

Office of Generic Drugs

**Inspections of Clinical Facilities and Analytical Laboratories
Conducting Bioequivalence Studies Submitted in ANDAs**

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PURPOSE

- This MAPP outlines policies and procedures to use in (1) identifying when to request inspections of clinical facilities or analytical laboratories associated with bioequivalence (BE) studies and (2) applying inspection information to the review of abbreviated new drug applications (ANDAs).
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BACKGROUND

- In vivo BE studies are used to support the approval of many ANDAs. To help ensure that these studies are reliable, the Office of Generic Drugs (OGD) needs information on the inspection status of clinical facilities and analytical laboratories where the studies are conducted.
- OGD requests information on the compliance status of relevant clinical facilities and laboratories from the Good Laboratory Practice (GLP)/ Bioequivalence Branch (GBIB), Division of Scientific Investigations (DSI), Office of Medical Policy.
- GBIB assigns inspections to FDA's Office of Regulatory Affairs (ORA). Led by ORA field staff, inspections are conducted as described in the FDA Compliance Program Guidance Manual (CPGM), Compliance Program 7348.001 – Bioresearch Monitoring – In Vivo Bioequivalence. GBIB may also participate in inspections to provide scientific expertise.

REFERENCES

- 21 CFR part 54, Financial Disclosure by Clinical Investigators
 - 21 CFR part 314, Applications for FDA Approval to Market a New Drug
 - 21 CFR part 320, Bioavailability and Bioequivalence Requirements
 - The Federal Food, Drug, and Cosmetic Act, Section 505(k)(2)
 - FDA Compliance Program Guidance Manual (CPGM), Compliance Program 7348.001 – Bioresearch Monitoring – In Vivo Bioequivalence
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DEFINITIONS

- **Analytical Laboratory:** A facility used by a pharmaceutical sponsor or contract research organization to determine the nature and proportionate quantities of the constituents of a compound for an in vivo BE study. An analytical laboratory typically completes an assay to determine the drug concentration in body fluids.
- **Bioresearch Monitoring (BIMO) Goal Date (or Inspection Summary Goal Date):** The date by which the OGD Division of Bioequivalence (DBE) project manager anticipates a review of the inspection results from DSI. This date is determined in consultation with DSI staff and includes time to assess the inspection results.
- **BIMO Program:** The program responsible for FDA oversight of clinical and nonclinical studies conducted in support of marketing applications.
- **Clinical Facility:** A site where patients or subjects are examined and observed during an in vivo BE study.
- **Compliance Classification:** The compliance status of an inspection. Inspections can be classified as:
 - **No Action Indicated (NAI).** No objectionable conditions or practices were found during the inspection.
 - **Voluntary Action Indicated (VAI).** Objectionable conditions or practices that represented departures from the regulations were found, but were correctable by voluntary action.

- **Official Action Indicated (OAI).** Objectionable conditions or practices were found that represented significant departures from the regulations and could require administrative or regulatory sanctions.
 - **Directed Inspection:** An inspection based on substantive information suggesting scientific misconduct, major human subject protection violations, or compromised BE data.
 - **FDA Compliance Program Guidance Manual (CPGM), Compliance Program 7348.001: Bioresearch Monitoring – In Vivo Bioequivalence :** The program describing the procedures used by FDA staff in performing inspections of BE studies.
 - **Good Laboratory Practice and Bioequivalence Investigations Branch (GBIB):** The unit within the Division of Scientific Investigations responsible for assigning and/or performing inspections of facilities conducting BE and nonclinical studies.
 - **Routine Inspection:** An inspection to determine the compliance of a clinical facility or analytical laboratory with U.S. regulations. Typically there is no prior indication of misconduct, human subject protection problems, or suspect data.
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POLICY

- OGD requests that GBIB initiate a *routine inspection* of clinical facilities or analytical laboratories conducting BE studies included in an unapproved ANDA if:
 - A clinical facility or analytical testing site is identified in the ANDA that has no inspection history, was classified OAI on its last inspection, or has not been inspected within the past 3 years.
 - A clinical facility and/or analytical laboratory is performing a nonconventional BE study for which it has never been inspected by DSI (e.g., a study using pharmacodynamic endpoints to assess bioequivalence).
- OGD requests a *directed inspection* of a facility if there is a question about the quality or integrity of the data submitted in an ANDA. Instances of suspect data may include missing data points, errors in calculation, or inadequate documentation.

RESPONSIBILITIES and PROCEDURES**Regulatory Support Branch Project Manager**

- When an ANDA is accepted for filing, determines if any of the inspection criteria in this MAPP apply. If so, notifies the bioequivalence project manager.

Bioequivalence Project Manager

- Consults with the GBIB reviewers to identify analytical laboratories and clinical facilities that should be inspected.
- Prepares a memorandum to GBIB identifying the sites to be inspected, the reasons for the request, the BIMO goal date, and any additional information. This memorandum can be forwarded electronically to expedite the request.
- Monitors the status of inspection requests, obtains status information from GBIB, and alerts DBE management of any delays or potential problems.
- With the assistance of the DBE support staff, enters information into OGD's Study and Analytical Testing Sites (SATS) database.
- Updates OGD's Master Queue System and notifies the chemistry project manager of inspection request.
- Informs DBE management and the chemistry project manager of inspection results, and distributes the GBIB inspection summary memorandum and any other pertinent information.
- If a facility has been found in violation for a specific ANDA, checks other ANDAs (approved and unapproved) containing information from the same facility. Advises the Regulatory Support Branch to screen pending ANDAs for the suspect facility.
- Works with chemistry project managers to prepare necessary correspondence.

Chemistry Project Manager

- Monitors status of requested audits for pending ANDAs.
- Works with bioequivalence project managers to provide timely, accurate information for OGD approval meetings and correspondence.

Division of Scientific Investigations

- Provides the bioequivalence project manager and DBE reviewer with inspection history of facility to be inspected.
- Initiates an inspection assignment to ORA field staff.
- Participates in inspections to provide scientific expertise, as necessary.
- Provides DBE project manager with status reports on pending inspections, as requested.
- Provides DBE project manager with an inspection summary memorandum by the BIMO goal date.
- Recommends acceptance or nonacceptance of study data based on inspection results or any other applicable factors (e.g., compliance history of the facility).
- Provides quarterly updates to the Director, DBE, on the number of inspections requested and conducted (including percentage of work plan allotment).
- Ensures inspection planning and prioritization in accordance with ORA work plan and available resources in GLP/Bioequivalence Branch.

DBE Reviewer, Team Leader, and Division Director

- Identify and request directed inspection, with supervisory concurrence.
- Assess inspection information during review of applications and documents.

EFFECTIVE DATE

This MAPP is effective upon date of publication