CHAPTER 48 - BIORESEARCH MONITORING

SUBJECT:	IMPLEMENTATION DATE
CLINICAL INVESTIGATORS	OCTOBER 1, 1997
	COMPLETION DATE SEPTEMBER 30, 2000

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
45z, 46z 57z, 99z 60z, 61z 68z, 69z 73z, 74z, 94z, 95z	09811 Food Additives 41811 Biologics (Therapeutics) 42811 Biologics (Blood) 45811 Biologics (Vaccines) 48811 Human Drugs 68811 Veterinary Drugs 83811 Medical Devices.

FIELD REPORTING REQUIREMENTS

All establishment inspection reports (EIR's), complete with attachments, exhibits, and any related correspondence are to be submitted in a timely fashion to the assigning Center.

When a Form FDA 483 is issued, a copy should be faxed to the Center contact identified in the assignment.

If an EIR contains serious findings raising the possibility of one or more violations of the *Food, Drug, and Cosmetic (FD&C)* Act or other federal statues, a copy of the EIR should be forwarded to the District Compliance Branch at the time it is sent to the Center.

Current Change

PART I - BACKGROUND

Since the Investigational New Drug Regulations went into effect in 1963, *the Food and Drug Administration (FDA)* has exercised oversight of the conduct of studies with regulated products. The Bioresearch Monitoring Program was established in 1977 by a task force, *that* included representatives from the drug, biologic, devices, veterinary *drug* and food areas. *Compliance programs (CP) were developed *to provide uniform guidance and specific instruction for* inspections of clinical investigators (CP 7348.811), sponsors (CP 7348.810), biopharmaceutic laboratories (CP 7348.001) now known as in-vivo bioequivalence, institutional review boards (CP 7348.809) and *nonclinical* laboratories (CP 7348.808).

New regulations dealing with obligations 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.*

Guidance documents for the monitoring of clinical investigations were published in January 1988 and May 1997, ICH Good Clinical Practice: Consolidated Guideline (for human drugs and biologics); and Good Target Animal Study Practices: Clinical Investigators and Monitors (for veterinary drugs).*

Current Changes

PART II - IMPLEMENTATION

OBJECTIVE

*The purpose of the bioresearch monitoring program is to assure the quality integrity of data submitted to FDA to demonstrate the safety and efficacy of regulated products, and to determine that human rights and the welfare of human and animal research subjects are adequately protected.

The objective of this program is to obtain compliance of clinical investigators with the regulations and to assess through audit procedures whether records substantiate data submitted to FDA.*

PROGRAM MANAGEMENT INSTRUCTIONS

1. Coverage

All assignments for inspections will issue from Headquarters.

a. Clinical Investigators

Individuals within and outside the United States working under an application for research, or marketing permit. Areas to be covered include food additives, drugs, biologics, devices, and animal drugs (including animal food additives).

Foreign inspections of clinical investigators are assigned when the studies covered provide data critical to product approval regardless of whether the studies are conducted under an FDA application for research.

b. Sponsor/Investigators

This group consists of individuals who initiate and also conduct the study. Assignments covering this group will be relatively few in number. Most assignments of these investigators will come from the Center for Biologics Evaluation and Research.

* Current Changes *

OTHER REQUIREMENTS

1. All Headquarters and Field units are encouraged to recommend to the appropriate Center any investigator *that* they believe needs to be inspected. All recommendations should include the following:

   a. the name and address of the clinical investigator,

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

   c. the basis for recommendation.

   The Field should notify the Center contact when a previously uninspected *Institutional Review Board (IRB)* or an IRB not inspected within 5 years is identified during the course of a clinical investigator inspection.

2. The assignment memo *should* specify a due date *and the headquarters address where the EIR should be sent *. The reasons for expediting any assignment, including outstanding assignments, *should* be provided. To expedite inspections, Center personnel * may * contact the Director of the appropriate District Investigations Branch *to* request an FDA investigator *be assigned* to perform the inspection. The *designated investigator should contact* the Center contact person as soon as possible for a briefing on the background of the planned inspection and to make arrangements *for* participation by headquarters personnel. When the Center and the District agree upon arrangements, the Center will issue a confirmatory assignment, i.e. *electronic mail*, fax, mail, to the District.

3. Pre-Inspection Contact with the Center

   The District will resolve any questions it has on the assignment with the appropriate Center program contact.

   During the course of the inspection, additional communications will often occur between the District and the

* Current Change *

Center. This is encouraged to ensure the rapid and efficient completion of the inspection and the report preparation.

4. Inspection Feedback

Any suggestions from the field for improvement in this program should be forwarded to the Division of Compliance Policy (DCP, HFC-230) with a copy to the Division of * Emergency and Investigational Operations* (DEIO, HFC-130)*.

5. Inspection Teams - Field/Headquarters

a. Team Leader

The field investigator will serve as team leader and is fully responsible for the conduct of the inspection in accordance with Investigations Operations Manual (IOM) section 502.4.

b. Headquarters Participants

Headquarters personnel will serve in a scientific advisory capacity to the team leader and will participate in the inspection by:

1) identifying specific studies to be covered by the inspection team and providing information pertinent to the scheduled inspection directly from the involved Center(s);

2) attending pre-inspection conferences;

3) participating in the on-site inspection; and

4) aiding as necessary in preparation of the establishment inspection report and the FDA 483 as required.

Any difficulties involving headquarters participation in the inspection should be discussed with district management and, if not resolved, immediately referred to DCP (HFC-230).

* Current Change *

PART III - INSPECTIONAL

Inspections will involve a comparison of the practices and procedures of the clinical investigator with the commitments made in the applicable regulations as described in this part of the program.

Many inspections will include a comparison of the data submitted to the sponsor with supporting data in the clinical investigator's files. This will always be the case in human drugs and biologics inspections. Original records should be examined and may include office records, hospital records, laboratory reports, records of consultations, etc.

INSPECTIONAL OPERATIONS-GENERAL INSTRUCTIONS

1. The nature of these inspections makes unannounced visits to the clinical investigator impractical. Appointments to inspect should, therefore, be made by telephone, unless otherwise instructed in special cases by the Center. To facilitate the inspection of a clinical investigator at a Veterans Administration (VA) facility, the FDA investigator should also contact the Medical Center Director. For military installations, the Chief of Professional Services should be the initial contact.

   The FDA investigator should, however, keep the time span between initial contact and actual inspection as short as possible. What appears to be undue delay * (such as more than ten working days without sufficient justification) * of the inspection on the part of the clinical investigator shall be reported immediately to the Center.

2. If during the inspection, access to records or copying of records is refused for any reason, the FDA investigator should call the supervisor and report the refusal so that the assigning Center can be advised promptly by telephone. The same procedure should be followed when it becomes evident that delays instituted by the inspected are such that they constitute a de facto refusal. IOM section 514 provides additional guidance.

*Current Changes *

If actions by the *person being inspected* take the form of a partial refusal of 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, and if the refusal persists, proceed with the inspection and then telephone your supervisor. The assigning Center should be contacted for instructions.

If a course of action to deal with a refusal cannot be resolved expeditiously by the Center or the Office of Regional Operations (ORO), DCP should be advised by the assigning Center.

3. If deviations from the regulations * that might affect data validity, endanger test subject health or welfare,* are encountered during an inspection, call the Center contact so that a determination can be made as to whether the inspection should be expanded to be more intensive or to include other studies or target groups. The appropriate Center will provide guidance on initiating an in-depth audit inspection; however, the FDA investigator should continue the inspection.

4. For efficiency, a concurrent inspection may be indicated for a previously uninspected IRB or an IRB, which has not been inspected within the past five years. If such an IRB is found during the course of a clinical investigator inspection, contact the assigning Center for guidance and assignment. See CP 7348.809 for the IRB contact for each Center.

5. Issue a Form FDA 483, Inspectional Observations, at the conclusion of the inspection when deviations from regulations are observed. Deviations from guidance documents do not warrant inclusion on the FDA 483, however, they should be discussed with management and documented in the EIR.

* Current Changes *

INSPECTION PROCEDURES

This part identifies the nature of the information that must be obtained during each inspection to determine if the clinical investigator is meeting obligations under appropriate regulations. This outline provides only the minimal scope of the inspection and each FDA investigator should extend the inspection as the facts evolve. The inspections conducted should be sufficient in scope to determine the clinical investigator's practices for each point identified. The FDA investigator should not attempt to scientifically evaluate the data or protocols maintained by the clinical investigator; however, relevant documents should be reviewed, as appropriate. Evaluation of the scientific merit of the study is done by the FDA scientific reviewers receiving the application. Full narrative reporting of any deviations from existing regulations is required, and deviations must be documented sufficiently to form the basis of a legal or administrative action. For example, any records containing data not comparable with data submitted to FDA should be copied and documented as to what caused the discrepancy. Title 18 violations may require extensive documentation. Discuss the situation with your supervisor and the appropriate Center prior to embarking on this type of coverage.

Each inspection must include a list of all studies performed by the clinical investigator including those for government agencies and for commercial sponsors. This is needed in case a problem is found in an inspected study which requires reevaluation of claims in other agency documents or which requires notification of another government agency.

AUTHORITY AND ADMINISTRATION

1. Determine how (e.g., telephone, memo, etc.) the monitor explained to the clinical investigator the status of the test article, nature of the protocol, and the obligations of a clinical investigat*or*.

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

3. Determine if and why the investigator discontinued the study before completion.

* Current Change *

4. List the name and address of the facility performing laboratory tests.

   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.

PROTOCOL

1. *Obtain copies of the protocol and all IRB approvals and modifications (including dates) to the protocol. Unavailability should be reported and documented. If a copy of the protocol and IRB approvals and modifications is sent with the assignment background material, they should be compared to the protocol and approvals at the site. If they are identical, duplicate copies do not need to be obtained, but the documents sent with the assignment should be returned with the EIR. The narrative should note that the protocol and IRB approvals and modifications were identical.*

2. Did the protocol remain unchanged with respect to:

   a. subject selection *(i.e., inclusion and exclusion criteria)*,

   b. number of subjects,

   c. frequency of subject observations,

   d. dosage,

   e. route of administration,

   f. frequency of dosage,

   g. blinding procedures,

   h. other (specify)?

*Current Changes *

3. Determine whether all changes to the protocol were:

   a. documented by *an approved amendment*,

   b. dated,

   c. maintained with the protocol,

   d. * approved by the IRB and reported to the sponsor before implementation *, and except where necessary, to eliminate apparent immediate hazard to human subjects.

NOTE: * DEVIATIONS FROM * PROTOCOL ARE NOT CHANGES IN THE PROTOCOL

SUBJECTS' RECORDS

1. Describe the investigator's *source documents* in terms of their organization, condition, 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 documents* in the clinical investigator's records with the case report forms completed for the sponsor. Determine whether clinical laboratory testing (including 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 documents*.

   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 and* severity) in any written information regarding the test article.

   Concomitant therapy and/or intercurrent illnesses might interfere with the evaluation of the effect of the test article. Were concomitant therapy and/or intercurrent illnesses included in the case report forms?

*Current Changes *

Determine whether the number and type of subjects entered into the study were confined to the protocol limitations.

Determine whether the existence of the condition for which the test article was being studied is documented by notation made prior to the initiation of the study or by a compatible history.

4. Determine whether each record contains:

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

   b. records of exposure of the subject to the test article;

   c. 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

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

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

OTHER STUDY RECORDS

Review information *in* the clinical investigator's records *that* will be helpful in assessing any under-reporting of adverse *experiences* by the sponsor to the agency. The Centers will send you the following information obtained from the sponsor with the assignment (currently not routine for CVM):

1. the total number of subjects entered into the study,

2. the total number of dropouts from the study (identified by subject number),

3. the number of assessable subjects and the number of inassessable subjects (the latter identified by subject number), and

*Current Changes *

4. *the adverse experiences, including deaths (with subject number and a description of the adverse experience or cause of death).*

The data supplied by the sponsor to the agency should be compared to the information submitted by the clinical investigator to the sponsor from the clinical investigator's files. For the adverse reactions and deaths use the clinical investigator's correspondence files as it is not practical to search through each case report form. Document any discrepancies found.

CONSENT OF HUMAN SUBJECTS

1. Obtain a copy of the consent form *that was* used.

2. Determine whether written informed consent was obtained from subjects prior to their entry into the study. *A representative sample of consent forms should be reviewed for compliance with 21 CFR 50. If any problems are found the sample should be expanded to determine the extent of the problem.* If oral consent was obtained, *determine if it conformed to 21 CFR 50?

INSTITUTIONAL REVIEW BOARD (IRB)

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

   Determine whether the investigator submitted a report *to the IRB* of all deaths, adverse experiences and unanticipated problems involving risk to human subjects [21 CFR 312.66].*

3. Did the investigator submit to and obtain IRB approval of the following before subjects were allowed to participate in the investigation?

*Current Changes *

a. protocol

b. modifications to the protocol

c. report of prior investigations

d. materials to obtain human subject consent

e. media ads for patient/subject recruitment

4. Did the investigator disseminate any promotional material or otherwise represent that the test article is safe and effective for the purpose for which it is under investigation? Were these*promotional materials* 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 if periodic reports were submitted to the sponsor.

3. Determine if and how the investigator submitted a report of all deaths and adverse reactions to the sponsor.

4. Determine whether all intercurrent illness and/or concomitant therapy were reported to the sponsor.

5. Determine whether all case report forms on subjects were submitted to the sponsor shortly after completion.

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

7. 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 research organization, etc.) and <u>frequency</u> of monitoring. Do the study records include a log of on-site monitoring visits and telephone contact?

*Current Changes *

TEST ARTICLE ACCOUNTABILITY

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

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

   If copies of the FDA-1572s were sent with the assignment background material, they should be compared to the FDA-1572s at the site. If they are identical, duplicate copies do not need to be obtained, but the FDA-1572s sent with the assignment should be returned with the EIR. The narrative should note that the FDA-1572s sent with the assignment and examined at the site, were identical.

2. Determine accountability procedures for test article; verify the following:

   a. receipt date(s) and quantity;

   b. dates and quantity dispensed, identification *numbers of subjects*;

   c. whether distribution of the test article was limited to those *subjects* under the investigator's *or subinvestigator's* direct supervision;

   d. whether the quantity, frequency, duration, and route of administration of the test article, as reported to the sponsor, was generally corroborated by raw data notations;

   e. date(s) and quantity returned to sponsor or alternate disposition, authorization for alternate disposition, and the actual disposition.

   f. Compare test article usage with amount shipped and returned. If available, inspect unused supplies and verify that blinding, identity, lot number, and package and labeling agree with other study records describing the test article.

*Current Changes *

3. Inspect storage area.

Determine whether the test article was stored under appropriate conditions.

*Determine whether the test article is a controlled substance and whether it is securely locked in a substantially constructed enclosure.

Determine who had access to the controlled substance.*

4. What is the date the last subject completed the study?

Were test articles returned when either:

a. The investigator discontinued or completed his/her participation;

b. The sponsor discontinued or terminated the investigation; or

c. The FDA terminated the investigation.

If none of the above, determine whether alternate disposition of the test article exposed humans or food-producing animals to *risks from the test article(s).*

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 the custody of required records, if the investigator does not retain them.

2. Determine whether the records are retained 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

*Current Changes *

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.

(For some studies selected as the basis of the inspection, the above time periods are not applicable.)

*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 that 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 electronic records and electronic signatures:

1. What is the source of the hardware and software?

2. Who was responsible for installation and training?

3. Was the same hardware and software used throughout the duration of the study?

4. Was there any maintenance, including upgrading, conducted on the systems?

5. Were there any problems experienced during the course of the study?

6. What is the source of data entered into the computer?

   a. Direct (no paper)?

   b. Case report form?

   c. Office record?

   d. Other?

7. Who enters data? When?

8. Who has access to the computer? Security procedures?

*Current Changes *

9. How are data previously entered changed? By whom? Is an audit trail produced?

10. How are data submitted to the sponsor (i.e. modem, network, fax, hard disk, floppy disk, electronic transfer, mail, messenger, picked up)?

11. If the sponsor discovers errors, omissions, etc., in the data received, what contacts are made with the investigator? How are corrections effected, and how are they documented?

12. Does the clinical investigator retain a copy of the electronic data submitted to the sponsor?*

ANIMAL CLINICAL STUDIES

The regulations for investigational new animal drugs, 21 CFR 511.1, do not contain all the provisions of the human drug regulations. There is no requirement that forms 1571 or 1572 be used. The sponsor must submit a Notice of Claimed Investigational Exemption per 21 CFR 511.1(b)(4)(i), (ii), (iii), (iv), and (v). There is no requirement that an approved protocol be used, or even that a protocol be submitted to CVM. For these reasons, inspections of animal clinical trials are extremely important as a means of interim review. CVM assignments will include, when available, the Notice of Drug Shipment, the version of the protocol provided to CVM by the sponsor for the study(ies) to be conducted, and a checklist or list of questions provided by the reviewer to focus the direction of the inspection on critical attributes of the study(ies). *The investigator should contact the assigning office prior to initiating the inspection and maintain communication during and after the inspection.*

*CVM's guidance document "Good Target Animal Study Practices: Clinical Investigators and Monitors" was issued in May 1997. The guidance document supersedes the January 1988 "Guidance for Monitoring of Clinical Investigations" as it relates to clinical studies of new animal drugs and replaces CVM's 1992 guidance document "Conduct of Clinical Investigations: Responsibilities of Clinical Investigators and Monitors for Investigational New Animal Drug Studies." The guidance document offers focus to field investigators as to what study procedures CVM considers acceptable. This guidance document is listed in the reference

*Current Changes *

section of this program. When CVM issues an assignment, a copy of the guidance document will be included and may be given to the clinical investigator at the exit discussion. Deviations from this guidance document should not be recorded on the FDA Form 483, but may be discussed at the exit interview.

1. Examine the facilities if possible, including requirements of animal quarters, segregation of animals, and method of identification. If appropriate, take photographs of the research facilities for inclusion in the EIR.

2. Report on the condition of the animals and adequacy of husbandry practices.

3. Report the method of identification in trials using food-producing animals.

4. Compare the protocol submitted to the CVM by the sponsor with the copy of the protocol used by the clinical investigator. Note any differences and document any deviations from either protocol in the EIR.

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, i.e. paper and electronic media.

7. 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 and describe any differences.

12. Document any other drugs, vaccines, or pesticides 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. Determine whether the medicated feed is mixed on premises. (If not, report name and address of the mill utilized.)

15. Review the drug mixing procedures for animal feeds.

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 assigning office 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, toxic symptoms, or other observations in the investigator's notes. Include observed symptoms, clinical pathology, and diagnostic procedures.

19. Account for all the animals and drugs that were authorized for the study. Collect documentation of animals lost from a study and those that are removed from or added to the study. Examine necropsy and disposal reports for all animals lost during the trial and determine the method of disposal of animal wastes and carcasses.

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

*Current Changes *

DEVICE STUDIES

The regulations for investigational devices are found in 21 CFR 812. They do not contain all the provisions of the drug regulations. 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 investigator has used the test articles under the emergency use provisions. If so, determine if the clinical investigator has adequately complied with the guidance documents for emergency use.

2. Determine if the clinical investigator is involved in any nonsignificant risk studies and if so, provide a list of these studies and ascertain if they are being conducted in compliance with regulations. (must have nonsignificant determination by IRB and IRB approval).

3. Determine if the clinical investigator has been involved in any use of a custom device, if so determine compliance with 21 CFR 812 regulations.

* 4. Determine if the clinical investigator has been involved in any studies using humanitarian devices as provided by 21 CFR part 814. A Humanitarian use Device (HUD) is a device that is intended to benefit subjects by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States annually. Determine whether IRB approval was properly obtained.*

REPORT FORMAT

*Reports covering inspections of clinical investigators should be prepared in accordance with IOM section 590.

When significant violations of the FD&C Act or other Federal statutes are suspected, OAI reports must contain full narratives and accompanying documentation to support the inspectional findings. If obtaining all documentation will unduly delay the submission of the report to the Center, prepare and submit the report to the Center and then continue the investigation after consultation with the assigning Center to obtain necessary documentation. (See also Part V.)

*Current Changes *

The assigning Center may request a full EIR narrative in the assignment memorandum.

Abbreviated establishment inspection reports (EIR) may be prepared in a "Summary of Findings Report" format as described below for all non-violative inspections (NAI). For VAI inspections, abbreviated reports must contain sufficient narrative and accompanying documentation to support the inspectional findings. The abbreviated report must contain information about prior inspectional history, where the study was conducted, the responsibilities and functions of the primary personnel involved, and a definitive statement about what documents were examined, e.g. "I was provided in the inspection package ten case report forms. I attempted to compare them with corresponding hospital charts. All were available. No discrepancies were found. Signed consent forms were present in each chart."

NOTE: An abbreviated report does not mean that an abbreviated inspection can be conducted. All inspections conducted under this compliance program shall be complete and full data audit inspections. The specific headings appearing under Part III, Inspection Procedures, should be fully addressed during the data audit inspection.

Abbreviated Report Format

NOTE: The following statement should precede the abbreviated EIR: "This is an abbreviated report of a full Clinical Investigator/Data Audit Inspection."

The following items must be included in an abbreviated report:

1. Reason for inspection
   - identify the headquarters unit that initiated and/or issued the assignment.
   - state the purpose of the inspection.

2. What was covered
   - identify the clinical study, protocol number, sponsor, NDA/PMA/PLA/ANDA, etc.
   - location of study

3. Administrative Procedures
   - report the name, title, and authority of the person to whom credentials were shown and FDA-482 Notice of Inspection was issued.
   - persons interviewed

- who accompanied you during EI
- who provided relevant information
- identify the IRB
- prior inspectional history.

4. Individual Responsibilities
   - identify study personnel and summarize their responsibilities relative to the clinical study.
   - statement about who obtained informed consent and how it was obtained.
   - identify by whom the trial was monitored, and when, etc.

5. Inspectional Findings
   - statement about comparison of data recorded on the case report forms or tables supplied by the Center with the clinical investigator's source documents.
   - state what records were covered, i.e. patient charts, hospital records, lab slips, etc.
   - number of files and case report forms reviewed our of the total study population.
   - statement that test article accountability records were or were not sufficient.
   - discussion of 483 observations, reference the exhibits/documentation collected.
   - state whether there was evidence of under reporting of adverse experiences/events.
   - statement about protocol adherence.

6. Discussion with Management
   - discussion of 483 observations and non-483 observations.
   - clinical investigator's response to observations.*

SAMPLE COLLECTION

Routine collection of samples from clinical investigators is not contemplated. If samples are desired or appropriate, specific instructions will be issued by the Center(see item 16, Animal Clinical Studies). If there is a noticeable difference (such as color, size, shape, dosage form, route of administration, etc.) between the test article and the placebo or control, collect investigational samples (1 package) of each.

Current Changes

PART IV - ANALYTICAL

Sample analysis will not normally be required of the field laboratories.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

1. Each Establishment Inspection Report and the exhibits will be forwarded directly to the appropriate Center. All letters will issue from the appropriate Center. * The EIRs should be sent by overnight express or certified mail, but never by interoffice mail. Exhibits should be banded, bound, or secured. *

   Copies of inspection reports, which contain findings of such a serious nature that they raise the possibility of one or more violations of the FD&C Act or other federal statutes should also be forwarded to the District Compliance Branch. Based on this review, the District Compliance Branch may issue investigation assignments for the development of the case. These intentions will be communicated promptly to the Center for consultation and concurrence prior to issuance of such investigational assignments.

2. Centers will coordinate their regulatory/administrative efforts when more than one Center is involved. The Associate Commissioner for Regulatory Affairs will resolve all regulatory policy disagreements between Centers prior to action.

3. District EIR Classification Authority

   The District Investigations Branch is encouraged to review and initially classify inspection reports generated under this compliance program, including those containing data audits. The final classification decision will be made by the Center and communicated to the District as described below.

4. Center EIR Classification Authority

   The Center has the final classification authority for all bioresearch monitoring inspection reports.

* Current Changes *

Instances may arise when Center review results in a reclassification of an EIR reviewed and classified by the District. The Center will provide to the appropriate District copies of all final classifications including any reasons for changes.

5. EIR Classifications

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

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

b. VAI - Objectionable conditions or practices were found, *but the District is not prepared to take or recommend any administrative or regulatory action.*.

c. OAI - *Regulatory and/or Administrative actions will be recommended.*

* Follow Up Actions *

1. All District follow-up action, including reinspection, will usually be done *in response to an assignment from headquarters*. On occasion, district compliance branches may initiate case development activities and may issue investigative assignments whenever review of the inspection report raises the possibility of severe violation of the FD&C Act or other Federal statute. This intention *should* be *prior to initiation of these activities* communicated to the affected Center and to *DCP* (HFC-230).

2. The regulatory/administrative actions that can be used under this compliance program are not mutually exclusive. Follow-up of an OAI inspection may involve the use of one or more of the following:

a. Issuance of a Warning Letter.

* Current Changes *

b. Informing the sponsor that the study is not acceptable in support of claims of * safety or * efficacy in an application for research or marketing permit.

c. Sponsor inspection (may be concurrent with other action including termination of the IND according to 21 CFR 312.44, or the INAD according to 21 CFR 511.1, or the IDE according to 21 CFR 812.30).

d. Initiation of disqualification procedures or entry into a consent agreement with the clinical investigator under 21 CFR 312.70, 21 CFR 511.1, *or 21 CFR 812.119.*

Disqualification of the investigator may be simultaneously considered along with a recommendation for criminal prosecution.

e. Initiation of stock recovery by sponsor. (See Regulatory Procedures Manual Part 5, 5-00-10)

f. Seizure of test articles if not exempted by regulation.

g. Injunction.

h. Prosecution under the FD&C Act, e.g., 301(e) or Title 18, e.g., Sec. 2, 371, 1001 or 1341.

3. If, following the inspection, the District has communication (written or oral) with the firm concerning the inspection, Headquarters should be kept advised of any such communications. Similarly, if the Headquarters unit has communication (including any written correspondence) with the firm following the inspection, including any judicial/ administrative action, the District will be advised of such communication and will be provided a copy of memorandum of contact.

Districts are encouraged to consult with the appropriate Center compliance or regulatory management unit contact prior to recommending action.

* Current Changes *

PART VI- REFERENCES AND PROGRAM CONTACTS

REFERENCES

1. 21 CFR
   - *Part 11 Electronic Records; Electronic Signatures*
   - Part 50 Protection of Human Subjects
   - Part 56 Institutional Review Boards
   - Part 312 Investigational New Drug Application
   - *Part 314 Applications for FDA Approval to Market A New Drug or An Antibiotic Drug*
   - Part 361 Prescription Drugs for Human Use Generally Recognized As Safe And Effective And Not Misbranded: Drugs Used In Research
   - Part 511 New Animal Drugs For Investigational Use
   - Part 514 New Animal Drug Applications, Sections 514.1, 514.8, 514.111
   - Part 571 Food Additive Petitions
   - Part 812 Investigational Device Exemptions
   - *Part 814 Premarket Approval of Medical devices (section 100 - Humanitarian Use Devices) *

2. 45 CFR Part 46 Protection of Human Subjects (NIH Requirements)

3. FD&C Act Secs. 301(e), 501(i), 505(i), 507(d), 510(b),(e),and (i), 512(j), 520(g)

4. Specific Forms

   a. Form FDA-1571, Investigational New Drug Application, 21 CFR 312.40

   b. Form FDA-1572, Statement of Investigator, 21 CFR 312.53(c)

   c. Notice of Claimed Investigational Exemption for a New Animal Drug, 21 CFR 511.1(b)(4)

*Current Changes *

5. CVM guidance document, May 1997, "Good Target Animal Study Practices: Clinical Investigators and Monitors"

6. Guide for Detecting Fraud in Bioresearch Monitoring Inspections, April 1993

PROGRAM CONTACTS

When technical questions arise on a specific assignment, or when additional information or guidance is required, contact the assigning Center. Operational questions should be addressed to ORO (HFC-132).

Specific Contacts

Office of the Associate Commisioner for Regulatory Affairs

*James F. McCormack, Ph.D.
Bioresearch Monitoring Program Coordinator
Division of Compliance Policy (HFC-230)
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Thaddeus Sze, Ph.D.
Bioresearch Program Monitor
*Division of Emergency and
Investigational Operations(HFC-132)*
Telephone 301-827-5649, FAX 301-443-6919.

Center for Drug Evaluation and Research (CDER)

Bette Barton, Ph.D. M.D.
Chief, Clinical Investigations Branch (HFD-344)
Telephone 301-594-1032, FAX 301-594-1204.
(or specific contact person named in the assignment)

Center for Biologics Evaluation and Research (CBER)

Patricia Holobaugh
Bioresearch Monitoring Team (HFM-650)
Telephone 301-827-6221, FAX 301-594-1944
(or specific contact person named in the assignment)

*Current Changes *

Center for Veterinary Medicine (CVM)
Dorothy Pocurull
Bioresearch Monitoring Program Staff (HFV-234)
Telephone 301-594-1785, FAX 301-594-1812.

Center for Devices and Radiological Health (CDRH)
Robert K. Fish
Division of Bioresearch Monitoring (HFZ-312)
Telephone 301-594-4723, FAX 301-594-4731.

Center for Food Safety and Applied Nutrition (CFSAN)
John J. Welsh, Ph.D.
Division of Product Policy (HFS-207)
Telephone 202-418-3057, FAX 202-418-3126.

*Current Changes *

PART VII - HEADQUARTERS RESPONSIBILITIES

After review of EIRs containing findings of a serious nature the Centers will initiate necessary action with notification to the Division of Compliance Policy. Potentialregulatory/administrative approaches are discussed in PART V.

The Center will inform the field via copies of letters or reviewer's memo of the Center classification. Optionally a special memo may be generated. * HFC-130 and HFC-230 should receive copies of correspondence from all OAI classifications and when the final classification differs from the initial classification. *

Copies of all correspondence generated by this program should be supplied to the field.

a. Division of Compliance Policy/ORA

Coordinates policy issues.

Is the liaison with other Federal Agencies with whom FDA has Memoranda of Agreement or Memoranda of Understanding concerning this program.

Notifies interested governmental third parties whenever a regulatory action is effected against a clinical investigator.

b. Center

Identifies studies to be audited, and develops the inspection assignment package. Assignments issue directly from the Center to the field.

Reviews all EIRs, makes final classifications of EIRs and initiates and follows up on all regulatory action*s*. Reviews and approves prosecution recommendations made by the field.

Supplies to the field copies of all correspondence between the inspected and FDA.

* Current Changes *

c. Office of Regional Operations (ORO) - Division of * Emergency and Investigational Operations (DEIO) and Division of Field Science *

1. DEIO:

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

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

Coordinates and schedules joint Center and multi-District inspections.

2. DFS:

Assigns laboratories for sample analysis and responds to method inquiries.

* Current Changes *