CHAPTER 48 - BIORESEARCH MONITORING: HUMAN DRUGS

SUBJECT:	IMPLEMENTATION DATE
IN VIVO BIOEQUIVALENCE	**10/01/99**
	COMPLETION DATE: Continuing

DATA REPORTING

PRODUCT CODES	PROGRAM ASSIGNMENT CODES
Product coding not required for biopharmaceutical analytical and clinical establishment types.	48001 Human Drugs (Use for both foreign and domestic inspections)

FIELD REPORTING REQUIREMENTS

One copy of each EIR and all exhibits covering clinical testing and analytical testing will be forwarded to the GLP and Bioequivalence Investigations Branch (GBIB), Division of Scientific Investigations (DSI), HFD-48, for final classification. When the clinical and analytical portions of a study have been performed at separate locations, separate reports should be prepared and submitted for each site. Completion of Attachment B is required for each study and for each study site subjected to inspection. Also complete Part I & II of Attachment A for clinical facilities, and Parts I and III of Attachment A for analytical facilities.

The District should immediately notify GBIB (via e-mail, FAX, or telephone) of any significant adverse information related to a firm that could affect the agency's new product approval decisions.

PART I - BACKGROUND

Bioequivalence studies are generally performed to support Abbreviated New Drug Applications (ANDAs) and New Drug Applications (NDAs). In ANDAs, approvals of generic versions of innovator drug products are normally based on results of bioequivalence studies. In NDAs, bioequivalence studies are frequently conducted to link the to-be-marketed formulation(s) with the clinical trial formulation(s), and to support approval of a new formulation or a new route of administration of a marketed drug.

The Bioequivalence Regulations (21 CFR 320) of January 7, 1977 and the amendments of April 28, 1992, April 28, 1993, and January 5, 1999, stated the requirements for submission of in vivo bioavailability and bioequivalence data as a condition of marketing a new (i.e., new chemical compound; new formulation, new dosage form, or new route of administration of a marketed drug) or generic drug. 21 CFR 320 also provided general guidance concerning the design and conduct of bioavailability/bioequivalence studies. However, it should be noted that bioequivalence studies conducted to support ANDAs involve testing of already approved drug entities and therefore, generally do not require an investigational new drug application (IND)[*]. The Food and Drug Administration (FDA) does not require bioequivalence studies on pre-1938 drug products.

Bioequivalence studies involve both a **clinical component** and an **analytical component**. The objective of a typical bioequivalence study is to demonstrate that the test and reference products achieve a similar pharmacokinetic profile in plasma, serum and/or urine. Bioequivalence studies usually involve administration of test and reference drug formulations to 18-36 normal healthy subjects, but patients with a target disease may also be used. Formulations to be tested are administered either as a single dose or as multiple doses. Sometimes formulations can be labeled with a radioactive component to facilitate subsequent analysis. In a bioequivalence study, serial samples of biologic fluid (plasma, serum, or urine) are collected just before and at various times after dose administration. These samples are later analyzed for drug and/or metabolite concentrations. The study data are used in subsequent pharmacokinetic analyses to establish bioequivalence.

This program will cover both the clinical and analytical components of bioequivalence studies. In some situations the clinical and analytical facilities for a study may be part of the same

[*]However, sponsors of generic drugs need to file INDs when studies involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product [21 CFR 312.2(b)(iii)].

organization and therefore may be covered by one District. In other situations, the two facilities may be located in different Districts. For the purpose of this program, the District where the clinical facility is located will be referred to as the Clinical Component District, and the District where the analytical facility is located will be referred to as the Analytical Component District.

PART II - IMPLEMENTATION

OBJECTIVES

1. To verify the quality and integrity of scientific data from bioequivalence studies submitted to the Center for Drug Evaluation and Research (CDER);

2. To ensure that the rights and welfare of human subjects participating in drug testing are protected; and

3. To ensure compliance with the regulations (21 CFR 312, 320, 50, and 56) and promptly follow-up on significant problems, such as research misconduct or fraud.

PROGRAM MANAGEMENT INSTRUCTIONS

A. Coverage

1. Clinical Facilities[**]

Clinical facilities conduct bioequivalence studies (including screening, dosing, monitoring of subjects' safety, etc.) in order to obtain biological specimens (e.g., plasma, serum, urine) for analysis of drug and/or drug metabolite concentrations.

Facilities that conduct bioequivalence studies in human research subjects for pharmacodynamic measurements (i.e., clinical or pharmacological effects) are also included.

2. Analytical Facilities[**]

[**]It is important to draw distinctions between a clinical laboratory, a clinical facility, and an analytical facility. A clinical laboratory generally uses blood and/or urine to conduct medical screening or diagnostic tests such as blood counts (CBC), liver function tests (ALT, AST) or kidney function (BUN, creatinine clearance, etc.) tests. Clinical laboratories are usually certified under programs based on the Clinical Laboratories Improvement Act (42 USC 263a), and are not routinely inspected by the FDA. A clinical laboratory may be visited during a bioequivalence study audit to confirm that reported screening or diagnostic laboratory work was indeed performed. The clinical facility and the analytical facility as described above are the laboratories that will be routinely inspected under this program.

Analytical facilities analyze biological specimens collected in bioequivalence studies and other human clinical studies for drug and/or metabolite concentrations to measure the absorption and disposition of the drug.

3. Clinical and Analytical Investigators

The clinical investigator in a bioequivalence study is involved in the screening and dosing of human subjects, and will ordinarily be a physician. Ph.D. clinical pharmacologists and Pharm.D.'s are acceptable if a physician is available to cover medical emergencies. The clinical investigator may also perform pharmacodynamic measurement(s) and evaluation activities of clinical or pharmacological endpoints.

The analytical investigator in a bioequivalence study is the scientist in the analytical facility responsible for assay development and validation, and analyses of biological specimens, e.g., Scientific Director or Laboratory Director.

B. Process

Facilities where bioequivalence studies are conducted are to be inspected under this compliance program. The inspection should include a review of the clinical and analytical testing procedures plus an audit of source data from one or more specified studies.

Assignments under this program are of two basic categories:

1. Directed Data Audit - Covers studies and/or facilities in which gross problems/inadequacies are suspected (including, but not limited to research misconduct**,** or fraud). Such assignments require rapid evaluation and resolution.

2. Routine Data Audit - Covers (1) pivotal studies under current review in the Divisions of Pharmaceutical Evaluation I (HFD-860), II (HFD-870), or III (HFD-880) in the Office of Clinical Pharmacology and Biopharmaceutics (HFD-850); and (2) bioequivalence studies supporting the approval of a generic product.

Assignments will be issued by the GLP and Bioequivalence Investigations Branch (GBIB, HFD-48) to the field. For each assignment, a scientific reviewer in GBIB with expertise in chemical assays, bioavailability/bioequivalence, biopharmaceutics, pharmacokinetics or pharmacodynamics will (1) assist the field in coordinating and as necessary conducting the inspection; (2) provide technical guidance and on-site support to the field as necessary; and (3) serve as the liaison between the field investigator(s) and the Review Divisions in CDER.

GBIB will generate assignments under this program based on information provided by the Review Divisions in CDER. GBIB will send assignment memos to the Director of the Investigations Branch in the appropriate District office(s) (for domestic inspections), or the Division of Emergency and Investigational Operations, International Operations Group (for foreign inspections).

The assignment memo will include the following information:

(a) NDA/ANDA number
(b) Name of the drug
(c) Name of the sponsor
(d) Study/protocol number(s)
(e) Title of each study identified for inspection
(f) Address(es) of the clinical and analytical facilities
(g) Instructions on inspectional areas
(h) Deadline(s) such as preferred date for completion of inspection, Review Division action goal date, or the user fee goal date, etc.
(i) The name of the GBIB contact.

After a field investigator has been assigned, background material (including source data from the specific study(ies)) will be forwarded to the field investigator. In the event that a clinical or analytical facility designated for inspection is found to be located elsewhere, the district should contact GBIB immediately in order to redirect the assignment.

For all inspections in which a Form FDA-483 is issued, a copy of the Form FDA-483 should be forwarded by facsimile to the GBIB contact or the Branch Chief of GBIB.

PART III - INSPECTIONAL

OPERATIONS

A. Inspectional

A complete inspection report under this compliance program consists of inspectional findings covering:

(1) Clinical testing, which includes the adequacy of facilities and procedures utilized by the clinical investigator along with a data audit of the specific study(ies) identified by GBIB; and

(2) Analytical testing, which includes the adequacy of the facilities, equipment, personnel, and methods and procedures utilized at the analytical facility including an audit of the method validation and analytical data for the study(ies) identified by GBIB.

Attachment A provides guidance on the clinical and analytical portions of the inspection report. Attachment B, Bioequivalence Testing Report Summary, must be completed for each study audited. In cases where the clinical and analytical facilities are not in the same location, each inspection team will complete the appropriate parts of Attachment A for the facility inspected. Close communication among all parties is critical in cases where two different inspectional teams are involved in the coverage of a study.

Attachment A identifies the information that must be obtained to determine if the facility is operating in a satisfactory manner. The inspection should be sufficient to describe the usual practices for each point identified in Attachment A and to review the appropriate documents related to the adequacy of the equipment and methods used to obtain data. Each FDA investigator should develop additional information as the facts evolve (subject to the limitations in B and D below).

A full narrative report of any deviations from existing regulations is required. Deviation(s) must be documented sufficiently to support legal or administrative action. For example, any records containing data that are inconsistent with data submitted to FDA should be copied and the investigator should identify the discrepancy. Generally, serious violations will require more extensive documentation. Discuss the situation with your supervisor and the appropriate Center contact prior to embarking on this type of coverage.

B. Investigational

If inspections of institutional review boards and/or clinical laboratories are indicated, contact your supervisor and GBIB contact for guidance prior to initiating the inspection.

C. Refusals

If access to, or copying of records is refused for any reason, promptly contact your supervisor so that the GBIB contact can be advised of the refusal. Send follow-up information via EMS to GBIB, and ORO contacts. Follow the same procedure when it becomes evident that delays by the firm constitute a de facto refusal. [See also Inspection Operations Manual, Section 514.]

If actions by the firm take the form of a partial refusal for inspection of documents or areas to which FDA is entitled under the law, call attention to 301(e) and (f) and 505(k)(2) of the FD&C Act; if the refusal persists, telephone your supervisor and the GBIB contact for instructions.

If the proper course of action to deal with a refusal cannot be resolved expeditiously by GBIB or ORO, GBIB will notify the Bioresearch Program Coordinator (HFC-230).

D. Findings

1. If you encounter serious problems with the data, methodology, quality control practices, etc., continue the originally assigned inspection, but contact GBIB for advice on possibly expanding the inspection. GBIB will determine if an in-depth inspection, involving additional bioequivalence studies, should be initiated.

2. If you encounter questionable or suspicious records and are unable to review or copy them immediately and have reason to preserve their integrity by officially sealing them, contact your supervisor immediately for instructions. Procedures exist for your District to clear this type of action by telephone with the ORA/Bioresearch Program Coordinator (HFC-230). See Inspection Operations Manual, Section 453.5.

3. Issuance of a Form FDA-483, Inspectional Observations, is appropriate when (1) practice at the clinical site deviates from the standards for conduct of a clinical study as set forth in 21 CFR 312 and 320 and 361, (2) practice at the analytical site deviates from the standards of laboratory practices as set forth in 21 CFR 320, and (3) discrepancies have occurred between source data and reported data in the case report forms. Items that need to be checked for compliance to study standards are provided in Attachment A. Examples of noncompliance to study standards at the clinical and analytical sites are listed in Part V of this guidance. Observed deficient practices should be discussed with the responsible officials.

E. Clinical and Analytical Facilities

Generally, unannounced visits to the clinical or analytical investigator will be impractical. Appointments to inspect may be made by telephone, but the time interval until the actual inspection should be kept as short as possible. Any undue delay of the inspection on the part of the clinical or analytical investigator should be reported immediately to GBIB. In the event that an unannounced visit becomes necessary, this will be addressed and clearly stated in the inspection assignment memo sent to the appropriate District office(s).

Inspection of clinical and analytical facilities should include review of the practices, qualifications of personnel, and procedures utilized during conduct of the clinical study and analytical testing. The clinical and analytical data provided by the GBIB should be compared with the records at the clinical and analytical study sites. Analytical testing procedures, including controls, should be reviewed by the GBIB scientist or FDA field chemist for scientific soundness with relation to the data submitted in the NDA/ANDA.

F. Instructions for Data Audits

See Attachment A for guidance.

OTHER REQUIREMENTS

A. All Headquarters and Field units are encouraged to recommend any sponsor(s), or clinical or analytical facility to the GBIB for inspection. All recommendations should include:

1. Establishment name and address.
2. If known, the name of the drug(s) being investigated and the NDA or ANDA number(s).
3. Why the inspection should be made.

B. State and local inspectors do not ordinarily participate in inspections conducted under this program. If State/local officials make such requests, clearance must be obtained in advance from DSI.

TECHNICAL SUPPORT-INSPECTION TEAMS

See Inspection Operations Manual, Section 502.4 for guidance on team inspections. The District

performing the inspection should use District or Regional experts whenever possible. The use of field chemists and microbiologists on the inspection team is strongly recommended when their expertise in the analytical methodology, equipment quality control, or adequacy of laboratory records is identified in the assignment. A member from the Bioequivalence Team in GBIB may participate in domestic and foreign inspections where expertise in pharmacokinetic and/or pharmacodynamic data analysis is needed, when complex scientific issues are involved, or when a field chemist/microbiologist is not participating in the analytical portion of a bioequivalence study inspection. **For a Bioequivalence Assignment where an on-site Analytical Audit is requested, a field chemist or GBIB scientist must accompany the investigator.**

ESTABLISHMENT INSPECTION REPORT (EIR) FORMAT

The format of the EIR should be based on each section in Attachment A that is pertinent to the inspected facility. EIRs of facilities under this program will not normally be abbreviated. Where appropriate "negative", "not applicable", and "narrative" responses to points in Attachment A, should be documented and/or explained. Some of these responses will be clear enough that documentation/explanation is not necessary. Complete a separate Attachment B for each bioequivalence study and for each site audited. If a GBIB scientist participated in an inspection, the GBIB scientist should prepare the section of the EIR which he or she audited during the inspection.

Reports involving serious violative findings such as research misconduct or fraud should focus on the violative conditions, rather than the routine reporting set forth in Attachment A.

SAMPLE COLLECTION

Since November 8, 1990, clinical investigators have been required to retain samples from the test and reference drug products actually used in bioequivalence studies they performed. Routine collection of these samples from bioequivalence testing facilities is anticipated under CP 7346.832, Pre-Approval Inspections/Investigations. In the event that samples have not been previously collected under CP 7346.832, the District office is responsible for collecting the samples (related to the study identified in the assignment) at the time of the bioequivalence inspection. The task of sample collection will be clearly identified in the inspection assignment memo. Please see PART IV - ANALYTICAL for sample size to be collected.

PART IV - ANALYTICAL

Routine analytical work is anticipated for this compliance program (See preceding sections).

Collected study retention samples will be sent to the Division of Drug Testing and Applied Analytical Development, St. Louis, MO for screening. The sample size should be sufficient to allow the FDA laboratory to perform all of the release tests required in the ANDA, NDA, or supplemental applications five times. If the clinical investigator is not sure of the amount that constitutes the “five times quantity,” the clinical investigator should contact the study sponsor. The clinical facility must provide a written assurance (e.g.,an affidavit) that the retained samples are representative of those used in the specific bioavailability/bioequivalence study, and that they were stored under conditions specified in accompanying records.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Field investigators should send a copy of any EIR and supporting exhibits that document possible violations of the FD&C Act or other federal statutes to the District Compliance Branch (DCB) at the same time as the report is sent to GBIB, HFD-48. The DCB should review the EIR and discuss with HFD-48 coordination of follow-up regulatory or administrative actions, as appropriate.

GBIB will evaluate all EIRs for biopharmaceutical, clinical, and analytical significance, and assign a final classification to each EIR. After final review and classification, DSI will issue follow-up letters and provide copies to ORO (HFC-132) and the District(s) involved. If serious misconduct is found, a Warning Letter and/or other administrative actions (e.g., informing the sponsor that the study is not acceptable in support of ANDA or NDA; disqualification of clinical investigator or CRO that conducted the study) would be taken by DSI to the responsible CRO or sponsor. ORA would not normally recommend any regulatory actions unless requested by the Center.

CLINICAL TESTING

Examples of non-compliance:

1. Subjects not receiving the test or reference drug formulation according to the study randomization codes.

2. Biological samples compromised by improper identification, handling or storage.

3. Failure to report adverse experiences, such as vomitting, and diarrhea, which may affect absorption and elimination of drugs.

4. Inadequate drug accountability records.

5. Inadequate medical supervision and coverage.

6. Significant problems/protocol deviations/adverse events not reported to the sponsor.

7. Failure to adhere to the inclusion/exclusion criteria of the approved protocol.

8. Inadequate or missing informed consent for participating subjects.

9. Any other situation in which the health and welfare of the subjects are compromised.

ANALYTICAL TESTING

Examples of non-compliance:

1. Inconsistencies between data reported to FDA and at the site.

2. Inadequate or missing validation of assay methodology with respect to specificity (related chemicals, degradation products, metabolites), linearity, sensitivity, precision, and reproducibility.

3. Failure to employ standard, scientifically sound quality control techniques, such as use of appropriate standard curves and/or analyte controls that span the range of subjects' analyte levels.

4. Failure to include all data points, not otherwise documented as rejected for a scientifically sound reason, in determination of assay method precision, sensitivity, accuracy, etc.

5. Samples are allowed to remain for prolonged periods of time without proper storage.

6. Failure to maintain source data, e.g. source data written on scrap paper and/or discarded in trash after transferring to analytical documents.

7. Lack of objective standard for data acceptance of calibration standards, quality controls, etc.

8. Unskilled personnel conducting analytical procedures.

9. No documentation of analytical findings.

10. Inadequate or no written procedures for drug sample receipt and handling.

11. Inadequate or missing standard operating procedures.

Note: The above are not all-inclusive lists of examples of clinical and analytical noncompliance.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

REFERENCES

FD & C Act Section 301 (e), 505 and 510

Code of Federal Regulations, Title 21:

Part 11, "Electronic Records; Electronic Signatures"

Part 50, "Protection of Human Subjects"

Part 56, "Institutional Review Boards"

Part 200.10, "Contract Facilities (Including Consulting Laboratories) Utilized as Extramural Facilities by Pharmaceutical Manufacturers"

Part 207, "Registration of Producers of Drugs"

Part 312, "Investigational New Drug Application"

Part 314, "Applications for FDA Approval to Market a New Drug or An Antibiotic Drug"

Part 314.125, "Refusal to Approve an Application or Abbreviated Antibiotic Application"

Part 320, "Bioavailability and Bioequivalence Requirements"

Part 361.1, " Radioactive Drugs for Certain Research Uses"

FDA Website for Regulatory Guidances:

http://www.fda.gov/cder/regguide.htm

Compliance Program Guidance Manual (CPGM)

CPGM 7348.811, "Clinical Investigators"

ATTACHMENTS

A. Bioequivalence Testing Report Parts I, II and III.

B. Bioequivalence Testing Report Summary

PROGRAM CONTACTS

Center for Drug Evaluation and Research

If a specific contact is named in the assignment, that person should be contacted first. If that person is unavailable, contact:

Division of Scientific Investigations
GLP and Bioequivalence Investigations Branch (HFD-48)
C. T. Viswanathan, Ph.D.
Telephone: 301-827-5460

Division of Emergency and Investigational Operations (HFC-130)

Thaddeus Sze, Ph.D.
Telephone:301-827-5649

Office of Regulatory Affairs

Office of Enforcement
Bioresearch Monitoring Program Coordinator (HFC-230)
James McCormack, Ph.D.
Telephone: 301-827-0425

PART VII - HEADQUARTERS RESPONSIBILITIES

Office of Medical Policy, Division of Scientific Investigations, GLP and Bioequivalence Investigations Branch, (HFD-48), will:

- Provide technical guidance, expertise, and on-site support to the field.

- Notify ORO/Division of Emergency and Investigations Operations (HFC-130) of assignments issued.

- Initiate, after review of EIR's tentatively classified by the Field, necessary administrative action with appropriate notification to the Bioresearch Program Coordinator (HFC-230) and HFC-130. DSI is responsible for final classification of the inspection. If DSI changes a District's tentative classification, a brief explanation with proposed follow-up will be submitted to HFC-130 and the District.

- When an in-depth inspection is required, notify ORO, make arrangements with the District, and coordinate any problems encountered through HFC-130.

- Provide the background material and the necessary clinical and analytical data needed for conducting the inspection to the appropriate field District. **This will be done only after the appropriate field District has identified the investigator(s) who will particiate in the inspection.**

OFFICE OF REGIONAL OPERATIONS (ORO)

- Monitor District workload, and in consultation with GBIB, redirect assignments in cases of District overload.

- Coordinate with the Districts to identify persons with the expertise required in a specific assignment.

ATTACHMENT A

BIOEQUIVALENCE INSPECTION REPORT

PART I - FACILITIES and PROCEDURES (Clinical and Analytical)

A. FACILITIES (Clinical and/or Analytical)

1. Evaluate the general facilities for adequate space, work flow patterns, separation of operations, etc.

2. Comment on potential or actual problems, such as:
   - adjacent clinic rooms housing concurrent studies;
   - open windows allowing ingress of unauthorized food, drugs, etc., into clinic rooms;
   - are dropped ceilings sealed or monitored to prevent storage of non-permitted materials;
   - other conditions that may compromise study security, contribute to the potential for sample mix-up, sample contamination/degradation, etc.

3. Comment if the facilities do not appear adequate to support their normal workload.

4. Are there written, dated and approved standard operating procedures, readily available to all personnel in their work areas? Are working copies kept current?

5. Are outdated procedures archived for future reference?

6. Are visitors to the clinical facility permitted? How are visitors monitored to prevent passage of non-permitted materials to the study subjects?

7. Are off site trips for smoking or other reasons monitored to prevent consumption of non-permitted materials or passage of such materials to or from unauthorized persons?

B. PERSONNEL

1. Check the relevant qualifications, training, and experience of personnel. Assess staff's ability to perform assigned functions. Document any deficiencies that relate to the audited study(ies).

C. SPECIMEN HANDLING AND INTEGRITY

In the Clinic. Check and describe:

1. Procedures for positive subject and sample identification so that study, drug, subject, sampling time, etc., are linked.

2. Procedures for adherence to processing time, temperature, and light conditions as specified by analytical method.

3. Storage conditions before and after processing, as well as during transit to the laboratory.

4. Precautions against sample loss and mix-up during storage, processing and transit to the laboratory.

In the Analytical Laboratory

1. Determine if the analytical facility receives bioequivalence samples from other locations. If yes:

    a. Are there freight receipts for sending/receiving samples?

    b. Is a documented history of sample integrity available (e.g., the sample storage time and conditions prior to shipment)?

    c. Is the length of time in shipment recorded?

    d. Evaluate the type of transportation employed, and type of protection provided (e.g., shipped by air in insulated containers of dry ice). Report any questionable practices.

    e. What arrangement(s) can be made for receiving shipments outside of normal working hours?

    f. Are the conditions of the samples noted upon arrival at the analytical laboratory, along with the identity of the person(s) receiving the samples?

    g. Are there procedures and documentation to assure that the samples remained at the proper temperature during shipment and holding?

2. Describe the storage equipment for bioequivalence samples until analysis (e.g., GE Freezer, chest type, Model #417 etc.)

3. Evaluate the equipment and procedures (e.g., ultraviolet light protection) for storing and maintaining bioequivalence samples, prior to and during analysis.

    a. Compare storage capacity vs. number of samples in storage.

    b. Examine set points for alarms and temperature controlling/recording devices.

    c. Review procedures for calibration and maintenance of alarms and controllers/recorders.

    d. Determine practices for monitoring, review, and storage of temperature records.

    e. Report any evidence of sample thawing.

    f. Check integrity of study samples.

    g. Determine if action plans are in place in case of power loss leading to abnormal storage conditions, i.e., emergency procedures.

4. Determine if samples are labelled and separated in storage and during analysis to prevent sample loss or mix-up between studies, subjects, and test/reference drug?

5. Examine how sample identification is maintained through transfer steps during analysis.

6. Is there accurate documentation to show how many freeze and thaw cycles the samples have been subjected to, including accidental thawing due to equipment failure(s)?

D. ELECTRONIC RECORDS AND SIGNATURES

FDA published the Electronic Records; Electronic Signatures; Final Rule [21 CFR 11] on March 20, 1997. The rule became effective on August 20, 1997. Records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirement set forth in agency regulations must comply with 21 CFR 11. The following questions are provided to aid evaluation of electronic records and electronic signatures:

1. Are electronic data systems used to gather clinical (e.g., adverse experiences, concomitant medications) and analytical data (e.g., peak heights, peak areas of chromatograms)? Are such systems used to store, analyze, and/or calculate

pharmacokinetic/pharmacodynamic modeling, or to transmit clinical and analytical data to the sponsor? If so, identify the system(s), and summarize the system(s)' capabilities. If electronic data systems are not used, omit coverage of the remainder of this section.

2. Determine the source(s) of data entered into the computer for accuracy, security and traceability.

   a. Direct electronic transfer of on-line instrument data.

   b. Case report forms, analytical worksheets or similar records requiring manual data entry.

   c. Chromatograms requiring evaluation prior to manual extraction of data.

   d. Other.

3. Determine the following:

   a. Who enters data and when?

   b. Who verifies data entry and when?

   c. Who has access to computer and security codes?

   d. How are data in computers changed? By whom? Audit trail?

4. Determine if the sponsor gets source data or tabulated, evaluated data.

5. Determine how data are transmitted to sponsor (Hard copy, computer disk, fax, modem, etc.)

6. If the sponsor discovers errors, omissions, etc., in the final report, what contacts are made with the investigator; how are corrections effected, and how are they documented?

7. Determine how data are retained by the investigator? (Hard copy, electronic, etc.)

8. Determine if the firm has standard operationg procedures (SOPs) for validation of computer systems involved in storing, analyzing, calculating, modeling, and/or transmitting clinical and analytical data. Have the computer systems been validated

according to the SOPs? Are results of the validations documented and available for audit? Summarize the validated capabilities of the computer systems with respect to their effect on the validity of the study data.

ATTACHMENT A

BIOEQUIVALENCE INSPECTION REPORT
PART II - CLINICAL DATA and OPERATIONS

GENERAL

Inspections of clinical facilities should include a comparison of the practices and procedures of the clinical investigator with the requirements of 21 CFR 312, 320.

Inspections should also include a comparison of the source data in the clinical investigator's files with the data submitted to the FDA. Original records should be reviewed, including medical records, dosing records, clinical laboratory test reports, adverse reaction reports, concomitant medications records, nurses' notes, etc.

INSPECTION PROCEDURES

This part identifies the minimum information that must be obtained during an inspection to determine if the clinical investigator is complying with the regulations. Each FDA investigator should expand the inspection as facts emerge. The inspections should be sufficient in scope to determine the clinical investigator's general practices for each point identified, as well as the particular practices employed for the study(ies) under audit.

STUDY RESPONSIBILITY AND ADMINISTRATION

1. Determine if the clinical investigator was aware of the status of the test article(s), nature of the protocol, and the obligations of the clinical investigator.

2. Determine whether authority for the conduct of various aspects of the study was delegated properly so that the investigator retained control and knowledge of the study.

3. Determine if the investigator discontinued the study before completion. If so, provide reason.

4. Determine the name and address of any clinical laboratory performing clinical laboratory tests for qualifying and/or safety monitoring of study subjects.

    a. If any clinical laboratory testing was performed in the investigator's own facility, determine whether that facility is equipped to perform each test specified.

    b. Determine if individuals performing the clinical tests are adequately qualified.

PROTOCOL

Obtain a copy of the written protocol. Unavailability should be reported and documented. If a copy of the protocol is sent with the assignment background material, it should be compared to the protocol on site. If the protocols are identical, a duplicate copy does not need to be obtained. The narrative should note that the protocols were identical. If the protocol has been accepted by a Review Division in CDER, a copy of the acceptance letter should be attached to the EIR. If the Agency has recommended the incorporation of additional material, method, or information into the protocol, verify that appropriate modifications were made.

1. Compare the written protocol and all IRB approved modifications against the protocol provided with the assignment package. Report and document any differences.

2. Determine if the approved protocol was followed with respect to:

   a. Subject selection (inclusion/exclusion criteria)

   b. Number of subjects.

   c. Drug dose form, strength and route of administration.

   d. Frequency of subject dosing, monitoring and sampling.

   e. Washout period between study arms (test vs. reference drug)

   f. Other (specify)?

3. Determine whether all significant changes to the protocol were:

   a. Documented by an approved amendment that is maintained with the protocol;

   b. Dated by the investigator;

   c. Approved by the IRB and reported to the sponsor before implementation except where necessary to eliminate apparent immediate hazard to human subjects.

   d. Implemented after IRB approval.

NOTE: CHANGES IN PROTOCOL ARE NOT VIOLATIONS OF PROTOCOL

SUBJECTS' RECORDS

1. Describe the investigator's source data files in terms of their organization, condition, accessibility, completeness, and legibility.

2. Determine whether there is adequate documentation to assure that all audited subjects did exist and were alive and available for the duration of their stated participation in the study.

3. Compare the source data in the clinical investigator's records with the case reports completed for the sponsor. Determine whether clinical laboratory testing (including blood work, EKGs, X-rays, eye exams, etc.), as noted in the case report forms, was documented by the presence of completed laboratory records among the source data.

4. Determine whether all adverse experiences were reported in the case report forms. Determine whether they were regarded as caused by or associated with the test article and if they were previously anticipated (specificity, severity) in any written information regarding the test article.

5. Concomitant therapy and/or intercurrent illnesses might interfere with the evaluation of the effect of the test article. Check whether concomitant therapy or illness occurred. If so, was such information included in the case report forms?

6. Determine whether the number and type of subjects entered into the study were confined to the protocol limitations and whether each record contains:

    a. Observations, information, and data on the condition of each subject at the time the subject entered into the clinical study;

    b. Records of exposure of each subject to the test article;

    c. Observations and data on the condition of each subject throughout participation in the investigation including time(s) of drug administration; dosing according to pre-established, randomization schedules; results of lab tests; development of unrelated illness; bleeding times and any other specimen collections; wash-out periods for subjects; and other factors which might alter the effects of the test article; and

    d. The identity of all persons and locations obtaining source data or involved in the collection or analysis of such data.

OTHER STUDY RECORDS

Review information in the clinical investigator's records that would be helpful in assessing any under-reporting of adverse experiences by the sponsor to the agency. The following information will ordinarily be obtained from the sponsor and sent with the assignment:

a. The total number of subjects entered into the study;

b. The total number of dropouts from the study (identified by subject number);

c. The number of evaluable subjects and the number of non-evaluable subjects (the latter identified by subject number); and

d. The adverse experiences identified by subject number and a description of the adverse experience.

Compare the information submitted to the sponsor according to the clinical investigator's files with the information obtained from the sponsor, and document any discrepancies found.

CONSENT OF HUMAN SUBJECTS

1. Obtain a copy of the consent form actually used.

2. Determine whether proper informed consent was obtained from all subjects prior to their entry into the study. Identify the staff who obtain and witness the signing of informed consent for study subjects.

INSTITUTIONAL REVIEW BOARD (IRB)

1. Identify the name, address, and chairperson of the Institutional Review Board for this study.

2. Determine whether the investigator maintains copies of all reports submitted to the IRB and reports of all actions by the IRB. Determine the nature and frequency of periodic reports submitted to the IRB.

3. Determine whether the investigator submitted reports to the IRB of all deaths and serious adverse experiences and unanticipated problems involving risk to human subjects [21 CFR 312.66].

4. Determine if the investigator submitted to and obtained IRB approval of the following before subjects were allowed to participate in the investigation:

   a. Protocol.

   b. Modifications to the protocol.

   c. Materials to obtain human subject consent.

   d. Media advertisements for subject recruitment.

5. Determine if the investigator disseminated any promotional material or otherwise represented that the test article was safe and effective for the purpose for which it was under investigation. Were the promotional material(s) submitted to the IRB for review and approval before use?

SPONSOR

1. Did the investigator provide a copy of the IRB approved consent form to the sponsor?

2. Determine whether the investigator maintains copies of all reports submitted to the sponsor.

   Determine if and how the investigator submitted any report(s) of deaths and adverse experiences to the sponsor.

3. Determine whether all intercurrent illnesses and/or concomitant therapy(ies) were reported to the sponsor.

4. Determine whether all case report forms on subjects were submitted to the sponsor shortly (within 6 months) after completion.

5. Determine whether all dropouts, and the reasons therefore were reported to the sponsor.

6. Did the sponsor monitor the progress of the study to assure that investigator obligations were fulfilled? Briefly describe the method (on-site visit, telephone, contract reserach organization, etc.) and frequency of monitoring. Do the study records include a log of on-site monitoring visits and telephone contactS?

TEST ARTICLE ACCOUNTABILITY

1. Determine whether unqualified or unauthorized persons administered or dispensed the test article(s).

   What names are listed on the FDA-1571 (for Sponsor-Investigator) and FDA-1572 (for studies conducted under an IND) ? Obtain a copy of all FDA-1572s.

2. Determine accounting procedures for test articles:

   a. Receipt date(s) and quantities.

   b. Dates and quantities dispensed.

   c. Quantities of bioequivalence testing samples retained (see SAMPLE COLLECTION Section under Part III).

3. Inspect storage area.

   a. Reconcile amounts of test article used with amounts received, returned, and retained. Report any discrepancy.

   b. If not previously sampled under CP 7346.832, collect samples of both the test and reference products for FDA analysis.

4. If test articles are controlled substances, determine if proper security is provided.

RECORDS RETENTION

1. Determine who maintains custody of the required records and the means by which prompt access can be assured.

   Determine whether the investigator notified the sponsor in writing regarding alternate custody of required records, if the investigator does not maintain them.

2. Be aware that records should be retained at the study site for the specified time as follows:

   a. Two years following the date on which the test article is approved by FDA for marketing for the purposes which were the subject of the clinical investigation; or

b. Two years following the date on which the entire clinical investigation (not just the investigator's part in it) is terminated or discontinued *by the sponsor*. If the investigator was terminated or discontinued, was FDA notified?

ABBREVIATED REPORT FORMAT

For inspection of a clinical facility, abbreviated report is allowed if (1) there are no significant violations and no FDA Form 483 is issued, and (2) in cases where there are objectionable findings but the findings are not serious and clearly do not have any impact on data integrity and study
outcomes. The following is a guideline for preparation of the abbreviated report:

1. Reason for inspection:

   a. Identify the headquarters unit that initiated and/or issued the assignment.

   b. State the purpose of the inspection.

2. What was covered:

   a. Identify the clinical study, protocol number, sponsor, NDA, ANDA, etc.

   b. Location of study.

3. Administrative procedures:

   a. Report the name, title, and authority of the person to whom credentials were shown and FDA-482 Notice of Inspection was issued.

   b. Persons interviewed.

   c. Who accompanied you during establishment inspection.

   d. Who provided relevant information.

   e. Identify the IRB.

   f. Prior inspectional history.

4. Individual responsibilities:

   a. Identify study personnel and summarize their responsibilities relative to the clinical study (e.g., who screened the subjects, who administered the drugs, who supervised collection, identification and processing of samples, etc.

   b. A statement about: (i) who obtained informed consent, (ii) how it was obtained, and (iii) was informed consent signed by each subject.

   c. Identify by whom the clinical study was monitored, and when, etc.

5. Inspectional findings:

   a. A statement regarding the comparison of data on the case report forms to the source data at the investigator's site. Indicate the number of records compared and what was compared (patient charts, hospital records, lab slips, etc.), and specific information about any discrepancies.

   b. A statement indicating if the drug accountability records were sufficient to reconcile the amount of drug received, dispensed, returned, and retained.

   c. A statement about protocol adherence. Describe in detail any non-adherence.

   d. A statement concerning doses in accordance with pre-established, randomization schedules.

   e. The EIR should identify the IRB and state if it approved the study and was kept informed of the progress of the study.

   f. A statement on: (i) follow-up activities in response to reports of adverse experiences (including death) if any occurred; (ii) whether there was evidence of under reporting of adverse experiences/events.

   g. Discussion of 483 observations, reference the exhibits/documentation collected.

6. Discussion with Management

   a. Discussion of 483 observations and non-483 observations.

   b. Clinical investigator’s response to observations.

Remember that the above deals with abbreviated reports, not abbreviated inspections. All assignments issued for-cause must have full reporting. The assignment EMS or memo will indicate the need for full reporting for any special inspection.

ATTACHMENT A

BIOEQUIVALENCE INSPECTION REPORT
PART III - ANALYTICAL DATA and OPERATIONS

Information required by this section must be obtained with the assistance of a qualified analyst from the field and/or a reviewer in GBIB with expertise in the type of analysis used in the bioequivalence study under review.

At random, compare the analytical source data with data provided in the inspection assignment for accuracy of transference and for scientific soundness/bearing on the validity of the study. Analytical source data are: codes used to blind samples; data establishing the sensitivity, linearity, specificity and precision of the analytical assay; data determining the stability of the drug in the biological specimen; all standard curves; blinded and unblinded spiked control samples; blanks; data on reagent preparation; instrumental readings**;** calculations; etc. The data comparison and the testing procedural review should include an evaluation of any discrepancies found.

A. PRE-STUDY ANALYSIS

If the analytical laboratory is involved in analysis of drug standards and products employed in the bioequivalence studies, determine if:

1. Appropriate samples were analyzed by the laboratory to determine potency and content uniformity for tablets and capsules**.** Include a description of procedures used to prepare the sample(s) used in the study.

2. If testing of the samples described above was not performed by the analytical laboratory, did the sponsor provide test results to the laboratory?

3. For both the test and reference drug products studied, were the products' appearance, potency, dosage form (capsule, tablet, suspension, controlled release, etc.), lot numbers and expiration dates the same as that reported to FDA?

B. PROTOCOL ACCEPTANCE

If the Review Division reviewed the protocol and recommended protocol modifications, verify that the modifications were incorporated into the protocol.

C. EQUIPMENT

Check on the following with respect to both current equipment and practices and those in place at the time of the study:

1. Does the laboratory have the same type, brand, and model (not serial) numbers of all major pieces of analytical equipment and instrumentation used in their testing procedures, as reported in the ANDA or NDA? (For example, gas chromatographs, high performance liquid chromatographs, ultraviolet spectrophotometers, colorimeter, fluorescence or atomic absorption spectrophotometer, pH meter, etc.). If not, describe the discrepancy and include its effect on the validity of the study data.

2. Assess the general condition of the major pieces of equipment (e.g., gross mistreatment) which may render them inaccurate or unreliable. Examples: damaged gas chromatograph inlet port, dry pH meter electrodes, etc. Review maintenance and repair logs for indications of past problems.

3. Are there written operating instructions for these major pieces of equipment, and are they available to the laboratory personnel?

4. Are there written and scheduled calibration/standardization procedures, and preventative maintenance procedure for all analytical instruments employed in the study? Determine whether these calibration/standardization procedures are actually employed and documented? If not, describe the deficiencies and determine whether the instruments have been calibrated during the time of the study.

5. Were specific instrument operating parameters documented during the study? If so, where?

D. ANALYTICAL METHODS VALIDATION - DETERMINE THROUGH DATA AND PROCEDURAL REVIEW IF:

1. The analytical laboratory has scientifically sound data to support claims for the specificity of the assay employed in this study. Ascertain the laboratory's justification for non-interferences, both endogenous and exogenous (e.g. metabolites, solvent contamination, etc.) in measuring the analytes (drug, metabolites, etc.) studied.

2. The analytical laboratory has data to support the claims for the linearity of the assay employed in this study.

3. The laboratory analyst who analyzed the biological samples has generated data

demonstrating the sensitivity of the assay using the same instrumentation as that employed in the bioequivalence study. The sensitivity of the assay (or limit of detection) may be defined as the lowest quantifiable limit that can be reproducibly determined for the measured analyte(s) being carried through the method.

4. The laboratory analyst who analyzed the biological specimen has generated data demonstrating the precision of the assay using the instrumentation employed in the bioequivalence study. The data should be available for both standard and quality control samples and should include the consistency of precision of the standard and control samples carried through the assay procedure. Ascertain the laboratory's justification for the precision based on the separation procedure, instrumentation, and analyte concentration levels in the biological fluids.

5. The laboratory has data to demonstrate drug recoveries (percent recovery) for the measured analyte(s). This should include both analyte extraction efficiency from the biological fluid and recovery of the analyte(s) carried through the analytical testing procedure.

6. The analytical laboratory determined the stability of the drug both in the biological specimen and in the sample preparation medium under the same condition as in actual analysis of subject samples.

7. The analytical laboratory showed that the storage procedures (e.g., freezing and number of freeze/thaw cycles) have no adverse effect on drug stability for the period of time the samples were stored, from subject dosing until last sample analysis.

8. The water quality specified for sample and reagent preparation is consistently and readily available in the lab.

E. SAMPLE ANALYSES - DETERMINE IF:

1. The analytical assay employed was the same as that specified in the ANDA or NDA.

2. The assay parameters observed for the study's sample analysis are similar to those (e.g. specificity, precision, etc.) obtained during method validation. Review study subjects' source analytical data to check this; pay particular attention to analytical runs determined toward the end of analytical testing.

3. Coding techniques were used to blind the analytical laboratory to the sample. Was the code available to the analytical chemist?

4. The samples were analyzed in a randomized fashion or in some specific order. Were samples of test and reference products for the same subject analyzed at the same time under identical conditions with the same standard curve, same control, and same instrument?

5. Standard curves are prepared each time a batch of unknown samples is assayed. If not, how often are standards run? Have all the standard curves run during the study been reported? How many standards are used to define each standard curve? (Should be 5-8, excluding blank). Does the laboratory have scientifically sound procedures for acceptance or rejection of a standard point and/or a standard curve?

6. The standard curve encompasses the concentration values reported. Were any values reported which were derived from points extrapolated on the standard curve?

7. The laboratory has a scientifically sound SOP in place to guide the acceptance/rejection of data. Did the laboratory adhere to the SOPs in the reporting of repeated determinations, or was supervisory discretion used to accept/reject data points?

8. Blinded or non-blinded spiked control samples have been included and reported with each run. Who prepared these samples? Were the controls made from a standard weight different from the standard weight used to prepare standards for the standard curve (i.e., two separate independent weighings for calibration standards and QC stock solutions)? Do the controls span the expected analyte concentration range (low, midrange and high) found in the subjects' samples? Have all control values been reported individually, as opposed to averages?

9. The control samples were processed and analyzed exactly the same as the unknown samples. Were the controls interspersed throughout the entire analytical run?

10. The source of blank biological fluids. (Was each subject's zero hour serum used as the blank, pooled plasma, etc.?) Were interferences noted in the analytical source data for these samples? Specifications should be established to assure that blank biological fluids are as similar as possible to the biological matrix for the subject samples.

11. The source of the drug standards used for the in vivo sample analysis. If not compendial standards, how was the quality and purity of the standard assured?

12. All sample values were recorded and reported. If not, were reasons for rejection documented and justified? Were any samples re-run? When repeated determinations were made, were new standard curves and control samples run concurrently?

13. The procedure employed for determining which value of a re-run sample is reported. Was this procedure scientifically sound and consistently followed? Was an established written procedure followed?

14. The submitted chromatograms are representative of the quality of the chromatograms generated throughout the study.

15. There are written procedures for preparing reagents used in these assays. Are reagents properly labelled with date of preparation, storage requirements, as well as chemist who prepared them? Were the original weighings for calibration standard and QC stock solutions checked and countersigned by a second party?

16. Copies of the following chromatograms are available: (If not submitted by the applicant, the Field investigator or chemist should obtain copies.)

    a. Reagent blank
    b. Sample blank
    c. Internal standard
    d. A standard run
    e. A quality control run
    f. A set of chromatograms for one subject over the entire span of the study

F. <u>FOR ANTIBIOTIC ANALYSES - DETERMINE:</u>

1. Are incubators available? Specify dimensions and type.

2. Whether:

    a. The bench tops are level.
    b. The room temperature is controlled and, if so, what are the temperature tolerances.
    c. Agar, propagation cultures and other necessary resources are available and properly monitored.
    d. Zone readers are available, if so, specify type.
    e. Autoclaves are available and, if so, specify type and determine if the autoclave sterilization process has been validated.
    f. The room where these studies are conducted is "environmentally sterile" and what monitoring is done to determine the degree of "environmental sterility".

3. Whether the samples were run properly through the incubator, i.e. times and temperatures are controlled to desired specifications and properly documented.

4. Whether the standards, controls and samples are incubated at the same time, in the same incubator.

5. Whether the micro-organisms used in the media are the same as described in the AADA.

6. Whether a burner is used to heat the wire for transfer purposes.

7. Whether calibrated zone readers were used for zone size determinations.

8. Whether turbidimetric methodology was employed. Also, determine the type of spectrophotometry used.

9. Whether the turbidimetric standardization procedure was the same as that specified in the AADA. If not, describe differences.

10. Whether all samples were read in duplicate. Were all samples read by the same person? Did zone diameters or turbidimetric readings correlate with drug concentration levels?

11. Are standard operating procedures in place to calibrate the incubator, autoclave, etc., used in antibiotic analysis? Are the SOPs readily available to laboratory personnel?

G. FOR RADIOMETRIC ANALYSES-IN ADDITION TO THE GENERAL GUIDANCE ABOVE, DETERMINE:

1. How the specific activity of the radiochemical standards employed was determined.

2. Whether all counts specified in records submitted to the Agency were actually counted for the time interval specified.

3. Whether an inventory of all radiolabeled compounds is maintained by the laboratory.

4. If the background level has been determined? If yes, by what method?

5. For RIA methodology, determine if a commercial kit was used in the analysis. If so, report the type of kit, the expiration date and whether the laboratory validated the laccuracy, specificity, precision, sensitivity and linearity of the kit assay in relation to the reported study assay procedure.

H. DATA HANDLING AND STORAGE - DETERMINE:

1. Whether bound notebooks and/or source data worksheets are used by the laboratory.

2. If bound notebooks are used, are the pages filled in sequentially on a chronological basis? Does the analyst sign the notebook/worksheet daily? Does a supervisor initial the notebook/worksheet after checking it for accuracy?

3. Whether the laboratory retains all source data, such as notebooks, worksheets, chromatograms, standard curves, etc. Is there justification for source data excluded from the study report, such as rejected runs, missing samples, etc.?

4. Whether the analyst(s) sign and date all source data records.

5. How long the source data is retained.

6. Describe the maintenance and accessibility of laboratory source data (e.g., repeated determinations, rejected analytical runs, etc.). Document problems with data recording and verification, such as lack of dates and signatures, erasures, white-out, etc.

ATTACHMENT B

BIOEQUIVALENCE TESTING REPORT SUMMARY

Complete one form for each study audited.

Check one or both:

G Clinical Facility, complete Attachment A - Parts I and II.

G Analytical Facility, complete Attachment A - Parts I and III.

1. District: _____

2. Date(s) of Inspection: _____

3. Application No. (if applicable): _____

4. Application Sponsor (if any):

   a. Name: _____
   b. Address: _____
   c. City: _____ State: ___ Zip: ____

5. Location where testing performed:

   Clinical Facility Name: _____
   Address: _____
   City: _____ State: _____
   Zip: _____

   Central File No.: _____

   Analytical Facility Name: _____
   Address: _____
   City: _____ State: ___ Zip: _____

   Central File No.: _____

6. Responsible Official (Recipient of Notice of Inspection):

   Name and Title: _____

7. Person receiving FDA-483 (if issued):

   Name and Title: _____

8. Drug under study:

   a. Generic Name: _____

   b. Trade Name: _____

   c. Dosage Form: _____

   d. Strength(s): _____

9. Number of subjects in clinical test: _____

10. Status of clinical testing:

    Date Started: _____

    Completion Date: _____

11. Sample Collection **G** Sample Lot # _____

12. FDA Investigator(s): _____

    _____

13. Remarks:

A:\FOI48001.
September 19, 2000