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) submitted for bioavailability (BA) or bioequivalence (BE) studies under 21 CFR 320.31. The term Bio-INDs distinguishes them 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 no-new chemical entities are safe for use in human test subjects and do not expose them 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 regulations in April of 1992. The revisions made the requirements for the submission of a Bio-IND consistent with the OGD practice at that time. The regulations state specifically when a Bio-IND

must be submitted for an in vivo BA or BE study in humans (21 CFR 320.31) and the required content of the IND (21 CFR part 312.23).

- As stated in 21 CFR 320.31(a), any sponsor planning to conduct an in vivo BA or BE study in humans should submit a Bio-IND 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 sponsor planning to conduct a bioavailability or bioequivalence study in humans using a drug product that contains an already approved, non-new chemical entity should 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 a bioequivalence study protocol, sufficient information should be available in a Bio-IND for OGD to determine the safety of the formulation to be used in the proposed bioequivalence study. For example, a qualitative and quantitative listing of all active and inactive ingredients 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 route of administration, OGD may request additional safety data from the sponsor and/or may place the Bio-IND on hold.

- OGD 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.

- When FDA concludes that there may be grounds for imposing a clinical

hold, the Agency will attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order (21 CFR 312.42(c)).

- The Director of OGD's Division of Clinical Review, or assigned designee, will convene a meeting with the appropriate subject matter experts (SMEs) within the Agency and the sponsor to discuss any safety related deficiencies identified in the proposed protocol and suggest modifications to resolve safety concerns or place Bio-INDs on clinical hold (21 CFR 312.42).

RESPONSIBILITIES

- The Document Room Staff will:
  - Receive and identify a Bio-IND based on the cover letter and Form SF-1571.
  - 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. If the sponsor had not previously requested a pre-assigned application number, the document room staff will assign the submission an IND application number and enter the data into the Document Archiving, Reports and Regulatory Tracking System (DARRTS), or the appropriate database.
  - Upload electronic data onto the Electronic Document Room (EDR) servers and link the file location to the DARRTS record.
  - For Bio-INDs submitted in paper format, route all three copies (original - red, duplicate - green, and triplicate - orange) to the IND coordinator in OGD's Division of Filing Review.
  - Process outgoing clinical hold and other necessary letters, and issue them to the sponsor.
  - Process incoming amendments, new correspondence, and periodic reports, and forward them to the IND coordinator in OGD's Division of Filing Review.
- The IND Coordinator will:
  - 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*). Specific

items that should be present include, but are not limited to:

- Protocol for conducting an in vivo bioequivalence study in humans

- 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

  Any other information necessary to determine the safety of the formulation to be used in the proposed bioequivalence testing, including but not limited to the following:

- Tests and specifications for identity, strength, quality, and purity for each active ingredient, and certificates of analysis for all excipients

- Method and place of manufacture, including a description of the type of equipment, batch size, and batch records

- Tests to be performed and specifications to be established for the finished dosage form (certificates of analysis)

- Stability testing data on the drug product stored for three months at 40 degrees C and 75% relative humidity, including information on the container/closure system used in the stability tests

- Within 7 working days of the receipt of the Bio-IND, issue an acknowledgement letter by fax, and mail a copy of the letter to the sponsor.

- Notify the appropriate team leads in OGD's Office of Bioequivalence and the appropriate Regulatory Business Project Manager in the Office of Pharmaceutical Quality's (OPQ) Office of Program and Regulatory Operations (OPRO) of the receipt of the Bio-IND submission. The notice would include relevant details such as the assigned IND application number, the identity of the drug product, the appropriate regulatory citation, the date of receipt, and the requested deadline.

- Send the acknowledgement letter to the sponsor and inform the following individuals of the receipt of a Bio-IND and the projected response date:

Director, Division of Filing Review (OGD)
Director, Division of Clinical Review (OGD)
Director, Office of Bioequivalence (OGD)
Director, Office of Program and Regulatory Operations (OPRO)

- Monitor the drug quality and clinical review processes to ensure that each review is complete within 25 days of the IND receipt date.

- Identify and coordinate resolution of potential safety issues with the discipline review teams. When possible, the discipline review teams will attempt to resolve safety matters with the sponsor before issuing a clinical hold order.

- Prepare the clinical hold letter to include chemistry, BE, and clinical review comments for the signature of the Director of OGD's Division of Clinical Review.

- If the reviewer in any discipline recommends a clinical hold, forward the recommendation of the reviewer and team leader to the Director of OGD's Division of Clinical Review to assess the need for a clinical hold.

- If applicable, schedule an internal review team meeting to discuss clinical hold issues between Day 25 and Day 29 (where Day 1 is the date of the sponsor's IND submission).

- If a clinical hold is necessary, the IND Coordinator will schedule a teleconference involving the review team and the sponsor on or before Day 30 to impose a clinical hold.

- If needed, ensure that a clinical hold letter is sent to the sponsor no later than 30 days after imposition of the clinical hold; detailing the reasons for the clinical hold decision and the steps the sponsor shall take to address the issues. The letter may also contain non-hold recommendations.

- Project Manager in OGD's Division of Clinical Review (If a secondary clinical review is needed from an OND review division) will:

  - Prepare the consult.

  - Notify the OND project manager.

  - Assign the review as an IND review.

  - Specify the date by which a response is needed.

- Notify the IND coordinator at the time a consult is issued to OND.
- Forward completed consult response to the respective review discipline.

- The Director of OGD's Division of Clinical Review will:
  - Review the review team's recommendation for clinical hold.
  - Provide concurrence to review team's recommendation for a clinical hold, as appropriate.
  - Provide clearance and serves as primary final signatory for the clinical hold letter.

PROCEDURES

1. The primary review (chemistry, bioequivalence, and clinical, in addition to microbiological or statistical, as appropriate) will be completed expeditiously. All safety issues will be identified by Day 25 after the initial IND receipt. If the discipline recommendation is clinical hold, the discipline will complete a written and archived safety review in time to issue the hold by Day 30.

2. If there are no deficiencies identified that would compromise patient safety, the study will be allowed to proceed.

3. If a primary reviewer has identified a potential reason for a clinical hold, he/she will communicate the potential for a hold to both his/her respective team leader and the review team. The respective discipline team leader involved will concur or non-concur with the recommendation of the respective primary reviewer. The recommendation will be reviewed through the discipline's management chain, as appropriate.

4. If any discipline makes a hold recommendation, the Director of OGD's Division of Clinical Review will provide an assessment and make the final decision (including any input from secondary reviews from OND and the documentation from the review that is the basis for a clinical hold).

5. When the need for a clinical hold is identified (complete or partial) and approved by the OGD Director of Clinical Review:

   The IND Coordinator schedules a teleconference with the sponsor and the Director of OGD's Division of Clinical Review. The Division Director will

notify the sponsor representative during the meeting of the need for a clinical hold and the reasons why it is needed. The IND Coordinator will document the telephone notification in the IND file, in the electronic file, and will send a copy to the OGD Office Director to inform them of the clinical hold.

The IND Coordinator will prepare a clinical hold letter for the signature of the Director of OGD's Division of Clinical Review, documenting the reasons for the clinical hold. Consistent with 21 CFR 312.42, the clinical hold letter will be issued no later than 30 days after the imposition of the clinical hold. Other recommendations identified in reviews 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.

6. A clinical hold will be lifted after the relevant discipline reviewers have determined that the sponsor has submitted a satisfactory response to the clinical hold letter. The IND Coordinator will prepare a remove hold letter for the signature of the director of OGD's Division of Clinical Review.

7. If the review team determines that the clinical hold cannot be lifted, the IND Coordinator will schedule a teleconference with the sponsor and the Director of OGD's Division of Clinical Review. The Division Director will notify the sponsor of the reason for the clinical hold by telephone. The IND coordinator will appropriately document the call, prepare a letter, obtain the Director's signature for the letter, and issue the letter to the sponsor.

REFERENCES

MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)*

21 CFR 320.31 *Applicability of requirements regarding an "Investigational New Drug Application"*

21 CFR 312.23 *IND content and format*

DEFINITIONS

Clinical hold: An order issued by the FDA to the sponsor of an IND to delay a proposed investigation or suspend an ongoing clinical investigation. It may be complete (i.e., to suspend all studies under the IND) or partial (i.e., to suspend only a portion of a study or studies).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
5/10/2004	Initial	N/A
7/7/2006	1	Updating the MAPP to reflect changes in procedures.
10/25/16	2	Updating the MAPP to reflect current OGD policy and procedures and the changes from a recent office reorganization

ATTACHMENT 1

IND CHECKLIST FOR COMPLETENESS AND ACCEPTABILITY

IND # _____

REGULATORY BASIS FOR IND SUBMISSION 21 CFR _____

DRUG NAME _____

DOSAGE FORM _____

DATE OF RECEIPT _____

DEADLINE (30 DAYS FROM DATE OF RECEIPT) _____

	YES	NO
Type of IND (Basis) -		
FDA Form 1571 - Completed/Original Signature		
Table of Contents		
Introductory Statement		
General Investigational Plan		
Protocol		
Components & Composition		
Manufacturing Controls for Active Ingredient DMF -		
Specification and Tests for Active Ingredient		
Source of Active Ingredient		
COA from Manufacturer of Active Ingredient		
Specification and Tests for Inactive Ingredients		
Source of Inactive Ingredients		
COA for Inactive Ingredients		
COA for Finished Dosage Form		

Manufacturing Controls (Method and Equipment)		
Address of Manufacturing Site -		
Manufacturing Procedure (Batch Records) Batch/Lot # -		
Stability Profile Including Stability Data		
3 Months Accelerated Stability Data		
Batch/Lot # Listed on Stability Records		
Container/Closure Information		
Environmental Assessment or Claim for Exclusion		
Compliance Statement		
Additional Information (Special Topics)		
Duplicate copy to HFD-_____for consult. Type of consult: Date:		
Primary Review _____ Date _____		
Recommendation: File Refuse to File		
Secondary Review _____ Date _____		

ATTACHMENT 2

PROCESSING RECORD

IND # _____
SPONSOR _____
FDA RECEIVED DATE _____
LETTER DUE DATE _____

REVIEW FOR ACCEPTABILITY

ACTION	DATE OF COMPLETION
Date received by Document Room	
Date received by OGD/ORO/DFR	
Date Acknowledgement Letter and Filing Checklist uploaded to DARRTS	

OPQ REVIEW

ACTION	DATE OF COMPLETION
Date consult sent to CDER/OPQ/OPRO RBPM	
Date CMC Reviewer Assigned	
Date Microbiology Reviewer Assigned (if applicable)	

OGD REVIEW

ACTION	DATE OF COMPLETION
Date consult sent to OGD/OB/DCR	
Date Clinical Reviewer Assigned	
Date consult Sent to OGD/OB/DBE	
Date DBE Reviewer Assigned	

REVIEW RECOMMENDATIONS

DISCIPLINE	RECOMMENDATION (Acceptable/Unacceptable)	Date
OGD DCR		
OGD DBE		
OPQ CMC		
OPQ MICRO (if applicable)		
OVERALL IND RECOMMENDATION (CLINICAL HOLD OR NON HOLD COMMENTS ONLY)		

APPLICANT CONTACT

ACTION	DATE OF COMPLETION

Teleconference with Applicant	
Letter signed by OGD/OB/DCR Director	
Letter issued to Applicant	