inactive Ingredients
	Supplier’s Certificate of Analysis for Inactive Ingredients
Select	Sponsor’s Certificate of Analysis for Inactive Ingredients
Select	
.....	
Comments	
Select	Manufacturing Controls (Method and Equipment) <ul style="list-style-type: none"> • Including a description of the type of equipment
Select	Address of Manufacturing Site
Select	Manufacturing Procedure (Batch Records) Batch/Lot# <ul style="list-style-type: none"> • Including batch size
.....	
Comments	
Select	Container/Closure Information
Select	Stability Profile Including Stability Data
	Stability Data
Select	<ul style="list-style-type: none"> • Minimum 1 batch
Select	<ul style="list-style-type: none"> • Stability Testing Data – 3 Months Accelerated Stability Data (40°C and
Select	<ul style="list-style-type: none"> 75% relative humidity)
Select	<ul style="list-style-type: none"> • Information on the container/closure system used in the stability tests • Batch/Lot # Listed on Stability Records
.....	
Comments	

Select	Blank Informed Consent Form (ICF)
Select	Investigator's Brochure (IB)
Select	Investigator Qualifications <ul style="list-style-type: none">• List of investigator names• The name and a statement of the qualifications (Curriculum Vitae or other statement of qualifications) of each investigator• Form FDA 1572
Comments	
Select	Any available preclinical in vitro and/or in vivo information on the investigational drug product
Select	Letter of cross reference authorization (if applicable)
Select	Current RLD Labeling
Select	Other relevant information related to a device that may be used with the investigational drug
Comments	