PROGRAM 7348.811

CHAPTER 48- BIORESEARCH MONITORING

CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS

Date of Issuance: December 8, 2008

Guidance for FDA Staff

SUBJECT: Clinical Investigators and Sponsor Investigators	IMPLEMENTATION DATE December 8, 2008
REVISION:	COMPLETION DATE Continuing

DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
FACTS does not require product codes for Bioresearch Monitoring Inspections	09811 Food Additives
	41811 Biologics (Cell; Gene Transfer)
	42811 Biologics (Blood)
	45811 Biologics (Vaccines)
	48811 Human Drugs
	68811 Animal Drugs
	83811 Medical Devices

FIELD REPORTING REQUIREMENTS:

For domestic inspections, copies of all establishment inspection reports (EIRs), complete with attachments, exhibits, and any related correspondence are to be submitted promptly to the Center contact, who is generally the reviewer in the Center's Bioresearch Monitoring (BIMO) program identified in the assignment.

For foreign inspections, all original EIRs, complete with attachments, exhibits and any related correspondence are to be submitted promptly to the Center contact identified in the assignment.

All EIRs should be completed in accordance with FMD No. 86, Establishment Inspection Report (EIR) - Inspection Conclusions and District Decisions (http://www.fda.gov/ora/inspect_ref/fmd/fmd86.htm). When a Form FDA 483, "Inspectional Observations" (483), is issued, a copy should be faxed to the Center contact, generally no later than 3 business days.

PART I - BACKGROUND

Since the Investigational New Drug (IND) Regulations went into effect in 1963, the Food and Drug Administration (FDA) has exercised oversight of the conduct of clinical studies involving FDA regulated products. The BIMO Program was established in 1977 by a task force that included representatives from the drug, biologic, device, animal drug, and food areas.

Compliance programs (CP) were developed to provide uniform guidance and specific instructions for inspections of Clinical Investigators (CP 7348.811), Sponsors (CP 7348.810), In-Vivo Bioequivalence facilities (CP 7348.001), Institutional Review Boards (CP 7348.809), and Non-Clinical Laboratories (CP 7348.808).

Regulations addressing requirements of clinical investigators, sponsors and monitors (21 CFR Parts 312, 314, 511, and 514) were published on March 19, 1987, and became effective on June 17, 1987. Regulations for clinical investigations of devices (21 CFR Part 812) became effective January 18, 1980, and for premarket approval of medical devices (21 CFR Part 814) on July 22, 1986.

PART II - IMPLEMENTATION

A. OBJECTIVES

The objectives of BIMO Program are:

1. To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;

2. To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and

3. To assess compliance with FDA's regulations governing the conduct of clinical trials.

The purpose of this compliance program is to provide instructions to the field and Center personnel for conducting inspections of clinical investigators and sponsor-investigators,and recommending associated administrative/enforcement actions.

B. PROGRAM MANAGEMENT INSTRUCTIONS

1. Coverage

This program covers domestic and foreign inspections of:

a. Clinical Investigators

A clinical investigator is the individual who actually conducts the clinical investigation.[1] The investigator is responsible for overall conduct of the study at the study site, including directing the administration or dispensing of the test article to the subject, and ensuring that data are collected and maintained in accordance with the protocol and regulatory requirements. When the investigation is conducted by a team of individuals, the clinical investigator is the leader of the team.

b. Sponsor-Investigators

A sponsor-investigator is an individual who initiates and also conducts the clinical investigation. A sponsor-investigator must comply with regulatory requirements applicable to both sponsors and clinical investigators.[2] While inspections of sponsor-investigators are assigned under CP 7348.811, CP 7348.810 (Sponsors, Contract Research Organizations and Monitors) should also be consulted for areas applicable to the sponsor responsibilities of the sponsor-investigator.

[1] 21 CFR 312.3, 21 CFR 812.3(i)
[2] 21 CFR 312.3; 21 CFR 812.3(o)

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2. Inspection Assignments

a. Center BIMO units issue inspection assignments of clinical investigator sites.

i. Domestic inspection assignments are issued to the district offices.

ii. International inspections are generally assigned when the studies covered are part of a marketing application to FDA and provide data critical to decision-making on product approval. Such assignments may include studies that are conducted under an FDA application for research (e.g., Investigational New Drug Application [IND], Investigational Device Exemption [IDE], Investigational New Animal Drug Application [INAD]), as well as non-U.S. sites or studies that are not conducted under an FDA application for research. Such assignments are issued to the Division of Field Investigations (HFC-130).

b. The assignment should identify:

i. The program assignment code (PAC) and Field Accomplishments and Compliance Tracking System (FACTS) number;

ii. The name, address and phone number of the clinical investigator or sponsor-investigator, and the study site(s) to be inspected;

iii. The type and purpose of the inspection;

iv. The background materials (e.g., study protocol; tables; sampling plan[3] for review of informed consent documents, case report forms (CRFs) or specific data, if appropriate) that are being sent from the Center to facilitate the inspection. For investigational device studies, the Center should identify the type of study (e.g., significant risk (IDE), non-significant risk (abbreviated requirements), or IDE exempt).

v. Specific issues or concerns (if applicable) that need to be addressed during the inspection;

vi. The due date for the Center contact to receive the completed EIR;

vii. The headquarters address where the EIR should be sent; and

viii. The name, telephone number, and fax number of the Center contact(s).

[3] A sampling plan provides instructions about the amount of data or number of documents to be reviewed, and how to select specific records for this purpose. Generally, a sampling plan will identify the minimum number of subjects' records (relative to the total number of subjects in the study) to be reviewed in order to provide a reasonable level of confidence that any problems at the site would be found (i.e., have a high probability of being detected).

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c. If the inspection involves a Veterans Administration (VA) facility, please see section B.6 for additional instructions.

d. When requesting expedited inspections, the Center should provide justification. If a Center's assignment needs high priority, follow Field Management Directive (FMD) No. 17, ORA Field Assignments - Guidelines for Issuance by Headquarters (http://www.fda.gov/ora/inspect_ref/fmd/fmd17.htm).

e. If, during the course of a clinical investigator or sponsor-investigator inspection, field personnel identify an institutional review board (IRB) that has never been inspected or has not been inspected within the past 5 years, the field investigator may request that the Center issue an inspection assignment for that IRB.

f. All headquarters and field personnel who become aware of complaints or problems related to a clinical investigator or sponsor-investigator are encouraged to refer the name(s) to the appropriate Center with a recommendation for inspection. All recommendations should include the following:

i. The name and address of the clinical investigator or sponsor-investigator;

ii. If available, the name(s) of the test article(s) being investigated, and the application for research or marketing permit number(s); and

iii. The basis for the recommendation and any relevant documentation.

3. Communication between the Centers and the Districts

Inspectional observations documenting that a clinical investigator is not operating in compliance with regulations governing the conduct of clinical trials may be used as evidence for taking appropriate administrative and/or enforcement actions. Ensuring that the evidence collected to support such actions is both appropriate and adequate requires that communication lines between the field investigator and the Center be established early and maintained throughout the entire process, i.e., until post-inspectional correspondence is issued by the Center.

a. Prior to an Inspection

i. The Center issues an assignment (B. 2. above) that includes contact information for the BIMO reviewer.

ii. The field investigator contacts the BIMO reviewer:
- Upon receipt of the assignment, to establish initial contact and/or provide an inspection start date;

- When the inspection date is firmly set, to alert the BIMO reviewer and/or a back-up to be available and to establish the most appropriate means of contact for both the investigator and the BIMO reviewer/back-up;
- To obtain any information that may change the focus of the inspection;
- To coordinate inspection arrangements if Center personnel plan to participate in the inspection

iii. Special Considerations.

In particular cases, the Center may arrange for a consultative teleconference immediately prior to the inspection(s) if, for example, the complexity of the product or study, data concerns, urgency of feedback, compliance history, etc., trigger the need to discuss issues further. Such conference calls are most likely when the agency is reviewing Biologic License Applications (BLAs), New Drug Applications (NDAs), Premarket Approval Applications (PMAs), or New Animal Drug Applications (NADAs), for novel or complex products, or in "for cause" inspections where pertinent information is either complex or needs discussion between the Center and the field. The assignment will usually state that this teleconference will occur, unless information necessitating this discussion emerges after the assignment is issued.

These teleconferences may include the following participants, as warranted and feasible:

- BIMO reviewer (and supervisor/division director or other staff, as appropriate);
- Lead application reviewer (along with branch and division chiefs, as appropriate) and other application reviewers as needed; and
- Field investigator(s) assigned to the inspection(s) and/or the BIMO coordinator (when not yet specifically assigned). Other district staff may also participate.

b. During an Inspection

i. The BIMO reviewer contacts the field investigator if significant new information becomes available.

ii. The field investigator contacts the BIMO reviewer or designated back-up person if he:

- Needs advice or clarification. The BIMO reviewer and field investigator should strive to be accessible to one another as much as possible during the time that the inspection is going on.
- Uncovers other evidence of concern warranting discussion with Center staff.

c. After an Inspection

i. Within 3 business days of concluding the inspection, the field investigator forwards to the BIMO reviewer (by facsimile, e-mail, or placement in the appropriate shared drive folder) any 483 that is issued.

ii. The field investigator forwards as soon as possible to the BIMO reviewer a copy of any response to the 483 by the inspected party. The BIMO reviewer forwards to the field investigator, a copy of any response to a 483 that does not appear to have been shared with the inspecting district.

iii. The BIMO reviewer consults with the field investigator as needed when reviewing the EIR.

iv. The Center consults with appropriate District personnel if contemplating an EIR classification different from the one recommended by the District.

v. If the Center's final classification is different from the one recommended by the field, the Center should ensure that District personnel are aware of the change and reasons for the change.The Center promptly forwards, to the field investigator and other appropriate district personnel, by e-mail if possible, copies of post-inspectional correspondence issued to the inspected party.

vi. The Center enters the final classification into FACTS.

4. Responsibilities of Field Investigators, Inspection Team Leaders, and Headquarters Participants

a. The field investigator's responsibilities include, but are not limited to, the following:

i. Scheduling and conducting the assigned inspection;

ii. Discussing with District management the need to adjust the workload in order to meet specific deadlines (e.g., deadline imposed for review of the application by the Prescription Drug/Animal Drug/Medical Device User Fee Act);

iii. Communicating inspectional issues and observations with the clinical investigator and the study staff during the course of the inspection, as appropriate;

iv. Communicating inspectional observations and issues with the Center contact, as directed in the assignment memorandum;

v. Preparing, issuing, and discussing the items listed on the 483; and

vi. Participating in discussions with the Center regarding potential changes in the EIR classification.

b. Inspection Team Leader

When inspections are conducted by a team, a field investigator serves as inspection team

leader and is responsible for the cooperative conduct of the inspection. The team leader's responsibilities include, but are not limited to, the following (see also Investigations Operations Manual (IOM; http://www.fda.gov/ora/inspect_ref/iom/default.htm), Team Inspections):

i. Scheduling and coordinating the participation of team members;

ii. Discussing inspection plans and objectives with team members;

iii. Setting team policy regarding communications with the clinical investigator or study staff;

iv. Assuring that team members understand their roles in conducting the inspection, taking notes, collecting documentation, preparing sections of the inspection report and exhibits, and signing the report;

v. Discussing personal conduct with team members as necessary; and

vi. Resolving disputes or differences of opinion among team members, including items to be listed on the FDA 483.

c. Headquarters Participants

A headquarters participant is a member of the inspection team who serves in a compliance or scientific advisory capacity to the Team Leader. The headquarters participant's responsibilities include, but are not limited to, the following:

i. Identifying specific objectives to be covered by the inspection;

ii. Providing information pertinent to the inspection;

iii. Contacting the Office of Regional Operations (ORO) to request permission to participate in field inspections; and

iv. Obtaining inspection credentials from the Division of Field Investigations (DFI, HFC-130);

v. Attending pre-inspection conferences if and when scheduled;

vi. Participating in the on-site inspection as permitted by agency priorities; and

vii. Providing guidance and expertise during the inspection, and preparing specific sections of the inspection report within timeframes established by the Team Leader.

5. Resolution of Disagreements

If there is disagreement among members of the inspection team, the issue should be discussed off-site and resolved cooperatively. Any difficulties in conducting team inspections should be discussed with both District management and the assigning Center, and, if not resolved, immediately referred to DFI (HFC-130).

6. Inspections of facilities under the jurisdiction of the Veteran's Administration (VA)

a. Pre-Inspection

Center. The assigning Center will provide the VA Project Officer with written notification of FDA's intention to inspect a clinical investigator at a VA facility at the time an assignment is being issued to the field, per the terms of FDA/VA Memorandum of Understanding (MOU) FDA-225-82-8400 (http://www.fda.gov/oc/mous/domestic/225-82-8400.html).

This notice should be sent to:

Chief Officer
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs
811 Vermont Avenue, N.W., Suite 574
Washington, D.C. 20420

Field. The field investigator should contact the VA Medical Center Director before an inspection of a clinical investigator or sponsor-investigator at a VA facility. For inspections of military installations, the field investigator should contact the Chief of Professional Services at the facility to be inspected

b. **Post-Inspection**.

The Center contacts are authorized to provide redacted copies of post-inspection correspondence issued to VA facilities or employees following any BIMO inspection (including the FDA-483s).[4] Such materials should be sent to:

Chief Officer
Veterans Health Administration
Department of Veterans Affairs

[4] This authorization, has been renewed every two years, and currently extends to November 28, 2009.

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Office of Research Oversight
811 Vermont Avenue, N.W.
Suite 574 (10R)
Washington, D.C. 20420

If, following receipt of the FDA correspondence, the VA-ORO requests a copy of the EIR, a redacted copy of the report should be obtained from the district office and provided to VA-ORO.

Centers should contact the Director, Division of Compliance Policy, Office of Enforcement (HFC-230) for detailed instructions for such disclosures and key contact information. (This activity is subject to 21 CFR 5.23(a)(4), 20.85, and supported by FDA's continuing MOU with the VA (FDA-225-07-4300, (http://www.fda.gov/oc/mous/domestic/225-07-4300.html), which provides for the exchange of information between the two agencies.).

PART III - INSPECTIONAL

Inspections involve evaluation of the clinical investigator's or sponsor-investigator's practices and procedures to determine compliance with applicable regulations. When the inspection occurs as a result of FDA's receipt of a marketing application/submission, it will include a comparison of the data submitted by the sponsor to FDA with source documents at the clinical Investigator's site (i.e., where original source data are recorded; also known as supporting data) and case report forms (CRFs) in the clinical investigator's files. In such cases, the study will usually have been completed, possibly for a considerable time. If it is a "for cause" or surveillance inspection of an on-going study, data comparison will generally involve only source documents and case report forms, because there may not always be data supplied by the sponsor. Source documents may include office records, hospital records, laboratory reports, records of consultations, etc.

A. GENERAL

The following areas should be covered during all inspections.

1. Clinical investigator inspections are product specific, i.e., human drugs and biologics, animal drugs, medical devices, or foods. Field investigators must apply the pertinent regulations to each clinical investigator inspection.

2. Inspections under this program will be announced unless otherwise instructed in the inspection assignment. The field investigator should keep the time span between initial contact and actual inspection as short as possible. The field investigator should immediately report to the Center contact any attempt by the clinical investigator or sponsor-investigator to unduly delay an inspection, by more than ten working days, without sufficient justification.

3. Inspection Refusals

   a. Refusal of entry

   If a clinical investigator or the investigator's staff refuses to permit an inspection by FDA personnel, the field investigator should inform the clinical investigator about the regulatory requirements[5] permitting such inspections. If entry is still refused, the investigator should issue the completed Form FDA 482 (Notice of Inspection) to the most responsible person available and leave the premises. The investigator should immediately notify his supervisor, the District Compliance Officer, the assigning Center contact, and DFI (HFC-130) of this refusal.

   b. Refusal of Information

   If at any time during the inspection, the clinical investigator or a staff member refuses to allow FDA personnel access to or copying of records to which FDA is entitled under the law and regulations, the field investigator should inform the clinical investigator or the staff member about the regulatory

[5] See Sections 301(f) and 704 of the Federal Food, Drug and Cosmetic Act (FFDCA), Sections 351(c), 360A(a), (b) & (f); 360B(a); and 361(a) of the Public Health Service (PHS) Act, and 21 CFR 312.68 or 812.145.

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requirements[6] permitting this access. If access to or copying is still refused, the field investigator should continue with the inspection and notify his/her supervisor, the District Compliance Officer, the assigning Center contact and DFI (HFC-130). The same procedure should be followed when it becomes evident that delays by the clinical investigator or his staff are such that they constitute a de facto (i.e., actual) refusal.

When a refusal of entry or refusal to supply necessary information cannot be resolved by the assigning Center contact or DFI, and it is deemed necessary to pursue an inspection warrant, follow the procedures in the Regulatory Procedures Manual, Section 6-3, Inspection Warrants, and notify the Division of Compliance Management and Operations (DCMO, HFC-210).

4. Field investigators who observe or suspect deviations from the regulations that affect data integrity or endanger subject rights, safety, or welfare should immediately discuss their observations with their supervisor, District Compliance Officer, and the assigning Center contact and continue the inspection. The assigning Center will promptly determine if the inspection should be expanded or modified and provide direction on how to proceed in order to obtain appropriate documentation for the noted observations.

5. The field investigator issues a 483 at the conclusion of the inspection when deviations from regulations are observed. Approaches that differ from those described in FDA's guidance documents should not be listed on the 483 unless they constitute deviations from the regulations. Such deviations may be discussed with the clinical investigator or sponsor-investigator during the exit interview, however, and reported in the EIR.

The field investigator encourages the firm to submit a prompt written response to the District Office and Center regarding any inspection observations listed on the 483.

B. INSPECTION PROCEDURES

The Center may provide background information and special instructions with the inspection assignment. Review of records should include a comparison of data in source documents with case report forms as well as with any sponsor-provided data tabulations that may be included with the assignment.

The following outline provides only the minimum scope of the inspection, and each field investigator should expand the inspection as the circumstances warrant. Inspections should be sufficient in scope to cover special instructions in the assignment and to determine if the clinical investigator's practices and procedures comply with regulations. The field investigator should **not** attempt to scientifically evaluate the study data or protocol(s).

Full narrative reporting of any deviations from regulations should be thoroughly **documented**. For example, any records demonstrating discrepancies between source data, case report forms, and/or data submitted by the sponsor to FDA should be **documented** and copied. Discuss potential violations involving fraud subject to Title 18 of the United States Code (18 U.S.C.) with your supervisor, District Compliance Officer, and assigning Center contact for appropriate referral to the Office of Criminal Investigations.

[6] See Section 301(f) of the FFDCA, applicable sections of the PHS Act, and applicable regulations (e.g., 21 CFR 312.68, 812.145(c)).

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C. AUTHORITY and ADMINISTRATION for STUDIES INVOLVING HUMAN DRUGS, BIOLOGICS, and DEVICES

1. If available at the clinical investigator's site, compare the Statement of Investigator Form FDA-1572 (human drugs and biologics) or the Investigator's Agreement (medical devices) with the information provided by the assigning Center. If they are different, or if the assigning Center did not provide one, **obtain** a copy.

2. **Obtain** a list of all studies performed by the clinical investigator. This list should include available information such as:

   a. Protocol number;

   b. Protocol title, including the product name, and the research or marketing permit number, if available;

   c. Name of sponsor (including government agencies and commercial sponsors); and

   d. Study dates.

3. For the assigned study, **document** in the narrative of the EIR:

   a. The addresses of all locations at which study subjects were seen;

   b. How the sponsor provided information to the clinical investigator about the test article, protocol, and the obligations of a clinical investigator (e.g., telephone, memo, meeting);

   c. Whether the authority for the conduct of the various aspects of the study was contracted and/or delegated properly so that the investigator retained control and knowledge of the study. Include a list of delegated tasks. If there are questions about appropriate delegation, obtain information (e.g., curriculum vitae, medical or other license) about the qualifications of the person performing the task.

   d. The following dates:

      1. IRB approvals (human studies) including initial review of the protocol, all amendments, the informed consent document and all revised informed consent documents;

      2. For human studies, when the Form FDA 1572 or Investigator Agreement was signed by the clinical investigator (when available);

      3. When the first subject was screened;

      4. When the first subject signed the informed consent document;

      5. First administration of the test article; and

      6. Last follow-up for any study subject.

e. If the clinical investigator discontinued his/her participation in the study, **describe** the reason(s).

4. **List** the name and address of the facility(ies) performing laboratory or diagnostic tests required by the protocol. **Describe** the clinical investigator's documentation of the laboratory or diagnostic testing facility's qualifications (e.g., certification under CLIA--Clinical Laboratory Improvements Act). If any laboratory testing was performed in the investigator's own facility, **determine** whether that facility is equipped to perform each test specified. List name(s) of individuals performing such tests and indicate their position. Consult with the Center if there are questions related to a facility's qualifications or necessary documentation.

5. **Determine** the process used to recruit subjects. If any recruitment materials or phone recruitment scripts were employed, **document** their review and approval by the IRB, or note the absence of such approval (see E. 2. c. below). Also, **document** any instances in which the investigator utilized methods or distributed information that appeared to be coercive in nature[7], distributed any promotional material or otherwise represented the test article as safe and effective for the purpose for which it is under investigation, or implied in any manner a favorable outcome or other benefits beyond what was outlined in the consent document and protocol.

6. Obtain a copy of the site's enrollment log.

D. PROTOCOL for HUMAN DRUG, BIOLOGIC, or DEVICE STUDY

1. Compare the copy of the protocol provided with the assignment to the clinical investigator's copy of the protocol and amendments. If the protocols are different, or one was not provided, **obtain** a copy of the clinical investigator's protocol and amendments.

2. Become familiar with sections of the protocol, such as primary endpoint, eligibility criteria, scheduling of visits, test article accountability. Did the clinical investigator follow the protocol with respect to:

   a. Subject selection (i.e., inclusion and exclusion criteria);

   b. Number of subjects enrolled;

   c. Randomization scheme (where applicable);

   d. Required procedures and evaluations (e.g., blinding procedures);

   e. Administration of the investigational product:

[7] FDA's Information Sheet Guidance on Payments to Research Subjects states, "While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document." [http://www.fda.gov/oc/ohrt/irbs/toc4.html]

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i. for human drugs and biologics - dosage, route of administration, and frequency of dosage

ii. for devices – use according to manufacturer's directions; proper surgical techniques (where applicable)

f. Frequency of observations and testing prescribed for subject follow up; and

g. Any other information specific to the study and/or the inspection assignment.

3. **Verify** that the clinical investigator followed the study protocol approved by the IRB. The investigator is responsible for ensuring that an investigation is conducted according to the investigational plan. (21 CFR 312.60; 812.100) **Review** any changes to and deviations from the protocol.

Protocol changes/amendments. During the course of a study, a protocol may be formally changed by the sponsor. Such a change is usually prospectively planned and implemented in a systematic fashion through a protocol amendment. Protocol amendments must be reviewed and approved by the IRB, prior to implementation, and submitted to FDA.

Protocol deviations. A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective exception to the protocol (e.g. agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria). Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35(a)(2)), and generally communicated to FDA. "Protocol deviation" is also used to refer to any other, unplanned, instance(s) of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. **Determine** whether changes to the protocol were:

i. Documented by an amendment, dated, and maintained with the protocol;

ii. Reported to the sponsor (when initiated by the clinical investigator); and

iii. Approved by the IRB and FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazard(s) to human subjects).

For device studies: **determine** whether deviations to the protocol were:

i. Documented, showing dates of and reason for each deviation;

ii. Documented, with prior approval from the sponsor for deviations from the investigational plan, except if emergency use (see iv).

iii. Documented, with prior approval from the reviewing IRB and FDA for deviations from the investigational plan that may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, except if an emergency (see iv).

iv. If emergency use, documented notification of the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well being of a subject. In addition, determine that this notice was given within 5 working days after the emergency occurred. (21 CFR 812.150(a)(4))

Collect correspondence or other documentation that supports adverse inspectional observations.

E. INSTITUTIONAL REVIEW BOARD (IRB) for HUMAN DRUG, BIOLOGIC, or DEVICE STUDY

1. **Identify** the name, address, and chairperson of the IRB for the study.

2. **Determine** and **describe** if the investigator obtained IRB approval of the items listed below before initiation of study-specific procedures on subjects:

   a. The protocol and any amendments;

   b. The informed consent documents; and

   c. Advertisements and other information provided to prospective study subjects.

3. **Describe** the nature and frequency of communications with the IRB. **Determine** whether the investigator submitted information promptly to the IRB, in compliance with the protocol and applicable regulations, of all deaths, serious adverse experiences, and unanticipated problems involving risk to human subjects.

4. If there is a question as to whether the correct consent document was used, **obtain** a copy of each version of the consent document approved by the IRB for the study(ies).

5. Collect correspondence or other documentation that supports adverse inspectional observations.

F. HUMAN SUBJECTS' RECORDS

1. Informed Consent

   a. **Describe** the informed consent process.

      For the study being inspected, include the following information:

i. Who (investigator, nurse, study coordinator, etc.) explained the investigational study and consent document to prospective study subjects, and was it provided in a language understandable to each subject?

ii. How did the informed consent process take place? (e.g., was this explanation given orally, by video, through a translator, etc.)?

iii. Was consent obtained prior to enrollment in the study (i.e., prior to performance of any study related tests and administration of the test article)?

iv. After signing and dating the informed consent document, was each subject or the subject's legally authorized representative given a copy of the consent document?

v. Was the appropriate IRB-approved version of the informed consent document used for all subjects?

vi. If the short form was used (per 21 CFR 50.27(b)(2)), was the informed consent process appropriately documented?

a. Did the subject or the subject's representative sign the short form?

b. Was a witness present, who signed the short form and the copy of the summary?

c. Did the person actually obtaining the consent sign a copy of the summary?

d. 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?

vii. **Review** the IRB approval letter for the study. Did the IRB stipulate any conditions for the informed consent process and, if so, did the clinical investigator follow those instructions/stipulations?

b. **Review** the informed consent documents signed by the subjects. If the number of subjects at the site is relatively small (e.g., 25 or fewer subjects), review 100% of the informed consent documents. For larger studies, a representative number of informed consent documents should be reviewed (for example, may be specified in a sampling plan provided with the assignment). **Determine** the following:

i. Did the subject or the subject's legally-authorized representative sign the informed consent document prior to entry into the study? 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.

ii. Whether subjects signed the version of the informed consent document that was current at their time of entry into the study.

iii. For pediatric studies, was assent obtained from the subjects in addition to the permission of the parents?

iv. Whether the written consent document(s) or oral consent complies with the eight (8) required elements in 21 CFR 50.25(a).

If any problems are found (e.g., investigator failed to obtain consent from one or more subjects, consent was not obtained prior to enrollment in the study, investigator failed to use the correct informed consent document, etc.), the sample should be expanded to **determine** the extent of the problem. Collect documentation to support each observation. **Report** the total number of informed consent documents that were reviewed and the number of documents exhibiting the problem.

2. Source Documents

a. **Describe** the investigator's source documents in terms of their organization, condition, completeness, and legibility.

b. **Determine** whether there is adequate documentation to ensure that all subjects were alive and available for the duration of their stated participation in the study.

c. **Determine** whether the records contain:

i. Observations, information, and data on the condition of the subject at the time of entry into the clinical study, as required by the protocol;

ii. Documentation of the subject's exposure to the test article, as required by the protocol;

iii. Observations and data on the condition of the subject throughout participation in the investigation, including results of lab tests, development of unrelated illness, and other factors which might alter the effects of the test article; and

iv. Identification of key personnel involved in collecting and analyzing data at the site.

3. Case Report Forms (CRFs)

a. **Describe** the process for obtaining and recording information in CRFs.

i. Who obtained and recorded the information;

ii. The source of the information (e.g., were data transcribed from another document or were data recorded directly onto the CRF); and

iii. Whether corrections were made to the CRF data entries. If corrections were made, **determine** who made them, the reason(s) for the changes, and whether the clinical investigator was aware of these changes.

b. Compare the source documents with the CRFs and any background information provided (e.g., data tabulations provided by the sponsor) per the assignment memorandum and sampling plan (if applicable). **Determine** whether:

i. The study subjects met the eligibility criteria (inclusion/exclusion);

ii. Protocol-specified clinical laboratory testing (including EKGs, X-rays, eye exams, etc.) was documented by laboratory records;

iii. All adverse events were documented and appropriately reported;

iv. The clinical investigator assessed the severity of the adverse event and documented the relationship of the event to the test article, including any adverse event that was previously anticipated and documented by written information from the sponsor; and

v. All concomitant therapies and/or inter-current illnesses were documented and reported.

c. **Determine** whether the clinical investigator reported all dropouts and the reasons to the sponsor.

G. OTHER STUDY RECORDS

Study-related information may also be recorded in other documents. **Determine** if the clinical investigator maintains other records pertinent to the study, e.g., administrative study files, correspondence files, master subject list, appointment books, sign-in logs, screening lists, and MedWatch forms. Review these records to ensure that all pertinent information has been reported to the sponsor. **Document** any discrepancies found.

H. FINANCIAL DISCLOSURE

1. Ask the clinical investigator if and when he disclosed information about his financial interests to the sponsor and/or interests of any subinvestigators, spouse(s) and dependent children. (21 CFR 54.4(b))

2. Ask the clinical investigator if and when he updated the information about such financial interests, to report changes that occurred in the value of the financial interests during the course of the clinical investigation or within one year following completion of the study. (21 CFR 54.4(b))

I. ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

Computerized systems are commonly used in clinical investigations to collect and preserve clinical

data. Computerized systems range from isolated pieces of equipment that are used at a clinical site to collect/archive clinical data (e.g., a laptop) to complex integrated systems that consist of a variety of hardware, firmware, and software components that are located at multiple sites (e.g., a web-based system managed by an independent software vendor to which the sponsor and clinical sites have controlled access).

Regardless of the type of system used by the clinical site, an important principle to understand when evaluating clinical research data is that the regulatory requirements for the clinical data do not change whether clinical data are captured on paper, electronically, or using a hybrid approach. Data must be reliable and usable for evaluating the safety and/or effectiveness of FDA-regulated products.

Another important point is that the agency has stated in its guidance entitled "Guidance for Industry Part 11, Electronic Records; Electronic Signatures" (Part 11 Guidance) that only certain electronic records will be subject to 21 CFR 11 (Part 11), and that the agency intends to exercise enforcement discretion with regard to specific Part 11 requirements. Part 11 describes the technical and procedural requirements that must be met if a firm chooses to maintain records electronically and/or use electronic signatures. Part 11 is a companion regulation to other FDA regulations and laws. It is in these other regulations and laws, called "predicate rules," where specific requirements for issues such as recordkeeping, record content, signatures, and record retention are addressed.

Section III. B. 2 of the Part 11 guidance states that Part 11 is applicable to the following electronic records and electronic signatures:

- Records that are required to be maintained under the predicate rules and that are maintained in electronic format *in place of paper format*.
- Records that are required to be maintained under the predicate rules, that are maintained in electronic format *in addition to paper format*, and *are relied on to perform regulated activities.*
- Records that are submitted to FDA, under predicate rules, that are in electronic format.
- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials or other general signings that are required by the predicate rules.

In Section III. C of the Part 11 guidance, specific requirements for which the agency intends to exercise enforcement discretion include the:

- Validation of computerized systems;
- Use of computer-generated, time-stamped audit trails;
- Use of legacy systems;
- Generation of copies of records;
- Protection of records (i.e., record retention and availability)

The field investigator should consult with the Center contact for guidance on the depth to which Part 11 issues should be covered during an inspection. When assessing study compliance, any discrepancies should be **documented** under the appropriate predicate rule requirement. Questions should be referred to the Center contact.

Current changes *{ED: Retain "current changes" only in sections where changes made}*

1. SCOPE OF ELECTRONIC RECORDS/ELECTRONIC SIGNATURES

a. **Determine** whether electronic records and/or electronic signatures are required by predicate rules, and/or are used in place of paper records (or relied upon to perform regulated activities) and handwritten signatures. If this is the case, requirements of Part 11, as interpreted by the "Scope and Application Guidance," apply. If this is not the case, Part 11 requirements do not apply, and the paper records should be evaluated for compliance with the applicable regulations.

b. **Determine** whether electronic data and data collection methods are defined in the study protocol. **Describe** any computerized system(s) used at the study site(s) to generate, collect, or analyze data (e.g., stand alone personal computer, web-based system, hand held computers).

c. **Determine** whether electronic records are available for inspection and have been retained for the required period of time.

2. PROCEDURES

a. How does the firm determine which records are used for regulatory purposes (e.g., does the firm have and did it follow an SOP)?

b. Does the firm have procedures and controls in place to create, modify, maintain, or transmit electronic records, e.g., operating instructions, access policies and procedures, training policies, or management controls?

c. Were the individuals who develop, maintain or use the computerized systems given the education, training, and experience necessary to perform their assigned tasks?

3. DATA COLLECTION:

a. Is the clinical investigator able to ensure accurate and complete electronic and human readable copies of electronic records, suitable for review and copying? (If you are unable to access records from the computerized system, contact the Center immediately.)

b. **Determine** whether electronic records and data meet the requirements applicable to paper records. For example, are electronic records used to meet case history requirements attributable, legible, contemporaneous, original, and accurate (ALCOA)?

c. **Describe** how data is transmitted to the sponsor or contract research organization.

d. **Determine** whether original data entries and changes can be made by anyone other than the clinical investigator.

e. **Determine** how the electronic data was reviewed during monitoring visits. Document unauthorized changes or modifications made to original data and by whom.

4. SECURITY

a. **Determine** who is authorized to access the system.

b. **Describe** how the computerized systems are accessed (e.g., password protected, access privileges, user identification).

c. How is information captured related to the creation, modification, or deletion of electronic records (e.g., audit trails, date/time stamps)?

d. **Describe** whether there is backup, disaster recovery, and/or contingency plans to protect against data loss. Were there any software upgrades, security or performance patches, or new instrumentation during the clinical trial? Could the data have been affected?

e. **Describe** how error messages or system failures were reported to the sponsor, CRO, or study site and the corrective actions, if any, that were taken.

f. How were the system and data handled during site closure?

J. TEST ARTICLE CONTROL

1. Accountability [312.62(a), 511.1(b)(7)(ii), and 812.140(a)(2)]

a. **Determine** who is authorized to administer or dispense the test article.

b. **Determine** whether the test article was supplied to a person not authorized to receive it.

c. **Compare** the amount of test article shipped, received, used, and returned or destroyed. **Verify** the following:

i. Receipt date(s), quantity received, and the condition upon receipt;

ii. Date(s), subject number, and quantity dispensed; and

iii. Date(s) and quantity returned to sponsor. If not returned to sponsor, **describe** the disposition of the test article.

d. **Determine** where the test article is stored, whether it was stored under appropriate conditions as specified in the study protocol, and who had access to it.

e. If the test article is a controlled substance:

i. **Determine** how it is secured; and

ii. **Determine** who had access.

2. **Inspect** unused supplies and **verify** that the test article was appropriately labeled.

K. RECORDS CUSTODY AND RETENTION

Determine whether study records are retained according to the protocol and 21 CFR 312.62(c), 511.1(b)(7)(ii), and 812.140(d) and (e).

L. REPORTS TO SPONSOR

Determine if required reports (including case report forms) are submitted to the sponsor in accordance with the study protocol and 21 CFR 312.64, 511.1(b)(7)(iii), and 812.150.

M. MONITORING

1. **Determine** if the sponsor monitored the progress of the study to assure that the investigator complied with the protocol and applicable regulations.

2. **Describe** monitoring activities.. Examples:

   a. Pre-study contacts with the clinical investigator (e.g., meetings, visits, correspondence);

   b. Frequency and nature of monitoring (e.g., on-site visits, telephone calls, facsimile, e-mail);

   c. **Determine** if the study records include a log of on-site monitoring visits,,written reports or other communication provided to the clinical investigator. **Obtain** a copy of the log (if any) and examples of monitor reports and communications; and

   d. Follow up activities performed by the clinical investigator when the monitor(s) found deficiencies or recommended changes, for example, in the conduct of the study or records associated with the study.

3. For sponsor-investigators, **determine** if any monitoring was done for the study and, if so, **describe. Obtain** a copy of the monitoring SOP, if available.

N. ANIMAL CLINICAL STUDIES

The regulations for investigational new animal drugs are found at 21 CFR 511.1. In order to carry out studies involving investigational new animal drugs, the sponsor must submit a Notice of Claimed Investigational Exemption per 21 CFR 511.1(b)(4). The regulations pertaining to new animal drugs for investigational use differ from the requirements of the human drug regulations in several ways. For example, there is no requirement that the sponsor obtain a commitment from the investigator to comply with applicable regulations or use Forms FDA 1571 or 1572; there is no requirement that an approved protocol be used, or even that a protocol be submitted to FDA's Center for Veterinary Medicine (CVM).

For these reasons, inspections of animal clinical trials are extremely important as a means of verifying that the clinical investigator is complying/has complied with regulatory requirements for these studies.

In 2001, CVM adopted "Guidance for Industry, Good Clinical Practice, VICH GL9" (also known as CVM Guidance 85; see Part VI, Reference Section). This represents CVM's current thinking on acceptable clinical trial practices for veterinary medicinal products in the target species. Ask the clinical investigator if he is aware of (e.g., has a copy, has read) this guidance. If necessary, provide the clinical investigator with a copy of the guidance. Approaches that differ from those described in FDA's guidance document should not be listed on the 483 unless they constitute deviations from the regulations. Such deviations may be discussed with the clinical investigator or sponsor-investigator during the exit interview, however, and reported in the EIR.

1. If the sponsor submitted a protocol, **compare** that protocol with the copy of the protocol used by the clinical investigator. Note any differences and **document** any deviations.

2. **Examine** the facilities for compliance with the protocol (if available) and any written procedures. **Describe** any differences observed. If appropriate, take photographs of the research facilities for inclusion in the EIR.

3. **Report** on the condition of the animals and adequacy of husbandry practices.

4. **Report** the method used to identify study animals.

5. **Collect** a copy of the clinical investigator's final report.

6. **Determine** if multiple versions of data exist and which data are source data. Document discrepancies between versions, e.g., paper and electronic media or source data and the final report.

7. Data may be collected on individual animals (e.g. weight) but other data may be collected on the "group" (e.g., feed consumption). To calculate feed conversion (i.e., weight of feed/weight of animal), individual body weights should be summed within a feed consumption group, in order to determine this measure. **Determine** whether scientific measurements are made on individual animals or on groups, i.e., herds, pens, or flocks. **Determine** whether the investigator maintains records on these groups.

8. **Determine** the number of animals by age, weight, sex, and breed. Compare to the protocol and report any discrepancies.

9. **Determine** whether this is the only study each test animal has participated in within a 30-day period prior to initiation or after completion of the study.

10. **Document** the history of the test animals including any prior treatments or vaccinations.

11. **Determine** the actual inclusion/exclusion procedure that was done compared to the procedures noted in the protocol. **Describe** any differences.

12. **Document** any other drugs, vaccines, pesticides or other chemicals used on the animals during the study.

13. **Determine** the scope and extent of the blinding procedures employed in the study and **document** any practices that may have compromised the blinding procedures.

14. For studies involving drugs in animal feeds, review the drug mixing and feed allocation procedures. **Determine** if proper drug mixing procedures were followed. **Reconcile** the amount of feed allocated during the study against the amount of feed mixed for each treatment group.

15. **Determine** whether the medicated feed is mixed on premises. (If not, report name and address of the mill utilized.)

16. **Determine** the method used to identify each lot of drug or medicated feed, and the number of samples and types of assays run on the finished feed to verify dosage level. If available for sampling, check with the Center contact on the need to collect a sample.

17. If the investigation involves food-producing animals, **determine** whether the investigator observed the time periods (withdrawal, withholding, or discard periods) required for authorization to use edible products from such animals.

18. **Determine** if there is any evidence of unreported adverse reactions. Study-related information may also be recorded in other documents. Review the investigator's notes, observed clinical signs, clinical pathology, and diagnostic reports to ensure that all pertinent information has been reported to the sponsor. **Document** any discrepancies.

19. **Reconcile** the number of animals allocated to the study with the number of animals that completed, were removed, or died during the study. **Document** and report any differences.

20. **Examine** animal waste and carcass disposal records, and **determine** if the methods of disposal were consistent with any protocol requirements.

21. **Determine** whether the investigator informed the owner(s) of each animal that the test article is being used for research purposes and whether owner consent was documented. (Current regulations do not require written consent.)

22. **Reconcile** the amount of investigational drug received, dispensed during the study, and returned to the sponsor or otherwise disposed of. Verify the dosing procedure was performed according to protocol requirements. Document and report any discrepancies.

23. **Confirm** whether additional studies were conducted with the test article and obtain copies of final reports for these studies.

24. **Determine** whether the clinical investigator has done/is doing any nonclinical animal studies (i.e., studies subject to FDA's Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies requirements at 21 CFR 58).

O. DEVICE STUDIES

The regulations for investigational devices are found in 21 CFR 812. They do not contain all the provisions of the drug regulations. For example, there is no requirement that Forms 1571 or 1572 be used but there is a requirement for a signed investigator agreement.

1. Determine whether the clinical investigation poses a significant risk (IDE), non-significant risk (abbreviated requirements at 21 CFR 812.2(b)), or is IDE exempt (21 CFR 812.2(c)).

2. **Determine** whether the clinical investigator has used the test article under the emergency use or expanded access[8] provisions.

3. **Determine** if the clinical investigator is involved in any nonsignificant risk (NSR) studies and, if so, obtain a list of these studies from the clinical investigator and ascertain if they are being conducted in compliance with the regulations (Note: Unless FDA made an NSR determination for the study, there must be an NSR determination by an IRB. IRB approval is also required for NSR studies; see 812.2(2)(b)(1)(ii).)

4. **Determine** if the clinical investigator has been involved in any use of a custom device.[9] If so, first make sure the device meets the definition of a custom device (21 CFR 812.3(b)) Contact the Center for further guidance.

5. **Determine** if the clinical investigator has utilized a Humanitarian Use Device (HUD)[10] as provided by 21 CFR Part 814, Subpart H. If so, **obtain** the following:

   a. Name of the device;

   b. Documentation of IRB approval (see 21 CFR 814.124);

   c. Number of patients treated and the indications for which the HUD was used; and

[8] Expanded access mechanisms for unapproved devices include emergency use and compassionate use. Emergency use is available when there is a serious disease or condition, no alternative, and no time to obtain FDA approval. Generally, FDA has considered this to be applicable when a patient is at risk for loss of life, limb or eyesight. Compassionate use is available for a single patient or group of patients that do not meet the study inclusion criteria where there is a serious disease or condition, and no alternative. Patient protection measures are the same for both: informed consent, IRB/chairperson's approval; independent assessment; and institutional clearance. Compassionate use of a device under an approved IDE requires submission of an IDE supplement requesting approval of a deviation from the study protocol. 21 CFR 812.35(a).

[9] A custom device is a device that has been custom developed for use by an individual patient under the order of a physician or dentist; or is intended to meet the needs of a physician or dentist in the course of professional practice. See 21 CFR 812.3(b) for a complete definition of custom device.

[10] A Humanitarian Use Device (HUD) is a device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. (21 CFR 814.3(n))

d. **Document** any emergency use.

P. ESTABLISHMENT INSPECTION REPORTS (EIRs)

If the inspection assignment resulted from FDA's receipt of a marketing application/submission, information contained in the EIR may be used in support of marketing approval or denial. If the inspection was assigned "for cause" or as part of general surveillance, information contained in the EIR may be used to determine if the on-going study should be allowed to continue, either in its entirety or at the specific site. Therefore, the EIR must **document** all observations that could significantly impact the decision-making process.

1. Standard Narrative Report

   a. A standard narrative report will be prepared and submitted in the following situations:

      i. The initial inspection of a firm;

      ii. Any inspections for which the field recommends an Official Action Indicated (OAI) classification; and

      iii. Any assignment specifically requesting a standard narrative report.

   b. Refer to IOM 5.10.4, Narrative Report. Individual sections that are relevant to a BIMO standard narrative report include: Summary; Administrative Data; History; Individual Responsibility and Persons Interviewed; Objectionable Conditions and Management's Response; Supporting Evidence and Relevance; Discussion with Management; Refusals; General Discussion with Management; Additional Information; Voluntary Corrections; Exhibits Collected; Attachments; and Signature. See also, IOM 5.2.9: Interviewing Confidential Informants.

   c. In addition to these, include the appropriate headings outlined in Part III of this Compliance Program (Sections III. C through O). The report must always include sufficient information and documentation to support the recommended classification.

2. Summary of Findings Report

   a. A Summary of Findings Report may be submitted for non-violative inspections of clinical investigators who have previously been inspected. A full inspection must be conducted even if a summary of findings report is appropriate, i.e., an abbreviated inspection is not justified. A Summary of Findings report must contain sufficient narrative and accompanying documentation to support the inspectional observations. The specific headings appearing under Part III. Inspection Procedures, should be fully addressed during the inspection. In addition, the EIR should be clearly identified as a summary of findings report.

   b. The report should include information described in IOM 5.10.4.1, Narrative Reports for Non-Violative Establishments:

i. Reason for inspection;

ii. Date, classification and findings of the previous inspection;

iii. The inclusive dates of the inspection;

iv. Name of the person to whom credentials were shown and the Notice of Inspection was issued and the person's authority to receive the Notice;

v. Scope of the inspection, including:

a. A definitive statement about the documents that were examined. For example, "The inspection package provided ten case report forms. I attempted to compare them with corresponding hospital charts."

b. Protocol title, protocol number, name of the sponsor, and the FDA research (IND, IDE, INAD) or marketing (NDA, BLA, PMA, NADA) permit numbers;

c. A list of the addresses of all locations at which study subjects were seen;

d. Statement about who obtained informed consent and how it was obtained;

e. Information regarding who monitored the trial, and when;

f. Statement of test article accountability records that were reviewed;

g. Statement whether there was evidence of under-reporting of adverse experiences/events; and

h. Statement about protocol adherence;

vi. Significant observations, if any;

vii. Statement of the close-out discussion and the clinical investigator's response(s) or correction(s);

a. Discussion of inspectional observations, including observations noted on the 483;

b. 483 observations should be referenced in the EIR; documentation of the observations should be included as exhibits;

c. Firm's response to the 483 observations. Attach any response to the EIR if provided by the clinical investigator prior to EIR submission to the Center;

viii. FDA Investigator's handwritten signature, and signature(s) of other members of the inspection team, if applicable.

Q. INTERNATIONAL INSPECTIONS (Human clinical investigations)

1. Inspections of U.S. Clinical Investigators by Foreign Health Authorities

Health authorities from European Union (EU) or other countries (e.g., Japan's Pharmaceutical and Medical Devices Agency [PMDA], Health Canada) may conduct inspections of clinical investigator sites in the U.S. In addition to complying with U.S. regulations, clinical investigator sites may be required to comply with non-U.S. requirements that are potentially more stringent (in some areas) than U.S. requirements.

If the field investigator becomes aware that a U.S. clinical investigator site has had an inspection by a non-U.S. inspectorate, this should be noted in the EIR (which inspectorate and the dates of the inspection).

2. Inspections of Non-U.S. Clinical Investigators – Human Drugs and Biologics

Sponsors are not required to conduct non-U.S. clinical trials under IND, but often submit data from such trials to FDA in support of marketing or research applications.

FDA recently revised its criteria for accepting non-IND, non-U.S. clinical studies as support for an IND or a new drug application (NDA). See 21 CFR 312.120 (http://www.fda.gov/oc/gcp/regulations.html). These regulations are effective October 27, 2008.

FDA's requirements for accepting such studies are as follows:

- The study must be conducted in accordance with Good Clinical Practice (GCP), which is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.

  GCP also includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or the subject's legally authorized representative if the subject is unable to provide consent) before initiating a study.

- FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

A sponsor or applicant is required to submit the following information for non-IND foreign clinical trials to FDA, as support for an IND or application for marketing approval:

a. The investigator's qualifications;
b. A description of the research facilities;

c. A detailed summary of the protocol and study results, and if we request them, case records or additional background data;
d. A description of the drug substance and drug product, including components, formulation, specifications, and, if available, the bioavailability of the drug product;
e. Information showing that the study is adequate and well controlled (if the study is intended to support the effectiveness of the product);
f. The name and address of the independent ethics committee (IEC) that reviewed the study and a statement that the IEC meets the definition in 21 CFR 312.3;[11]
g. A summary of the IEC's decision to approve or modify and approve the study or to provide a favorable opinion;
h. A description of how informed consent was obtained;
i. A description of what incentives, if any, were provided to subjects to participate;
j. A description of how the sponsors monitored the study and ensured that the study was consistent with the protocol; and
k. A description of how investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained (any signed commitments must be maintained and available for agency review).

If the inspection involves a non-U.S. study that is not conducted under an IND, the documentation listed above may need to be verified on-site during the inspection. **Consult** with the Center contact about the need to **verify** such documentation.

3. International Inspections - Devices.

In general, according to 21 CFR 814.15, FDA will accept research in support of a PMA, but which has not been conducted under an IDE, provided that the data are valid and the studies are conducted in conformance with the "Declaration of Helsinki,"[12] or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subjects.

Field investigators may be asked to conduct inspections of non-U.S. device studies, and to collect documentation as to the standards under which the study was conducted.

[11] 21 CFR 312.120 defines "independent ethics committee" as "a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board (IRB), as defined in § 56.102(g) of this chapter and subject to the requirements of part 56 of this chapter, is one type of IEC."

[12] 21 CFR 814 refers to the Declaration of Helsinki as revised in 1983. There have been subsequent revisions of the Declaration, but FDA has not officially adopted subsequent versions.

R. SAMPLE COLLECTION

Collect samples of the investigational product only upon specific instructions by the Center. For example, if irregularities in the product are suspected (e.g., if, in an investigational drug study, there is a noticeable difference in color, size, shape, dosage form, route of administration, etc., between the investigational drug and the placebo or control), the Center may request that investigational samples (1 package) of each be collected. Contact your supervisor and Center contact prior to collecting an investigational sample. [See Part IV - Analytical.]

PART IV - ANALYTICAL

Centers will provide specific instructions if sample analysis of investigational products is needed (e.g., complaint investigation or for-cause inspection of an ongoing study). Contact the Center for additional guidance. [See also III. Inspectional, R. Sample Collection.]

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

A. ADMINISTRATIVE GUIDANCE

1. District EIR Classification Authority

The District is encouraged to review and initially classify EIRs under this compliance program as outlined in item 3 below.

2. Center EIR Classification Authority

The Center has final classification authority for all EIRs generated under this compliance program. If the Center is considering a classification that differs from the District's recommended classification, the Center will contact the District to discuss the issues (see Part II B. 3. c) as soon as possible to avoid delays in the final classification process. In addition, the Center will provide the District with notice of all final classifications, including the rationale for any that differ from the District's initial classification.

3. EIR Classifications

The following guidance is to be used in conjunction with the instructions in FMD-86 for initial District and Center classification of EIRs generated under this compliance program:

a. NAI - No Action Indicated. No objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action);

b. VAI - Voluntary Action Indicated. Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action; and

c. OAI - Official Action Indicated. Regulatory and/or administrative actions will be recommended.

4. Administrative/Civil/Criminal Actions will be in accordance with 21 CFR Parts 312, 511, and 812. FDA can invoke other legal sanctions under the FFDCA and/or Title 18, USC where appropriate.

a. Administrative Actions. The following administrative actions are available:

i. Untitled Letters
ii. Warning Letters
iii. Reinspection to verify corrective actions
iv. Regulatory meetings
v. For a study subject to 21 CFR 312, placing a clinical hold on the study
vi. If inspection involves a study subject to 21 CFR 812, withdrawal of approval of IDE application
vii. If inspection involves a study subject to 21 CFR 511, termination of exemption.
viii. Rejection of data from that site
ix. Initiation of Disqualification Proceedings

x. Consent agreements
xi. Device detention
xii. Referral of pertinent matters, with headquarters concurrence, to other Federal, state, or local agencies for such action as that agency deems appropriate.
xiii. For Sponsor-Investigators, additional administrative/enforcement actions that may be applicable are described in the Sponsors, Contract Research Organizations and Monitors Compliance Program (7348.810)

c. Civil/Criminal Actions. The following actions are available:

i. Seizure of test articles
ii. Injunction
iii. Civil Money Penalties
iv. Prosecution under the FFDCA or other Federal statutes, e.g., 18 U.S.C. 2, 371, 1001, and 1341.

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B. REGULATORY GUIDANCE

The following criteria are relevant to FDA's classification of inspections of clinical investigator sites:

No Action Indicated (NAI). No objectionable conditions or practices (e.g., violations of 21 CFR Parts 50, 54, 56, 312, 511, 812) were found during the inspection, or the significance of the documented objectionable conditions found does not justify further FDA action.

Any post-inspectional correspondence acknowledges the investigator's basic compliance with pertinent regulations.

Voluntary Action Indicated (VAI). Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any further regulatory (advisory, administrative, or judicial) action because the objectionable conditions do not meet the threshold for regulatory action (i.e., regulatory violations uncovered during the inspection are few and do not seriously impact subject safety or data integrity).

Post-inspectional correspondence will identify the issues and, when needed, state that FDA expects prompt, voluntary corrective action by the investigator.

Official Action Indicated (OAI). If objectionable conditions were found, one of the actions listed below should be recommended. Specifically, regulatory violation(s) uncovered during the inspection is/are repeated[13] or deliberate[14] and/or involve submission of false information to FDA or to the sponsor

[13]Repeated violation means more than one violation, including the same violation, in one or more studies. See Commissioner's Decision, Regulatory Hearing on the Proposal to Disqualify Layne O. Gentry, M.D. (2008).
[14] Deliberate Violation is defined as a willful action that need not entail knowledge that it is a violation of law as long as there is some perception of wrongdoing or of reckless disregard for obvious or known risks. See Commissioner's Decision, Regulatory Hearing on the Proposal to Disqualify Layne O. Gentry, M.D. (2008).

Current changes *{ED: Retain "current changes" only in sections where changes made}*

in any required report. The regulatory violation(s) uncovered is/are significant/serious and/or numerous, and the scope, severity, or pattern of violation(s) support a finding that:

a) Subjects under the care of the investigator would be or have been exposed to an unreasonable and significant risk of illness or injury. OR
b) Subjects' rights would be or have been seriously compromised. OR
c) Data integrity or reliability is or has been compromised.

Post-inspectional correspondence should be either a Warning Letter (WL) or a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE).

Once an OAI decision is reached, additional information (e.g., previous inspectional findings, correspondence, or other information about the clinical investigator) may assist the Center in determining which type of post-inspectional correspondence is appropriate. If the Center chooses to issue a WL and allow the clinical investigator to submit a detailed corrective action plan or alternate approach that is acceptable to FDA, the Center should nevertheless be prepared to initiate disqualification proceedings should the clinical investigator not respond appropriately (i.e., fails to respond, fails to develop an adequate corrective action plan, or is found, during a subsequent inspection, to have failed to comply with a corrective action plan).

A Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) May be Considered When:

The inspectional findings meet the criteria for OAI above, indicating that an investigator (including a sponsor-investigator) has

1) Repeatedly or deliberately failed to comply with the requirements for conducting clinical trials (21 CFR 312, 511, 812, 50, or 56); and/or

2) Repeatedly or deliberately submitted false information to FDA or to the sponsor in any required report.

A Warning Letter may be considered when the violations can be corrected through specific action(s) by the investigator (e.g., preparation of, and compliance with, a detailed corrective action plan, that is acceptable to FDA) and adherence to the corrective action plan has a high probability of preventing similar or other violations from occurring in the future.

EXAMPLES

The following are intended to serve as examples of violations that, alone or in combination, would be considered significant and may warrant OAI classification. This list is not all inclusive; other circumstances may also merit OAI classification.

Violations included under "Data Integrity" categories could apply to studies conducted under 21 CFR 312, 511, or 812. Violations included under "Inadequate Human Subject Protection" would apply only to studies involving human subjects (i.e., conducted under 312 or 812).

When applying the classification criteria, Center reviewers will generally evaluate the impact of the investigator's actions (number, scope, and severity of the regulatory violations) on the protection of the subjects in the study, and the reliability and acceptability of the data. There are gradations in the severity of each example, and the specific observation(s) should support the seriousness of the violation(s) and the effect(s) on physical harm to subjects, compromise to subjects' rights, and/or the reliability and acceptability of data for FDA decision-making purposes.

Inadequate Human Subject Protection	
Violation/Related Citation	**Examples**
Failed to inform subjects that they could refuse to participate 21 CFR 50.25(a)(8); 50.20; 50.27	No documentation to show that subjects received either oral or written information about their right to refuse to participate
Repeated or deliberate failure to obtain informed consent in accordance with 21 CFR Part 50 21 CFR 50.20; 50.27; 21 CFR 312.60; 312.62(b); 21 CFR 812.100; 812.140(a)(3)(i); 812.150(a)(5)	Missing consent documents; omission of a description of one or more required elements when obtaining consent
Prevented subjects from withdrawing from study 21 CFR 312.60; 21 CFR 50.25(a)(8);	Study or institutional records indicate subject(s) request to withdraw was denied
	No documentation to show that subjects were informed they could withdraw without penalty
Repeated or deliberate failure to provide study information in language understandable to the subject(s) or his legally authorized representative (LAR) 21 CFR 50.20	Evidence of non-English speaking subjects but no translated informed consent document or short form and summary was provided to the subject or his LAR
Failure to supervise the clinical trial, such that subjects are or would be exposed to unreasonable and significant risk or injury 21 CFR 312.60; 21 CFR 812.100; 812.110(c)	Records showing the CI failed to appropriately delegate study related duties to qualified personnel (e.g., physical exams, Serious Adverse Event (SAE) evaluations), with resultant exposure of subjects to unreasonable and significant risk or injury

Inadequate Human Subject Protection	
Violation/Related Citation	**Examples**
Failure to ensure that study has IRB review and approval; failure to ensure that IRB has reviewed and approved changes in the research when such changes are not necessary to eliminate hazard to the subject 21 CFR 312.66; 21 CFR 812.150(a)(4); 812.110(a)	No documentation of IRB approval of protocol or amendments
Enrolled subjects before IRB approval obtained 21 CFR 312.66; 21 CFR 812.110(a)	Date of IRB approval after first subject(s) enrolled into study
Protocol Violations 21 CFR 312.60; 312.66; 21 CFR 812.100; 812.110(b)	Enrolling subjects who do not meet the entrance criteria because they have conditions that put them at increased risk
Failure to report serious or life-threatening adverse events to the sponsor 21 CFR 312.64(b)	No evidence that SAEs were reported to the IRB and/or sponsor
Failure to report to the IRB, and for devices, to the sponsor, unanticipated problems involving risk to human subjects or others 21 CFR 312.66; 21 CFR 812.150(a)(1)	No evidence that unanticipated problems were reported to the IRB or sponsor

Data Integrity: Submission of False Information to FDA or the sponsor	
Violation/Related Citation	**Examples**
Study records are fabricated, altered, or concealed 21 CFR 312.70; 312.62(b); 21 CFR 511.1(c); 511.1(b)(7)(ii); 21 CFR 812.119; 812.140(a)	CRFs for study subjects who did not exist or did not participate in the study
	Falsified consent documents (signatures do not match)
	Falsified records of IRB review and/or approval (human studies
	CRFs include results about protocol-required procedures that were never done
	Specimens and/or analytical results characterized as being from a study subject that were from a different individual
False or misleading reports were prepared and/or submitted 21 CFR 312.70; 312.64; 21 CFR 511.1(c); 21 CFR 812.119, 812.150(a)	False safety data or reports are submitted
Inadequate supervision of study personnel who, in turn, fabricated, altered, or contributed false information to study records or reports 21 CFR 312.60; 21 CFR 812.100; 812.110(c)	Signatures on CRFs and/or other study documents do not match

Data Integrity: Repeated or Deliberate Failure to Comply with the Regulations	
Violation/Related Citation	**Examples**
Failure to supervise the clinical trial, such that data collected are unreliable 21 CFR 312.60; 21 CFR 812.100; 812.110(c)	Records showing the CI failed to appropriately delegate study related duties to qualified personnel (e.g., physical exams, SAE evaluations)
Repeated or deliberate deviation from the investigational plan, investigator statement/agreement, FDA regulations, or condition imposed by FDA or the reviewing IRB 21 CFR 312.60; 312.61; 312.66; 312.68; 21 CFR 812.110(b);	Enrolling subjects who do not meet the entrance criteria because they have conditions that put them at increased risk
	Administration of the test article to persons not authorized to receive it
	Failure to perform protocol-required procedures
	No documentation of required IRB review of study changes
	No documentation of IRB continuing review, where required
	Refusal to allow FDA inspection
Inadequate and/or inaccurate case histories; inadequate study records 21 CFR 312.62(b); 21 CFR 812.140(a)(3)	Incomplete subject records (e.g., missing records or evidence records have been deliberately discarded or destroyed)
Inadequate accountability for the investigational product 21 CFR 312.60, 312.61, 312.62(a); 21 CFR 511.1(b)(7)(ii); 21 CFR 812.100, 812.110(c); 812.140(a)(2)	Use of investigational product by an unauthorized individual
	No or inadequate records on receipt, preparation, use, and/or disposition of the investigational product
Promotion or commercialization of investigational products 21 CFR 312.7; 21 CFR 812.7	Fliers, brochures, etc. that do not indicate investigational nature of product, or claim safety and/or efficacy for the indication under study
	Evidence study subjects were charged for the investigational drug without FDA approval

C. Follow-up Inspections.

1. Centers should evaluate whether the violations found indicate systemic problems with the conduct of the study or the reliability of the data and whether additional inspection assignments should be issued (e.g., IRB, sponsor, CRO, monitor, other CIs).

2. Following issuance of a Warning Letter, Centers should periodically review their clinical investigator databases for entries indicating that a Warning Letter recipient is actively conducting other clinical investigations. If such entries are found, the Center should schedule follow up inspections to verify if the clinical investigator is fulfilling the terms of any corrective action plans and in compliance with applicable HSP and GCP regulations.

Current changes *{ED: Retain "current changes" only in sections where changes made}*

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. REFERENCES

1. FDA Laws

Federal Food Drug and Cosmetic Act (FFDCA)

2. Most Relevant 21 CFR Regulations

Part 50 Protection of Human Subjects
Part 56 Institutional Review Boards
Part 312 Investigational New Drug Application
Part 511 New Animal Drugs for Investigational Use
Part 812 Investigational Device Exemptions

3. Other 21 CFR Regulations

Part 11 Electronic Records; Electronic Signatures,
Part 54 Financial Disclosure by Clinical Investigators
Part 314 Applications for FDA Approval to Market a New Drug or Antibiotic Drug
Part 514 New Animal Drug Applications
Part 601 Licensing (Applications for FDA Approval of a Biologic License)
Part 814 Premarket Approval of Medical Devices

4. FDA Guidelines, Guidances, and Inspection Guides

FDA Information Sheet Guidances for Institutional Review Boards and Clinical Investigators (http://www.fda.gov/oc/ohrt/irbs/default.htm)

Guidance for Industry: International Conference on Harmonization (ICH) E6, Good Clinical Practice: Consolidated Guidance (http://www.fda.gov/cder/guidance/959fnl.pdf)

Guidance for Industry: Computerized Systems Used in Clinical Investigations (http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf)

Guidance for Industry: Part 11: Electronic Records, Electronic Signatures-- Scope and Application (http://www.fda.gov/ohrms/dockets/98fr/5667fnl.pdf)

Guidance for Industry: Financial Disclosure by Clinical Investigators (http://www.fda.gov/oc/guidance/financialdis.html)

General Principles of Software Validation; Final Guidance for Industry and FDA Staff (http://www.fda.gov/cdrh/comp/guidance/938.html)

Investigations Operations Manual (IOM), Sections 5.3.8.3 (Filmed or Electronic Records) and 5.3.8.4 (Requesting and Working with Computerized Complaint and Data Failure) (http://www.fda.gov/ora/inspect_ref/iom/ChapterText/5_3.html#SUB5.3)

Current changes *{ED: Retain "current changes" only in sections where changes made}*

Draft Guidance for Industry: Protecting the Rights, Safety, and Welfare of Study Subjects – Supervisory Responsibilities of Investigators (http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0173-gdl0001.pdf)

Guidance for Industry (Guidance 85): Veterinary International Conference on Harmonization (VICH) GL9, Good Clinical Practice, Final Guidance (http://www.fda.gov/cvm/vich.html)

Compliance Policy Guide # 7150.09 Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities (http://www.fda.gov/ora/compliance_ref/cpg/cpggenl/cpg120-100.html)

Compliance Policy Guide # 7151.02 FDA Access to Results of Quality Assurance Program Audits and Inspections (http://www.fda.gov/ora/compliance_ref/cpg/cpggenl/cpg130-300.html)

Guidance for Industry and Food and Drug Administration Staff: The Review and Inspection of Premarket Approval Applications Under the Bioresearch Monitoring Program (http://www.fda.gov/cdrh/comp/guidance/1566.pdf)

B. PROGRAM CONTACTS

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

2. For operational questions, contact:

Office of the Associate Commissioner for Regulatory Affairs
Office of Regional Operations (ORO)
Division of Field Investigations: Ruark Lanham, HFC-130
301-827-6691, FAX 301-443-3757

3. For questions about GCP and Compliance program issues, specific to a Center product area, contact:

Center for Drug Evaluation and Research (CDER)
Division of Scientific Investigations:
Leslie Ball, M.D., HFD-45
301-796-3399, FAX 301-847-8748

Center for Biologics Evaluation and Research (CBER)
Bioresearch Monitoring Staff:
Patricia Holobaugh, HFM-664
301-827-6221, FAX 301-827-6748

Center for Veterinary Medicine (CVM)
Bioresearch Monitoring and Administrative Actions Team:
Vernon Toelle, Ph.D., HFV-234
240-276-9238, FAX 240-276-9241

Center for Devices and Radiological Health (CDRH)
Division of Bioresearch Monitoring:
Donna Headlee, HFZ-310
240-276-0125, FAX 240-276-0128

Center for Food Safety and Applied Nutrition (CFSAN)
Senior Science and Policy Staff:
John Welsh, Ph.D., HFS-205
301-436-1292, FAX 301-436-2972

4. For crosscutting questions about Good Clinical Practice (GCP) policy and program issues impacting the Agency's BIMO Programs for GCP, or suggestions to improve this compliance program, contact:

Good Clinical Practice Program
Office of Science and Health Coordination
Office of the Commissioner, HF-34
301-827-3340, FAX 301-827-1169

5. For information about inspection warrants and final issuance of Notice of Opportunity of Hearing (NOOH) letters for clinical investigator disqualifications, contact:

Office of Regulatory Affairs
Office of Enforcement (OE)
Director, Division of Compliance Management and Operations (HFC-210)
240-632-6862, FAX 240-632-6859

PART VII - CENTER RESPONSIBILITIES

A. CENTERS

Each Center:

1. Identifies the clinical investigators to be inspected (from information in research or marketing permits) and forwards inspection assignments and background data (e.g., protocols, correspondence, and Center concerns) to the field.

2. Reviews and makes final classifications of EIRs, and enters the classification into FACTS.

3. Conducts follow-up regulatory/administrative actions. Promptly provides copies of all relevant correspondence between the clinical investigator/sponsor-investigator and FDA to the field offices.

4. Provides expert technical guidance, advice, information, interpretation, analysis, and support related to implementation of the clinical BIMO Program for internal and external constituents.

B. DIVISION OF COMPLIANCE POLICY/ORA (HFC-230)

1. Provides policy and program assistance to agency units who carry out the BIMO Program.

2. Monitors compliance activities to assure uniform application of compliance policy and agency performance in meeting program accomplishment projections for the BIMO Program.

3. Resolves issues involving compliance or enforcement policy.

C. DIVISION OF COMPLIANCE MANAGEMENT AND OPERATIONS/ORA (HFC-210)

1. Serves as the Agency clearance point and coordinator for inspection warrants.

2. For disqualification actions, reviews and issues the Notice of Opportunity of Hearing (NOOH) letter with the signature of the Associate Commissioner for Regulatory Affairs (ACRA), and coordinates actions related to the investigator's initial response to the NOOH.

D. DIVISION OF FIELD INVESTIGATIONS/ORO (HFC-130)

1. Provides inspection quality assurance, training of field personnel, and operational guidance.

2. Maintains liaison with Centers and Field Offices and resolves operational questions.

3. Coordinates and schedules joint Center, multi-District and foreign inspections.

Current changes *{ED: Retain "current changes" only in sections where changes made}*

E. DIVISION OF FIELD SCIENCE /ORO (HFC-140)

1. Assigns laboratories for sample analysis and responds to inquiries about analytical methods.

F. GOOD CLINICAL PRACTICE PROGRAM, OC (HF-34)

1. Coordinates crosscutting clinical BIMO program activities including modifications of this compliance program.

2. Provides expert technical guidance, advice, information, interpretation, and analysis relevant to clinical BIMO Program implementation to internal and external program constituents to assure program consistency.

3. Serves as agency liaison to other Federal Agencies (e.g., OHRP, VA) for coordination of clinical BIMO and human subject protection issues