

**CHAPTER 48 – BIORESEARCH MONITORING**

SUBJECT: Procedures for FDA Staff: In Vivo Bioavailability/Bioequivalence Studies (Clinical)		IMPLEMENTATION DATE: 05/01/2018
DATA REPORTING		
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
Product coding not required for biopharmaceutical establishments	48003A CLINICAL IN-VIVO BA/BE (ANDAS) 48003N CLINICAL IN-VIVO BA/BE (NDAS AND BLAS) 48003P CLINICAL PEPFAR ANDA BA/BE 48003Q CLINICAL IN-VIVO PEPFAR NDA BA/BE 48003B CLINICAL BA/BE - BIOSIMILARS	

**FIELD REPORTING REQUIREMENTS:**

To meet the established deadline(s) issued by the Center, notify the Center via the e-mail address identified in the assignment when Establishment Inspection Report (EIR), EIR attachments, exhibits, or any related correspondence is available in OSAR.

All EIRs should be completed in accordance with Field Management Directive (FMD) No. 86, Establishment Inspection Report (EIR) – Inspection Conclusions and District Decisions (<http://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM382035.pdf>).

When a Form FDA 483, “Inspectional Observations” (483) is issued, a copy should be sent to the Center contact and the Center’s e-mail mailbox, generally no later than 3 business days following the close of the inspection, or upon return from an international inspection.

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## PART I – BACKGROUND

### 1. Scope of Document

This Compliance Program (CP)<sup>1</sup> outlines procedures for FDA investigators who inspect domestic or international sites to ensure that the clinical portions of *in vivo* bioavailability (BA) and bioequivalence (BE) studies,<sup>2</sup> including studies with pharmacokinetic (PK), pharmacodynamic (PD), or clinical endpoints (CE) submitted to the Center for Drug Evaluation and Research (CDER), are conducted in a manner that ensures subject safety and data integrity, and to document study conduct in accordance with applicable regulations. As stated, this CP is designed to ensure studies are conducted using the highest laboratory standards and in accordance with applicable regulations. The acceptability of any study mentioned herein, including any repeat study, will be determined during application review.

This CP replaces the clinical portions of the prior CP, 7348.001, Chapter 48 – Bioresearch Monitoring Human Drugs titled, “In Vivo Bioequivalence,” issued in September 1999.

### 2. Introduction

New Drug Applications (NDAs) may rely on comparative BA studies or BE studies to demonstrate that a new drug formulation or a new route of administration of a drug has the same pharmacokinetic properties<sup>3</sup> as a reference, marketed product. Abbreviated New Drug Applications (ANDAs) rely on BE studies to demonstrate that a generic version of a drug has the same circulatory properties as an approved, reference listed drug (RLD). Regulations pertaining to these studies are principally found under 21 CFR 320.

*In vivo* BA/BE studies generally consist of two distinct components, clinical and analytical. The clinical component involves recruitment of subjects, administration of drug products to subjects, monitoring subject safety during the study, and collection of biological samples (usually blood samples) for safety and PK assessments. The analytical component involves processing the biological samples collected during the clinical phase of the study to measure drug concentrations present in those samples. Subsequently, the measured drug concentrations are used to generate PK parameters, which serve as the basis for determining bioavailability or bioequivalence between test and reference formulations.

In addition to BA studies and BE studies with PK endpoints, this program covers inspections of BE studies with PD endpoints or CE. These studies rely on pharmacodynamic measurements or comparative clinical efficacy rather than measurements of systemic drug or metabolite concentrations. PD endpoint assignments will usually contain a clinical and an analytical inspection. Examples of PD endpoint studies are clinical studies that use surrogate markers to measure drug

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<sup>1</sup> This document represents procedures for the Compliance Program.

<sup>2</sup> For the purpose of this CP, all listed study types fall under the general term *bioavailability/bioequivalence (BA/BE) studies*.

<sup>3</sup> Pharmacokinetic properties in the context of this CP mean area under the concentration curve (AUC) and the peak or maximum concentration (C<sub>max</sub>).

effects (e.g., skin blanching, forced expiratory volume (FEV1)), or immunogenic responses. CE assignments will usually only include a clinical inspection. Examples of CE studies that do not have an analytical component include subject-recorded symptoms in diary records, or investigator ratings of clinical response on some validated clinical response scale (e.g., the Psoriasis Area and Severity Index Score), or studies that measure change in skin color (for topically applied drug products). Clinical BA/BE studies may be conducted under an Investigational New Drug Application (IND; 21 CFR 312) and submitted to the Agency if they meet the criteria for IND. If the BA or BE studies are submitted to FDA under an IND, then EIRs and Form FDA 483s generated under this Compliance Program should cite the IND regulations. However, if the studies do not meet the criteria to obtain an IND under 21 CFR 312, then the studies must meet the requirements for 21 CFR 320 – Bioavailability and Bioequivalence Requirements.

### 3. History and Application of Bioavailability (BA) and Bioequivalence (BE) Regulations

On January 7, 1977, FDA issued final regulations in part 320 (21 CFR 320) establishing definitions and requirements for BA and BE studies (42 FR 1624). The regulations outline the requirements for the submission of *in vivo* BA and BE data as a condition for marketing a new formulation for an NDA (e.g., for a new drug under regulatory review or an already marketed drug product[s]), or a generic drug formulation submitted under an ANDA. 21 CFR 320 also provides information concerning the design and conduct of BA and BE studies. Additionally, the FDA has published draft Guidance for NDAs/INDs (*Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations, March 2014*)<sup>4</sup> and ANDAs (*Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, December 2013*)<sup>5</sup>.

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<sup>4</sup><http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf>

<sup>5</sup><http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm377465.pdf>

## PART II – IMPLEMENTATION

### 1. Objectives

The objectives of the *in vivo* BA/BE Bioresearch Monitoring (BIMO) Program are:

- To ensure the protection of the rights, safety, and welfare of human subjects participating in drug studies;
- To ensure the quality, integrity, and validity of clinical, analytical, and statistical data from BA/BE studies; and
- To ensure compliance with applicable FDA regulations and to identify significant deviations.

### 2. Regulated Industry: Clinical Sites

Clinical sites may include independent contract research organizations (CROs), or exist as part of a pharmaceutical company or other institutions such as hospitals or universities. Clinical sites conduct studies (including screening, dosing, and monitoring subjects' safety) to obtain biological samples for pharmacokinetic measurements, to measure pharmacodynamic responses, or to assess clinical efficacy. For inspections conducted under this CP, the clinical site that directs or performs the BA/BE study is generally the responsible entity, not an individual clinical investigator. A BA/BE study site may conduct the clinical portion of the study, the analytical portion of the study, or both.

### 3. Inspection Assignments

The CDER Office of Translational Sciences (OTS)/Office of Study Integrity and Surveillance (OSIS) receives requests for BA/BE study inspections directly from CDER offices that review drug applications. Directed inspections may also originate from complainants and informants (self-identified or anonymously) from the public and private sectors, who may report potential fraud at a site, or a site's deviations from practices that protect subject safety and data integrity. Additionally, OSIS monitors incoming drug applications that include BA or BE studies, to identify sites for surveillance inspections. All inspection assignments will be generated by the Center and issued to Office of Regulatory Affairs (ORA) for completion. Center staff may accompany ORA investigators during inspections as subject matter experts.

#### A. Scheduling an Inspection

ORA staff alone or ORA and OSIS staff together may conduct BA/BE clinical inspections. FDA staff may also participate in BA/BE inspections with non-FDA international regulators, domestically and internationally.

For ORA-only domestic and international inspections, ORA field investigators should schedule inspections of clinical BA/BE sites and provide estimated inspection dates to the

Center point of contact (POC). For joint ORA-CDER inspections, Center staff should collaborate with ORA field investigators to schedule the inspection.

The primary objective of the inspection is to evaluate the overall quality of subject safety and data integrity at the site. Except when inspections are otherwise directed, routine BA/BE clinical inspections require approximately one week of on-site inspection time. An amended assignment may be issued from the Center to add studies to the original assignment prior to the start of the inspection. Extension of the inspection is not anticipated; rather, the time spent conducting the inspection will be apportioned across all studies to assess compliance. When multiple studies are included in the assignment, there is no expectation that all aspects of study records for all studies identified in the assignment will be examined. A thorough reconciliation of all study records is not necessary, except in rare instances when those directions are indicated in the assignment.

In the event that serious deficiencies are noted, the ORA investigator's supervisor and the Center POC should be informed to determine to what extent the scope of the inspection should be expanded.

#### B. Announced vs. Unannounced Inspections

Domestic inspections are usually not announced prior to arriving at the site. Any instructions for announcing the inspection will be in the inspection assignment. Should ORA investigators have questions on whether or not to announce the inspection, the center POC should be contacted.

International inspections will normally be announced prior to arriving at the site, due to the logistics involved in conducting these inspections. If an unannounced international inspection is required, the Center will contact ORA Office of Bioresearch Monitoring Operations (OBIMO) headquarters (HQ) at [ORAHQ BIMO Inspection POC](#) to discuss.

Announcement of inspection to the site should not include application numbers, identity of test article, study numbers, and/or study sponsors.

#### C. Roles and Responsibilities While Conducting the Inspection

If Center staff accompany ORA on the inspection, the ORA investigator will be the Team Lead. For international inspections, the ORA investigator may be on detail to Office of International Programs (OIP) in one of the Global Offices and will still serve as the Team Lead for the inspection in accordance with Investigations Operations Manual (IOM) Section 5.1.2.5.

On inspections that include both Center and ORA staff, Center staff will:

- Provide on-site support to the ORA investigator, including coordinating or conducting parts of the inspection, as needed.

- Provide expert technical guidance, advice, information, and support to ORA investigators prior to, during, and after inspection, including contacting the ORA investigator when new information becomes available.
- Attend daily wrap-up meetings held by the inspection Team Lead to discuss findings and status of the inspection, and to ensure that appropriate evidence is collected to document observed violations when warranted.
- Draft appropriate sections of the EIR and provide to the ORA investigator within agreed upon timeframes.

The Center may arrange for a consultative teleconference immediately prior to an inspection if, for example, there is new information concerning the site or the studies assigned, or there are data concerns not previously conveyed to ORA in the assignment.



## PART III – INSPECTIONAL

This section outlines the minimum components to be included in a clinical BA/BE inspection. This is not meant to be an all-inclusive list of components that may be covered during an inspection. Deviations from the minimum components should be documented with appropriate explanation in the EIR.

### 1. Organization

#### A. Responsible Persons

- Identify the most responsible persons at the site and those who had leading roles at the time the studies were conducted.
- Document the names, titles, duties, roles, and responsibilities of these individuals in the EIR as per IOM 5.10.4.3.7.
- Issue the FDA 482 and FDA 483 to the most responsible person at the site.

#### B. Personnel

- Obtain a copy of the organizational chart that details the most responsible person at the site and displays the reporting relationship of all staff. If no organizational chart is available, obtain full details/information regarding reporting lines of management up to the Chief Executive Officer (CEO)/President and document in the EIR.
- Identify the person who should receive official correspondence.
- For inspections that involve an entity contracted to conduct a service, determine if there is a written agreement between the sponsor and the entity that describes the study responsibilities the entity will perform, and collect a copy if available.
- Obtain the name, address, email, and chairperson of the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) which oversees the inspected studies.
- Obtain the name, address, and email of third party entities, if any, who might be responsible for any aspect of the study, such as storage of the test article and reference product reserve samples.

#### C. Clinical Site and Equipment

- Evaluate the site layout and determine whether there are obstacles that could impede the custody, processing and /or storage of drug products, biological samples, or records.

- Evaluate whether the clinical site has adequate space to enable work flow, conduct of operations, and separation of functions. Evaluate areas such as bedrooms, dining rooms, recreational rooms, restrooms, and lockers.
- Inspect and evaluate the area where drug is stored.
  - Assess test article storage areas and procedures. Is there adequate space to prevent contamination and mix-up of test and reference drug products?
  - Describe the storage conditions in the EIR. Is the drug stored under lock and key? Is the drug in a controlled environment?
  - Determine who may access the storage areas and test articles. Is access restricted to authorized personnel?
  - Review temperature and humidity records to ensure test articles are stored and maintained per labeling requirements and study protocol.
  - If the test article(s) are controlled substances, determine if proper security is provided.
- Document and discuss potential threats to the integrity of the study due to the characteristics and/or design of the site (e.g., adjacent clinic rooms housing concurrent studies; open windows allowing ingress of unauthorized items such as food, drugs, etc., into clinic rooms; unsealed dropped ceilings or other areas prone to storage of non-permitted items).
- Document conditions in areas where sample collection, processing, and storage occur that may compromise study integrity, or contribute to the potential for sample loss, mix-up, contamination/degradation, etc., during storage, processing, and transit.
- Determine whether the site has a standard operating procedure (SOP) index and whether the current versions of SOPs are readily available in locations where relevant processes are conducted.
- Determine whether calibration and maintenance of equipment are performed in accordance with SOPs on scales, centrifuges, refrigerators, electrocardiography equipment, and other critical equipment used during clinical studies.
- Determine if the site's policy for handling visitors is adequate to prevent the consumption of, or passage of contraband or other non-permitted materials to study subjects.
- Evaluate whether the site's procedures to monitor and control the movement of study subjects between different clinical site areas (e.g., from bedrooms to restrooms, from

dining room to recreational room, etc.) is adequate to prevent the consumption of, or passage of non-permitted materials.

## 2. Study Administration and Responsibility

### A. Administrative

Although sites are not required to maintain a list of BA/BE studies, FDA investigators should request a list when possible. Most sites maintain a master list of previously completed and ongoing BA/BE or other studies. Request and obtain the following information, when available:

- Protocol number and protocol title, including the product name
- Research (IND) number, or marketing (NDA, BLA, ANDA) number, if available
- Name of sponsor (including government agencies and commercial sponsors)
- Name of the IRB/IEC with oversight responsibilities for each study
- Study dates (e.g., IRB initial approval, first screened subject, last subject follow-up, IRB investigations, IRB amendments, revisions of informed consent documents, and study records closure)
- Identify if the study is a pilot or pivotal study
- Identify if the study is a fasted or fed study
- Total number of subjects enrolled in each study
- Identify the administered dose or dose regimen used
- The addresses of all locations where study subjects were seen
- The method (e.g., telephone, memo, meetings) the sponsor used to provide the test articles, protocol, training and other obligations to the site personnel
- Whether the inspected site conducted the clinical only, analytical only, or both portions of the studies
- Study outcome (if known): e.g., did the study meet criteria for bioequivalence?

[Form FDA 1572](#) is only required when a clinical study is conducted under an IND. Do not request any 1572 information if a study was not conducted under an IND. If conducted under an IND, collect all signed Forms FDA 1572, including updated versions, if available.

## B. Study Responsibility

- Determine whether the authority for the conduct of various aspects of the study was delegated properly so that the lead clinical investigator retained control and knowledge of the study. Obtain a copy of the Delegation of Authority Log (or equivalent document) to show delegated tasks of the clinical study. If there are questions about appropriate delegation, obtain information (e.g., curriculum vitae, medical or other license, training records) about the qualifications of the person performing the task.
- Provide details in the EIR of the roles and responsibilities of personnel who worked on the study.
- Determine if the clinical investigator in the study is involved in the screening and dosing of human subjects. If the clinical investigator is not a physician, determine whether a physician was available to cover medical emergencies. Collect copies of resumes/curriculum vitae of the clinical investigator and sub-investigators, as well as copies of current credentials (i.e., medical licenses), as necessary, to support objectionable conditions observed.
- Determine if study personnel were adequately trained to conduct the protocol. Verify training certificates or other records.
- Determine if there were tests of inter-rater reliability for those studies requiring scoring or investigator judgment of a treatment response.
- Determine if the lead investigator at a clinical site discontinued the study before completion. If so, provide the reason. Document when the lead investigator or other staff notified the IRB and Sponsor regarding the study discontinuation.
- Determine the name and address of any clinical laboratory (in-house or external) performing clinical laboratory tests for qualifying (enrolling) and/or safety monitoring of study subjects. Determine the relationship between the clinical site and the clinical laboratories.
- Determine who is responsible for the delivery of the samples to the clinical laboratory (including packing and transport, temperature controls, etc.) and whether that site is equipped to perform each test specified. Determine if the clinical laboratory participates in proficiency testing, e.g., Clinical Laboratory Improvement Amendments (CLIA).
- Determine where and how subjects' biological samples are maintained prior to transporting them to the bioanalytical laboratory. Document that samples are handled according to the protocol immediately after collection. Describe how the temperature is maintained and monitored to preserve the integrity of the samples.

### 3. Subjects' Records and Documentation

#### A. Study Source Records

- Describe the study source data files in terms of their organization, condition, accessibility, and completeness. For example, is the information on study source records attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Determine whether there is adequate documentation that all study subjects were alive and actively participated during the study.
- Determine whether the study subjects met the eligibility criteria (inclusion/exclusion criteria).
- Compare the study source data at the clinical site with the background materials provided by the Center. If discrepancies are found, document them and review the case report forms for accuracy. Collect copies of the relevant portions of case report forms and source documents demonstrating any discrepancies or inconsistencies. Information to review may include, but is not limited to:
  - The total number of subjects entered into the study
  - The total number of dropouts from the study (identified by subject number)
  - The adverse events identified by subject number and a description of the adverse events
- Determine whether adverse events (AEs) and serious adverse events (SAEs) were accurately and adequately documented in the source records.
- Determine whether SAEs were reported to the appropriate entity (e.g., sponsor, IRB/IEC, FDA), and if they were reported within the specified timeframe (e.g., per applicable regulations and the study protocol). Refer to the guidance “Safety Reporting Requirements for INDs and BA/BE Studies (Dec 2012)”.
- Determine whether all concomitant therapies including OTC drugs or herbals and supplements were reported in the source records and the study report.
- Verify documentation of subjects' food intake during the study and compare to the requirements established in the protocol. Verify the subjects were fasted per the protocol requirement (when applicable). Document any evidence of consumption of non-permitted items (e.g., food, drinks, tobacco).

- Determine whether the number and demographics of subjects were in accordance with the study protocol.
- Determine whether the clinical site reported all dropouts, and the reasons for them to the sponsor.
- If study drugs were administered at a geographic location other than the clinical site (e.g., a clinical endpoint study where dosing was by either the subject or a caregiver), examine the subject diaries or other documentation associated with drug disposition and determine whether dosing was performed according to the protocol.

## B. Informed Consent

Document the following informed consent process information in the EIR:

- The name and title of the person responsible for obtaining consent from prospective study subjects, and/or the legally authorized representative(s) (e.g., clinical investigator, study coordinator, study nurse).
- Was the consent document provided in a language understandable to the subject?
- How was the informed consent process conducted (e.g., orally face-to-face, video, translator)?
- Is there documentation in the case history to show that a copy of the signed and dated consent was given to the subject or the subject's legally authorized representative?
- Was the appropriate IRB/IEC-approved version of the informed consent document used for all subjects?
- If the short form was used (21 CFR 50.27(b)(2)), was the informed consent process appropriately documented?
  - Did the subject, or the subject's representative, sign the short form?
  - Was a witness, who signed the short form, and the required copy of the summary, present?
  - Did the person actually obtaining the consent with the short form sign a copy of the summary as required by 21 CFR 50.27(b)(2)?
  - Is the case history documented to show whether a copy of the summary and the short form were given to the subject or the subject's representative?

- Review the IRB/IEC approval letter for the study. Did the IRB/IEC stipulate any conditions for the informed consent process and, if so, did the clinical site follow those instructions/stipulations?
- Did the subject or the subject's legally-authorized representative sign the informed consent document prior to entry into the study (e.g., prior to performance of any study-related tests, and administration of the test article)? If the subject did not sign the informed consent document, determine who signed it and that person's relationship to the subject. Describe how the clinical investigator determined that the person signing the informed consent document was the subject's legally-authorized representative.
- For pediatric studies, if required by the IRB/IEC, was assent obtained from the subjects in addition to the permission of the parent(s) or guardians in accordance with 21 CFR 50.55?
- Determine whether the consent document(s) complies with the elements in 21 CFR 50.25, 21 CFR 50.56, and ICH E6, and document any discrepancies or concerns.

#### C. Other Study Records

- Determine if the site maintains other records pertinent to the study, such as, but not limited to: administrative study files, correspondence files, sign-in logs, financial disclosure records, written agreements (e.g., transfer of obligations), and third party storage records. Document anything potentially relevant to the study conduct.
- Determine if the study was monitored, and if so, obtain a copy of documentation of monitoring, including logs of on-site monitoring visits, and documentation of any remote or centralized monitoring, the name/address of monitor(s), and examples of monitor reports and communications (if any), include follow up activities performed by the investigator in response to the monitor report findings.

#### 4. Test Article Accountability and Disposition

- Request the drug shipment records (invoices, bills of lading, airway bill, packing slips, etc.) and determine:
  - The number of drug shipment(s) that were received by the site
  - The date(s) of receipt and drug quantities received
  - The lot/batch numbers of drug received
  - The expiration dates

- If the site shipped any received drug to an external location, document the reason for shipping drug and request a copy of communications between the site and representatives from the external location.
- Request the drug accountability records (i.e., dosing logs) and determine if drug product was properly accounted for by reviewing the dispensing activities.
  - Reconcile amount of drug received with amount of drug dispensed and drug remaining.
  - Verify the actual time of dosing of drug product, and that drug dispensing and dosing was performed according to the randomization schedule, written procedures, and/or the study protocol.
  - Determine if the lot/batch numbers of drug received by the site, and dispensed to study subjects, match the lot/batch numbers reported in the final study report submitted to the FDA.
  - Determine how the dispensed test articles were transferred from secure storage areas to subject dosing areas.
  - Evaluate the site's SOPs for dispensation of test articles from bulk containers to subject dosing units/containers, if applicable.
- Observe test article storage, dispensation and subject dosing activities for on-going studies. Evaluate if practices adhere to current SOPs and relevant protocols.

#### **5. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis**

- Review the source documents and determine if sample collection was performed according to the study protocol and the applicable SOPs. Evaluate the sample collection area for accessibility, visibility and accuracy of clocks used during the study. Verify if a centrally synchronized clock was used to record the time of blood collection or personal watches were used by individual phlebotomists.
- Evaluate SOPs for positive identification of subjects that link study drug, subject, and sample collection times. This may include:
  - Evaluation of SOPs for subject identification prior to sample collection.
  - Review of information on sample collection tube labels.
  - Review of information on aliquot tube labels.
- Review the SOPs and source documents for sample collection.



- Determine if samples were collected at protocol-specified time points and within allowable time windows.
- Evaluate if samples collected outside of the protocol-specified range were properly documented and reported in the study report as protocol deviations.
- Determine if missing samples were clearly documented along with an explanation.
- Determine if protocol specific anti-coagulants and/or additives were utilized in sample collection tubes.
- Determine if protocol specific “special handling” procedures were followed and documented (e.g., collection under special light conditions, samples to be placed in an ice bath after collection, sample processing temperature, addition of stabilizers to blood samples after collection, etc.).
- Verify that blood clotting was done between 20°C and 37°C, not refrigerated.
- Review records for biological sample processing.
  - Verify if samples were handled per the protocol/SOPs.
  - Evaluate whether critical steps during sample processing were properly documented. For example, evaluate if the duration and settings of sample centrifugation and the time until freezer storage were consistent with specifications in the protocol.
  - Document the number of sample aliquots created from each sample.
  - Determine if protocol specific “special handling” procedures related to sample processing were performed and documented (e.g., process under special light conditions, samples received in the processing area in an ice bath, etc.).
- Review records for sample storage.
  - Review temperature records for freezer(s) where study samples were stored during the period between the first sample collection and the last sample shipment out to an analytical or other site.
  - Determine if samples were stored under the protocol-specified conditions.
  - Evaluate the site’s SOPs on monitoring the freezers, handling of freezer failure, back-up freezers, alarm system, etc.

- Document if frozen samples/aliquots were allowed to thaw (freeze/thaw cycle) at the clinical site. For example, the site may have a lengthy sample segregation procedure where samples are removed from the freezer, arranged by subject number and study period, and returned back to the freezer.
- Review records for shipping/transfer of biological samples from the clinical site to an analytical lab or other site.
  - Document the name and location of the site where the biological samples were transferred or shipped to.
  - Determine if records were sufficient to track transfer/shipment of samples from the clinical site to an analytical lab, CRO, or another site.
  - Review the correspondence between the clinical site and sample recipient, and the sample shipping records. Verify that date(s) of sample shipment match with those reported in the study report.
  - Review the correspondence, if any, between the clinical site and the sample recipient concerning the conditions of samples upon receipt and/or sample accountability.
  - Review temperature records during sample shipping/transfer. Verify that the protocol specific storage/temperature conditions were maintained during transfer/shipment.
- Review the records for the total number of samples collected, total number of samples sent, samples that were missing, lost or with an insufficient volume (if any), and shipping records of each shipment in case of multiple aliquots. Verify the records with those in the study report.
- Determine if the clinical site documented and evaluated subject samples that had hemolysis, lipemia, or other issues.
- Review calibration and maintenance records of equipment utilized to collect, process, and store biological samples (e.g., freezer calibration and mapping, data loggers, pipettes, centrifuges, etc.).
- Observe PK sample collection, processing and storage activities for on-going studies. Evaluate if practices adhere to current SOPs and relevant protocols.

## 6. Randomization

### A. Randomization Schedules

The study protocol usually defines the randomization requirements for the study. The randomization schedule specifies the treatment that a subject is intended to receive, but it does not guarantee the treatment that a subject actually received. The randomization schedule may be stored on paper or in electronic formats.

For blinded studies, a randomization schedule will identify a code for the treatment assigned to a subject without revealing the actual identity of treatment. However, an independent randomization schedule may not exist separately from the blinding codes (i.e., when unblinded, the blinding codes reveal the randomized treatments.) Although the randomization schedule can be used to “break the blind,” it is not a blinding code.

#### B. Inspection Procedures

- Document if the site had a randomization schedule and who had access to it.
- Determine if access to the randomization schedule was limited to authorized personnel. Identify individuals who received copies of the randomization schedule and/or blinding codes.
- If the randomization schedule was electronic, e.g., Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS), evaluate the security/controls of the computer system that accesses or hosts the randomization schedule. Determine who could access these computer systems. Determine whether audit trail features were enabled. Describe the system and security controls used, in the EIR.
- Compare the randomization schedule submitted to FDA with the randomization schedule maintained on site, if applicable. Note any discrepancies in the EIR and collect documentation if the randomization schedule was not followed.
- Evaluate post-study control and long term storage of the randomization schedule and describe in the EIR.

### 7. Blinding Codes

The study protocol usually describes blinding requirements for a blinded study. Blinding codes are used to track drug products – test, reference, or placebo (when applicable) – that are given to each study subject without revealing the product identity to the subject, and/or the study personnel. The blinding code is usually generated by the packager of the test, reference, and placebo drug products during packaging.

The blinding code may exist in different forms, including (1) two part, tear-off “scratch-off” labels that are attached to kits containing the drug products; (2) sealed “code-break” envelopes that are included with each shipment of drug product sent to clinical sites; and (3) an electronic version maintained in the IWRS or IVRS systems.

For blinded studies that utilize two-part “scratch-off” labels, one part of the label remains on the drug unit and the other is typically attached to the subject’s case report form at the time of drug administration. The ORA Investigator will “unblind” the product administered to each study subject during the inspection by scratching the film off the label on each subject’s case report form. For studies utilizing “code-break” envelopes, the investigator should open the “code-break” envelopes used to identify each subject’s administered treatment. The “code-break” envelopes are distinct from the envelope containing the paper randomization schedule.

A. Access to Blinding Codes

- Determine how and when blinding codes were provided to the clinical site.
- Document whether the blinding codes remained at the clinical site throughout the duration of the study, and whether the blinding codes remained sealed until the FDA inspection.
- Report and evaluate the access to, handling of, and storage of the blinding codes during the conduct of the study and after study completion.
- Evaluate procedures in place to determine whether the appropriate individuals were blinded to study treatments and they remained blinded throughout the study per protocol (e.g., investigator, study staff, study subjects, etc.).
- If any study subjects were un-blinded during the study, document the subject identifier(s), who broke the blind, when the blind was broken, and the rationale for breaking the blind in the EIR.

B. Breaking the Blind During the Inspection (Performed by ORA investigator)

- For closed studies, the ORA investigator must unblind the blinding code to assure that study subjects received the assigned treatment that was reported to FDA in the study report. To unblind a study, locate and “break” the blinding codes to reveal the identities of treatments for each of the study subjects.
- ORA investigators usually do not unblind ongoing studies. However, there could be safety reasons that come to the attention of the ORA investigator or the Center that would support unblinding an ongoing study. If questions arise concerning unblinding ongoing studies, direct them to the Center POC for the assignment.
- If the study you are auditing is blinded and blinding codes are not available, notify the Center POC in the assignment immediately.

- If “code-break” envelopes were used to blind the study, open the envelope and record the date and your initials on the outside of the envelope, and copy (or photograph) the envelope for an exhibit to the EIR.
- If the blinding codes are in the form of scratch-off labels, remove the covered part of the label (e.g., scrape the film covering the printed codes with a coin or another object) to reveal the treatments. Record the date and your initials on the label or on the document where the label is attached, indicating that you un-blinded the treatment codes.
- If the blinding code is electronic and contained within IVRS or IWRS, request the site’s management to access the blinding code and print a copy. Also request documentation (e.g., electronic audit trail) supporting whether the randomization schedule and blinding code were accessed during the study, and if so, by whom and when.
- If the blinding codes were previously unblinded or unsealed, determine who, when, and why the blind was broken.
- After unblinding, compare the administered treatments with the treatments that subjects were randomized to receive (using the randomization schedule, if there is one). Document any discrepancies and collect relevant exhibits.
- Collect a copy of all unblinded blinding codes, randomization schedule, and dosing logs (as applicable); include as exhibits in the EIR.

## 8. Reserve Samples

### A. Selection, Identification, Storage, and Collection

- Review the site’s process for selecting reserve samples of the drug product and request a copy of their SOP, if available.
- If the reserve samples are stored at the clinical site, verify that the reserve samples are stored under conditions consistent with the product labeling and with access limited to authorized personnel.
- If the reserve samples are stored with a third party storage site:
  - Request a copy of the contract with the third party.
  - Request that the clinical site arrange for shipment of reserve samples for the studies inspected, to the clinical site for collection.
  - Determine, to the extent possible, if the third party stored the reserve samples according to the storage conditions on the product labeling.

- Determine if the clinical site received adequate quantity of test and reference products to conduct the study and retain reserve samples.
- For closed blinded studies, break the blinding codes to reveal the identity of the reserve samples.
- Verify that reserve samples are adequately identified so that each sample can be positively identified as having come from the same sample used in the inspected study.
- Verify that reserve samples of the test and reference products were randomly selected by the clinical study investigator (or designee) from each shipment of drug products to the clinical site where the BE study was performed. If the clinical site received multiple drug shipments for the study, verify that reserve samples were randomly selected and retained from each drug shipment used in the study. Verify that reserve samples from different shipments were labeled and separated, as necessary, to identify the reserves selected from each shipment.
- Verify that the lot numbers on the reserve samples match those in the study report submitted to FDA for the inspected study(ies).
- If directed in the assignment, collect reserve samples for the studies identified in the assignment for FDA analysis.
- If reserve samples were not retained, or questions arise related to the quantity retained, notify the Center POC in the inspection assignment.
- The quantity of reserve samples to be collected is based on the dosage formulation. The minimum quantity of reserve samples (test and reference product) to collect is shown below:

<b>Dosage formulation</b>	<b>Minimum number of units to collect from each site</b>
Oral solid dosage forms (e.g., tablets, capsules)	30 units each of test and reference
Topical creams, ointments, and gels	3 units each of test and reference
Inhalers, pumps, and vials for injection	3 units each of test and reference
Any dosage form in block design	1 block (containing kits of test and reference)

- Collect a quantity that has at least the amount specified above. Do not open and subsample bottles. For example, if tablets are kept in bottles of 100, collect one bottle. If tablets are kept in bottles of 10, collect three bottles.
- If the test and reference products were packaged in a single container, and part of the container was used during the study, the remaining test and reference products in the original container can provide reserve samples.
- Issue FDA Form 484, Receipt for Sample (to management, clinical investigator, or designee) describing the samples collected; follow IOM 4.2.5.
- Obtain a properly completed, signed and dated Form FDA 463a, Affidavit, or a statement on site company letterhead attesting that the test and reference product reserve samples are representative of those used in inspected BA/BE studies, and that they were stored under conditions specified in accompanying records, e.g. protocol or labeling.
- If the assignment memo instructs the investigator NOT to collect reserve samples, confirm that the reserve samples were retained for the specific BA/BE study(ies), and verify the lot/batch numbers on the reserve sample containers with those in the study report submitted to FDA.

#### B. Shipment of Reserve Samples

- Shipping conditions for reserve samples should be in accordance with the product label and/or storage conditions described in the study protocol.

**Complete Sample Collection Report(s) in FACTS or the appropriate electronic system; follow the IOM and ORA guidance. The collection report (C/R) need not be completed in its entirety prior to shipment of the sample to the ORA Detroit Laboratory (DETL) (see IOM 4.4.10.3 "Preparation"). All samples should be officially sealed before they are shipped to DETL (IOM 4.5.4 "Official Seals"). The minimum required data can be entered into FACTS, or the appropriate electronic system, and the C/R can be finished at a later date.**

- Collect photographs of the reserve sample product containers. Ensure writing is legible in the photographs, including product details, manufacturer, lot/batch numbers, production dates, expiration dates, etc.
- Use the IOM and ORA-specific sample collection/shipping forms to ship samples, in their original containers, to the person and address outlined in the assignment memo. For questions on shipping conditions for products that are not stored at ambient temperature,

please contact the assignment POC, and/or ORA/DETL: (313) 393-8207, for additional information.

- For reserve samples collected during international inspections, include a letter to U.S. Customs (template to be provided by the Trip Planner).
  - Describe in detail the name of the drug (brand and/or generic), type and size of container, number of containers (bottles/vials etc.), quantity of drug in each, NDC numbers, special handling requirements (i.e. temperature/light sensitive, etc.).
  - Include wording such as: “Investigational Drug Product” or “Investigational Drug Samples”.
  - Include a statement to contact US FDA if the official seal must be broken by US Customs. An FDA officer should be present to witness, if possible.
  - Include your name and contact information.
  - Place one copy inside, attached to the samples. Include a second copy outside the shipping package. Keep one copy for your records.
- Determine if the samples to be collected are considered controlled substances. Certain test and reference articles are considered controlled substances in a foreign country but not in the U.S., and vice versa.
  - Request a copy of Form DEA-223, *Controlled Substance Registration Certificate*, from the Trip Planner as soon as you determine applicability. This may happen before or during the inspection.
  - Place one copy inside the shipping package, attached to the samples.

## 9. Review of Electronic Data

- Determine whether electronic data and data collection methods were used in the study as specified in the study protocol or SOPs.
- Determine whether electronic records and/or electronic signatures are required by predicate rules, and/or are used in place of paper records or handwritten signatures (or relied upon to perform regulated activities).
- Describe any computerized system(s) used by the study site(s) to generate, collect, or analyze data (e.g., stand-alone personal computer, web-based system, hand-held computers).
- Do electronic records and data meet the requirements applicable to paper records?



- Determine how data are transmitted to the sponsor or another CRO.
- Determine how the electronic data were reviewed during monitoring visits. Document unauthorized changes or modifications made to original data, and by whom.
- Determine who at the site has access rights to make original data entries and/or changes.
- Verify that the analytical software used for hematology, clinical chemistry and urinalysis (etc.) are calibrated and qualified for the study purpose.
- Verify that the original data captured in process are available for all the analyses.
- Determine whether the site maintains audit trail(s) for all the electronically captured data, and, if so, whether the audit trail(s) are available for review.
- For electronic Case Report Forms (eCRFs), verify the following:
  - An audit trail captures information related to the creation, modification, or deletion of electronic records, including date, time, and responsible personnel.
  - Audit trail captures information for all eCRFs for all subjects.
  - Compliance with 21 CFR Part 11.
- Review electronic medical forms (if applicable).
- Evaluate how the computerized systems are secured/protected (e.g., password protection, access privileges, user identification).
- Determine whether there is backup, disaster recovery, and/or contingency plans to protect against data loss.
- Determine if the site has an SOP for the system maintenance and validation.
- Describe how error messages or system failures were reported and whether any corrective actions were taken.

#### **10. International Inspections of Clinical BA/BE Study Sites**

FDA will accept data from clinical BA/BE studies conducted outside the United States that conform with good clinical practice and where the data can be validated through an onsite inspection. See 21 CFR 312.120 and 314.106.

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Generally, when an inspection involves a site that is located outside of the United States, the inspection is conducted the same as a clinical inspection within the United States. One exception is FDA investigators should not issue a Form FDA 482 to open an inspection at an international location. See IOM 5.1.3.

## **11. Reporting**

If significant violations are disclosed during the inspection, prepare a Form FDA 483, Inspectional Observations, to issue to the most responsible individual. See IOM 5.2.3. Once issued, send the 483 to the Center as specified in the assignment. If the observations made during the inspection warrant an OAI classification (e.g., lack of reserve samples), inform the Center as soon as possible.

**PART IV – ANALYTICAL**

Not applicable to this Compliance Program

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**PART V – REGULATORY/ADMINISTRATIVE STRATEGY**

If significant violations are observed during the inspection, prepare a Form FDA 483, Inspectional Observations, to issue to the most responsible individual. Form FDA 483 observations should be factual statements. Avoid recording unsupported opinions on a Form FDA 483. Observations recorded on a Form FDA 483 should include supporting documentation attached to and discussed within the EIR whenever possible.

Study sites should conduct clinical BA/BE studies using good clinical practice to ensure subject safety and data integrity. Significant inspectional observations may not have specific, corresponding CFR regulations that support them. When observations are made with a potential to have significant impact on subject safety or data reliability, but there are no corresponding CFR regulations, collect the evidence related to these observations, discuss the observations with the most responsible individual and document the observations, discussion, and evidence in the EIR.

When a BA/BE study is conducted under an IND, significant violations of 21 CFR 312 should be included on a Form FDA 483. See 21 CFR 320.31. BA/BE studies may be exempt from 21 CFR 312 when certain conditions are met. See 21 CFR 320.31(d). It is important to determine whether the study was conducted under an IND when preparing to conduct the inspection.

When significant violations related to IRB review (21 CFR 56) or informed consent (21 CFR 50) requirements are observed, contact the center point of contact listed in the assignment to discuss.

Center reviewers will evaluate Form FDA 483 observations, as well as any discussion items and evidence contained in the EIR, and consider the impact of the site's actions (frequency, scope, and severity) on acceptability and reliability of study data. There are often varying gradations in the severity among similar Form FDA 483 examples. The specific observation(s) and information collected should support the Center's evaluation of the reliability and acceptability of data for FDA decision-making purposes.

## PART VI – REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

### 1. FDA Guidance Documents and References

#### A. FDA Laws

Federal Food, Drug, and Cosmetic Act (FFDCA)

(<https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/FederalFoodDrugandCosmeticActFDCAAct/FDCAActChapterVDrugsandDevices/default.htm>)

#### B. Relevant 21 CFRs

- Part 320 – Bioavailability and Bioequivalence Requirements  
(<http://www.ecfr.gov/cgi-bin/text-idx?SID=93111e2feefbb29bcaba7cb37a13aa9b&mc=true&node=pt21.5.320&rgn=div5>)
- Part 312 – Investigational New Drug Application  
(<http://www.ecfr.gov/cgi-bin/text-idx?SID=93111e2feefbb29bcaba7cb37a13aa9b&mc=true&node=pt21.5.312&rgn=div5>)
- Part 50 – Protection of Human Subjects  
(<http://www.ecfr.gov/cgi-bin/text-idx?SID=93111e2feefbb29bcaba7cb37a13aa9b&mc=true&node=pt21.1.50&rgn=div5>)
- Part 56 – Institutional Review Boards  
(<http://www.ecfr.gov/cgi-bin/text-idx?SID=93111e2feefbb29bcaba7cb37a13aa9b&mc=true&node=pt21.1.56&rgn=div5>)
- Part 11 – Electronic Records; Electronic Signatures  
(<http://www.ecfr.gov/cgi-bin/text-idx?SID=93111e2feefbb29bcaba7cb37a13aa9b&mc=true&node=pt21.1.11&rgn=div5>)

#### C. Relevant FDA Guidelines, Guidance Documents, and Inspection Guides

For an overview of bioavailability, bioequivalence, and other clinical pharmacology studies, please refer to the available FDA Guidance Documents referenced below.

- Guidance for Industry: Bioanalytical Method Validation, 2001  
(<http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf>)
- Draft Guidance for Industry: Bioanalytical Method Validation, 2013  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>)

- Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf>)
- Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, 2002 (<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070241.pdf>)
- Draft Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products, 1998 (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf>)
- Draft Guidance for Industry: Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection, 2013 (<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm360484.pdf>)
- Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, 2003 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070111.pdf>)
- Draft Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations, 2014 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf>)
- Draft Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application, 2013 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf>)
- List of FDA Guidance Documents (<http://www.fda.gov/RegulatoryInformation/Guidances/>)
- Investigations Operations Manual (<http://www.fda.gov/ICECI/Inspections/IOM/>)
- Field Management Directive (FMD-86): (<http://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM382035.pdf>)
- Form FDA 483: (<http://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM127434.pdf>)

- Form FDA 482:  
(<http://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM127428.pdf>)

## 2. Program Contacts

When technical or scientific questions or issues arise from a specific assignment, or if additional information is required about a specific assignment, consult the Center POC identified in the assignment.

For operational questions, contact:

- Office of Regulatory Affairs (ORA)/Office of Medical Products and Tobacco Operations (OMPTO)/Office of Bioresearch Monitoring Operations (OBIMO) –  
[ORAHQ BIMO Inspection POC@fda.hhs.gov](mailto:ORAHQ_BIMO_Inspection_POC@fda.hhs.gov)
- Center for Drug Evaluation and Research (CDER)/Office of Translational Sciences (OTS) Office of Study Integrity and Surveillance (OSIS) - [CDER-OSIS-BEQ@fda.hhs.gov](mailto:CDER-OSIS-BEQ@fda.hhs.gov)

For questions about the BE compliance program, contact:

- Center for Drug Evaluation and Research (CDER)/Office of Translational Sciences (OTS)/Office of Study Integrity and Surveillance (OSIS) - [CDER-OSIS-BEQ@fda.hhs.gov](mailto:CDER-OSIS-BEQ@fda.hhs.gov)

For questions about sample distribution, contact:

- Office of Regulatory Affairs (ORA)/Office of Regulatory Science (ORS) -  
[ORAORSMPTSCIENTIFICSTAFF@fda.hhs.gov](mailto:ORAORSMPTSCIENTIFICSTAFF@fda.hhs.gov)

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## PART VII – CENTER AND ORA HQ RESPONSIBILITIES

### 1. CDER Review Divisions – OND, OGD, OPQ, and OCP

- Request directed inspections of selected studies, including BA/BE studies.
- Send consults for directed inspections to OSIS. The inspection consults contain the site's name, study(ies) to be inspected, application number(s), and specific details about the Agency's concern with the site's operations or study data.
- Answer technical questions and provide technical guidance related to the application to the ORA investigator and the OSIS subject matter expert (SME) prior to, during, and after the inspection.
- Review Divisions receive EIR reviews from OSIS, and have the ultimate authority to accept or reject study data based on inspection findings.

### 2. OSIS

- For directed inspections, receives an inspection consult and drafts assignments.
- For surveillance inspections, identifies the sites to be inspected, based on the current OSIS surveillance model.
- Drafts and issues assignments and includes contact information for the OSIS SMEs and relevant FDA reviewer.
- Provides expert technical guidance, advice, information, and support to the ORA investigator prior to, during, and after inspection.
- Occasionally accompanies the ORA investigator on the clinical inspection.
- For a team inspection, OSIS will draft sections of the EIR and provide to the ORA investigator within agreed upon timeframes.
- May contact the ORA investigator for clarification on inspection findings.
- Reviews EIR and provides recommendations to Review Divisions regarding the reliability and/or acceptability of study data.
- Enters the final classification into the appropriate electronic system and notifies ORA.
- May issue Untitled Letters to inspected sites following voluntary action indicated (VAI) or no action indicated (NAI) final classifications.



- Promptly forwards to the ORA field investigator, and to any appropriate division personnel, copies of post-inspection correspondence issued to the inspected party.

### 3. **OSI**

- Receives potential official action indicated (OAI) cases from OSIS.
- Reviews the EIR for potential OAI cases to determine if the inspection observation(s) warrants compliance/enforcement action. Takes compliance/enforcement action as warranted.
- In collaboration with OSIS and ORA, may determine that a follow-up inspection of an inspected site is necessary to verify whether the site has implemented any proposed corrective plans, and that the site is in compliance with applicable regulations.

### 4. **Office of Regulatory Affairs (ORA)**

- ORA OBIMO HQ receives assignment from OSIS via ORAHQ BIMO Inspection POC email. OBIMO assigns to the appropriate division (OBIMO Division I (East) or OBIMO Division II (West)). OBIMO Division management assigns the inspection to an ORA investigator.
- International assignments are addressed to OBIMO and sent via ORAHQ BIMO Inspection POC email. OBIMO HQ issues the assignment to the ORA investigator selected to conduct the foreign inspection.

**ATTACHMENT A – Abbreviations and Acronyms List****A**

AE	Adverse event
ALCOA	Attributable, legible, contemporaneous, original, and accurate
ANDA	Abbreviated new drug application

**B**

BA	Bioavailability
BE	Bioequivalence
BIMO	Bioresearch monitoring

**C**

C/R	Collection Report
CDER	Center for Drug Evaluation and Research
CE	Clinical endpoint
CEO	Chief Executive Officer
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CP	Compliance program
CRO	Contract research organization

**D**

DEA	Drug Enforcement Agency
DPA	Division of Pharmaceutical Analysis (CDER/OPQ/OTR/DPA)

**E**

eCRF	Electronic Case Report Form
EIR	Establishment Inspection Report
etc.	Et cetera

**F**

FACTS	Field Accomplishments and Compliance Tracking System
FDA	Food and Drug Administration

FEV1 Forced expiratory volume during the first second of a forced expiratory maneuver, started from the level of total lung capacity  
FFDCA Federal Food, Drug, and Cosmetic Act  
FMD Field Management Directives  
FR Federal Register

**G**

GCP Good Clinical Practice

**H**

HQ Headquarters

**I**

IEC Independent Ethics Committee  
IND Investigational New Drug Application  
IOM Investigations Operations Manual  
IRB Institutional Review Board  
IWRS/IVRS Interactive Web Response System/Interactive Voice Response System

**N**

NAI No Action Indicated  
NDA New Drug Application  
NDC National Drug Code

**O**

OAI Official Action Indicated  
OCP Office of Clinical Pharmacology  
OGD Office of Generic Drugs  
OIP Office of International Programs  
OMPTO Office of Medical Products and Tobacco Operations  
OND Office of New Drugs  
OPQ Office of Pharmaceutical Quality  
ORA Office of Regulatory Affairs  
OSAR Online Search and Retrieval  
OSI Office of Scientific Investigations

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OSIS	Office of Study Integrity and Surveillance
OTR	Office of Testing and Research
OTS	Office of Translational Sciences

**P**

PD	Pharmacodynamic
PK	Pharmacokinetic
POC	Point of contact

**Q**

QC	Quality Control
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**R**

RLD	Reference Listed Drug
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**S**

SAE	Serious Adverse Event
SME	Subject Matter Expert
SOP	Standard operating procedure

**V**

VAI	Voluntary Action Indicated
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**Change History**

Item	Change	Date
Document	Initial Issuance	05/01/2018