SUBJECT:	IMPLEMENTATION DATE
INSTITUTIONAL REVIEW BOARD	10/01/94
	COMPLETION DATE 09/30/97

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
45Z Foods 46Z 57Z Biologics 99Z	09809 *41809 (therapeutics) *42809 (blood) *45809 (vaccines)
60Z Drugs 61Z	48809
73Z Devices 74Z	83809

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.

If an EIR contains serious findings raising the possibility of one or more violations of the FD&C Act or other federal statutes, 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 1 - BACKGROUND

The Kefauver-Harris Amendments to the Act in 1962 increased FDA's regulatory authority over the clinical testing of new drugs. Since the passage of the Drug Amendments of 1962, the Medical Device Amendments of 1976 and other legislation, FDA has provided additional safeguards to protect the rights, welfare, and safety of human subjects who participate in investigational trials involving FDA-regulated articles.

Congress has given a mandate to institutional review boards (IRB) to oversee research that is being conducted using FDA regulated articles that involves human subjects. FDA has published regulations that set forth standards and procedures for IRBs in 21 CFR Part 56 which became a final rule in the Federal Register on January 27, 1981. The requirements for informed consent, which are found in 21 CFR Part 50, were published as a final rule in the Federal Register on the same date.

The above regulations require IRB review of all clinical investigations using articles regulated by FDA under sections 505(i), 507(d), and 520(g) of the Food, Drug and Cosmetic Act, as well as clinical investigations conducted in support of applications for research or marketing permits for other products regulated by the Agency. The rewrite of the investigational new drug (IND) application regulations on March 19, 1987, includes informed consent and IRB review as conditions for exempting from the IND requirements certain studies involving marketed drugs [21 CFR 312.2(b)(1)(iv)]. Similar conditions are included in the IDE regulations [21 CFR 812.2(b)] for abbreviated requirements of certain categories of device investigations.

On June 18, 1991, the Federal Policy for the Protection of Human Subjects; Notices and Rules (Common Rule) was published in the Federal Register, pages 28002-28032. These regulations set forth, as a common rule, Federal requirements for the protection of human subjects involved in research conducted or funded by some 15 Federal agencies, including the Department of Health and Human Services, except for the Food and Drug Administration. In the same edition of the Federal Register, amendments to the FDA regulations on IRBs and on informed consent requirements were published; these amendments bring Parts 50 and 56 into conformity with the above Federal Policy. Existing FDA regulations governing the protection of human subjects share a common core with the new Federal Policy and implement the fundamental principles embodied in that policy. The new Federal Policy and the FDA amendments of Parts 50 and 56 became effective on August 19, 1991.

PART II - IMPLEMENTATION

OBJECTIVE

This program is an Agency-wide effort to achieve IRB compliance with the regulations. The program attempts to improve IRB performance by providing information and guidance to IRBs and by applying administrative sanctions when an IRB is found to be seriously out of compliance with regulations.

A. PROGRAM MANAGEMENT INSTRUCTIONS

This program provides for the inspection of all IRBs which review and approve investigational studies of biologics, drugs, food or color additives, or medical devices involving human subjects. Assignments may include IRBs in private and public hospitals, prisons, nursing homes, State and Federal Government facilities, and other organizations conducting or sponsoring clinical research, or independent IRBs.

All assignments will be issued from the Centers and will have a ninety (90) day completion date unless otherwise indicated.

B. TYPES OF INSPECTION

FDA will periodically inspect each IRB that reviews research of FDA-regulated products. These inspections will be either surveillance or directed.

1. Surveillance Inspections

a. Initial Inspection:

The assigning Center will provide evidence of FDA jurisdiction over the IRB, the name and address of the institution, and when available, the name of a contact person at the IRB.

b. Subsequent Inspections:

(1) Those IRBs found to be in full compliance (NAI) or with minor deficiencies (VAI) will usually be assigned for reinspection in 5 years to determine their continued compliance with the regulations.

(2) Those IRBs found to have major deficiencies will usually be assigned for reinspection within one year to confirm that adequate corrections have been made.

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*U.S. GPO: 1993-348-780/88001

2. Directed Inspection

A "directed" inspection may be assigned when the assigning Center receives information that calls into question the IRB's practices. A directed inspection may be limited to one area of concern or assigned to cover the entire compliance program.

C. INSPECTION TEAMS

1. Team Leader*

The District designates a field investigator to be team leader; the team leader is fully responsible for the conduct of the inspection in accordance with Investigators Operations Manual (IOM) 502.41.

2. Headquarters Participant

Personnel from the assigning Center may participate as team members by:

a. Serving as scientific advisors to the team leader.

b. Identifying specific studies to be covered by the inspection team.

c. Providing pertinent information directly from the Center(s).

d. Participating in the on-site inspection.

e. Providing support, when requested by the team leader, in the preparation of specific sections of the inspection report.

D. POLICIES AND PROCEDURES

1. Under current FDA regulations, clinical studies on human subjects involving the use of FDA-regulated articles generally may not begin until the study has IRB approval.

2. Emergency use of a test article is exempted from prior IRB review and approval provided it is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution requires IRB review.

3. Upon application of a sponsor or a sponsor-investigator, the FDA may waive any or all the FDA requirements for prospective IRB

review of investigational studies of drug or biologic products. Waiver by FDA does not preclude review of the study by an IRB under its own authority, nor does it eliminate the informed consent requirements. The appropriate Center Director, (CDER or CBER) has approval authority for waiver of the FDA requirements for IRB review. Since IRB review is a statutory requirement of the device law, waiver for device studies is not allowed.

Current Change

*U.S. GPO: 1993-348-780/48001

PART III - INSPECTIONAL

A. OPERATIONS

The FDA investigator will determine the current state of compliance with 21 CFR Parts 50 and 56 by evaluating the practices and operating procedures of the IRB. All assignments are issued from Headquarters. The investigator should select and track representative studies through the IRB's review process. The study referenced in the initial IRB assignment issued by the Center is included only to establish that FDA-regulated research has been reviewed by the IRB and should be covered.

Studies selected for coverage should represent current IRB practices, preferably studies initially approved within the previous three years. They should be chosen using the following priority:

(1) Safety and efficacy studies of investigational new drugs, devices and/or biologics performed under IND, IDE or B-IND applications.

(2) Comparison studies of one or more marketed products with an investigational product.

(3) Studies for which no FDA Research Permit is required, i.e., certain marketed drugs and non-significant risk devices.

B. REPORTING

The Districts are responsible for conducting inspections and preparing EIRs. All reports, including copies of exhibits, are to be submitted directly to the Center initiating the assignment.

Districts are encouraged to identify IRBs which have not been inspected. Efforts should be made to determine the type of studies that are being reviewed by the IRB and the program contact for the appropriate center should be notified.

When a duplicate IRB assignment has been issued or an inspection was recently completed, Districts should contact the assigning Center for instructions prior to initiating the inspection. To prevent such duplications, headquarters has initiated a system in which inventories, assignments, and correspondence will be distributed among the Centers.

The EIR should contain the headings as prescribed in the IOM. It should contain the information addressed in Attachment A. Any adverse findings should be fully explained and documented in the EIR.

An FDA-483 should be issued under this program when deviations from the

requirements in 21 CFR Parts 50, 56, 812, and 813 are observed.

*Reports must include the name and address of the head of the institution and the IRB chairman at which the IRB is located.

Documents that should be collected are:

- o IRB written procedures
- o IRB rosters for the time period covered by the inspection
- o Copies of IRB minutes which show
  - Recent practices
  - Violative procedures
  - Approval and follow-up on tracked studies
- o Records of tracked studies
  - Protocol and consent form (original and finally approved versions)
  - Investigator's brochure
  - Correspondence between the IRB and the clinical investigator

C. ESTABLISHMENT INSPECTIONS

The inspections should be guided by the regulations found in 21 CFR 50, 56, 812, and 813. Attachment A provides guidelines for inspection procedures and information to be considered.

D. PRIOR NOTIFICATION OF INTENT TO INSPECT

To assure that responsible individuals are present and that IRB records are available, the FDA investigator shall contact the institution to confirm the name and location of the IRB Chairperson to schedule the actual inspection. The primary purpose of such prior notice is efficient use of the field investigator's time. District management may elect to conduct unannounced inspections with approval of the assigning center, if conditions warrant.

For an IRB inspection at a Veterans Administration facility, the Medical Center Director should be the initial contact. For military installations, the Chief of Professional Services (CPS) should be the initial contact.

E. REFUSAL TO INSPECT

If the institution refuses to permit either the inspection, access to records, or copying of records, or if delays instituted by the inspectee are such that they constitute a de facto refusal, inform your supervisor so he or she can advise the assigning Center promptly by telephone. Send a follow-up INFO FAX to the listed Center and DFI contacts. IOM 514 provides additional guidelines.

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*U.S. GPO: 1993-346-760/80001

If the Center cannot resolve the refusal expeditiously, the Center should advise the Division of Compliance Policy (HFC-230), (301) 443-1500.

F. SUBSEQUENT RELATED SPONSOR/INVESTIGATOR INSPECTIONS

An IRB inspection may reveal significant regulatory deviations which may lead to clinical investigator and/or sponsor inspections. Districts may carry out such inspections after obtaining the necessary instructions from the appropriate Center. The Center may issue these assignments as directed inspections.

Current Change

PART IV - ANALYTICAL

No analytical workload is imposed by this Compliance Program.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

A. District EIR Classification Authority

The District is encouraged to review and initially classify inspection reports generated under this compliance program.

B. Center EIR Classification Authority

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

Instances may arise when a Center review results in a reclassification of an EIR classified by the District. The Center will provide to the appropriate District copies of all final classifications including any reasons for changes. A copy of this notification will be provided to HFC-230.

C. EIR Classifications*

The following guidance is to be used in conjunction with the instructions in FMD-86 for District and Center classification of EIR's:

1. NAI - No or minor objectionable conditions or practices were found during the inspection.

2. VAI - Objectionable conditions or practices were found that represented departures from the regulations.

3. OAI - The objectionable conditions or practices represented significant departures from the regulations and may require the imposition of administrative/regulatory sanctions.

D. Potential Actions

The regulatory/administrative actions that can be used under this compliance program are not mutually exclusive. An effective follow-up of an OAI inspection may require the use of more than one action to be accomplished concurrently or sequentially.

The following may be taken following an OAI classification:

1. Issuance of a Warning Letter.

2. Withhold approval of new studies.

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*U.S. GPO: 1993-348-780/60001

3. Terminate ongoing studies.

4. Informal Conference

5. Rejection of data.

6. Disqualification.

7. Injunction/Prosecution.

E. Communications

The District should advise Headquarters of written or oral communication from the institution following the inspection. Similarly, the Headquarters unit should advise the District of communication (including any written correspondences) with the institution following the inspection, including any judicial/administrative action.

Current Change

PART VI - REFERENCES ATTACHMENTS, AND PROGRAM CONTACTS

REFERENCES AND RESOURCE MATERIALS

1.	21 CFR 56	-	Institutional Review Boards
2.	21 CFR 50	-	Informed Consent of Human Subjects
3.	21 CFR 312	-	IND Regulations
4.	21 CFR 812	-	IDE Regulations
5.	21 CFR 813	-	IDE Regulations for intraocular lens (IOL)
6.	Form FDA-1571	-	Investigational New Drug (IND) Application Cover Sheet
7.	Form FDA-1572	-	Statement of Investigator
8.	IRB Information Sheets - OHA, DFI, or Centers		

ATTACHMENT A Inspectional Guidelines

PROGRAM CONTACTS

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

Mary L. Owens*
DIVISION OF BIORESEARCH MONITORING (HFZ-300)
(301) 594-4720

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

JOSEPH P. SALEWSKI
BIORESEARCH MONITORING BRANCH (HFM-640)
(301) 594-1077

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

PAUL W. GOEBEL, JR.
INSTITUTIONAL REVIEW BRANCH (HFD-343)
DIVISION OF SCIENTIFIC INVESTIGATIONS
(301) 594-1026

Current Change

*U.S. GPO: 1993-348-780/60001

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION (CFSAN)

JOHN WELSH*
ADDITIVES EVALUATION BRANCH (HFS-227)
(202) 254-3915

OFFICE OF ENFORCEMENT (OE)

STAN WOOLLEN*
DIVISION OF COMPLIANCE POLICY (HFC-230)
(301) 443-1500

OFFICE OF REGIONAL OPERATIONS (ORO)

THADDEUS SZE, PH.D.
INVESTIGATIONS BRANCH (HFC-132)
(301) 443-3340

Current Change

PART VII - HEADQUARTERS RESPONSIBILITIES

CENTER RESPONSIBILITIES

Assigns and sends IRB inspectional assignments directly to field offices. Assignments will issue as they become available. Provides a copy of each assignment's cover memorandum to DCP (HFC-230).

Provides information and advice to DCP/ORA (HFC-230), DFI/ORA (HFC-132), and Districts as requested.

Reviews all completed EIRs, establishes final classification and advises DFI, DCP, and District of final classification. If the Center changes the District's classification, the Center will inform the District in writing.

Issues a letter when necessary to the inspected institution after EIR review. Normally, this letter will be addressed to the appropriate institution head with a copy to the IRB chairperson and will state the Center's assesement of the IRB's performance. Copies of letters will be sent to the appropriate District Office.

DIVISION OF COMPLIANCE POLICY (DCP), ORA

Provides overall agency direction for entire bioresearch monitoring program.

OFFICE OF REGIONAL OPERATIONS (ORO) - DIVISION OF FIELD INVESTIGATIONS (DFI)

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

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

OFFICE OF HEALTH AFFAIRS

Coordinates/develops IRB education and training programs.

Acts as the Agency's focus for discussion and resolution of broad IRB policy issues.

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*U.S. GPO: 1993-346-780/89001

INSPECTIONAL GUIDELINES

This guideline describes the procedure needed to obtain the information sought by Part III Inspectional Operations. Carrying out the compliance program may be approached by a series of standardized procedures to determine the IRB's level of compliance with Parts 50 and 56.

The investigator should interview IRB representatives and evaluate the IRB's procedures and records. The results of these interviews and evaluations should be summarized in the EIR narrative and the pertinent records, and other documents should be attached as exhibits.

A. THE IRB MEMBERSHIP

1. Determine whether the IRB membership has the representation required by section 56.107.

   Discussion: FDA recommends that the membership include at least one physician, and that at least one physician is present and eligible to vote on proposed studies of FDA regulated articles.

2. Determine that no IRB member participates in the deliberation or voting in the initial or continuing review of any study in which the IRB member has a conflicting interest except to provide information required by the IRB [section 56.107(e)].

3. If alternate members are used, determine whether the IRB's use of alternate members satisfies the following criteria:

   a. Alternate members are appointed in advance by the same procedures as primary IRB members.

   b. Alternate members are listed on the IRB roster and identified as to the primary IRB members for whom they may substitute at convened meetings.

   c. IRB minutes record when alternate members act in the absence of primary members.

   d. Alternate members receive the same information as primary members.

B. WRITTEN PROCEDURES

Determine that the IRB has written procedures as required by Section 56.108.

Discussion: There are significant differences between the DHHS regulations (45 CFR 46) and the FDA regulations (21 CFR 50 and 56) which

apply to research involving products regulated by FDA. These differences are outlined on page 85 of the FDA IRB Information Sheets. Therefore, compliance with the DHHS requirements does not automatically ensure compliance with the FDA regulations.

The use of Multiple Project Assurance (MPA) document approved by DHHS as the IRB's written procedures does not necessarily meet the requirement for written procedures in Section 56.108. The MPA document is merely a promise to follow the DHHS regulations, and may not contain day-to-day how-to procedures required by the FDA regulation.

C. INITIAL AND CONTINUING IRB REVIEW AND APPROVAL OF INVESTIGATIONAL USE OF FDA REGULATED PRODUCTS

1. Determine whether the IRB has the authority to approve, modify or disapprove proposed studies, and to modify, or terminate approval of ongoing studies.

2. Determine whether the institution overrides negative or restrictive IRB decisions.

3. Determine whether the IRB provides a system for receiving and distributing the materials submitted by the clinical investigators.

   Discussion: An acceptable package for initial review would contain the proposed protocol, the consent form, and the investigator's brochure provided by the sponsor. When an investigator's brochure is not available, the protocol should contain an appropriate description of the previous animal and human experience associated with use of the investigational article. Any payment schedules, information sheet or instruction summaries given to human subjects should be included. When advertising is to be used for recruiting subjects, a copy of the advertisement should be submitted for review by the IRB. When the consent process is to be conducted in a language other than English, the IRB should review and approve a translated consent form.

4. Determine that at least one IRB member is assigned the responsibility for an in-depth evaluation of the investigational proposal, the consent form, and when available, the investigator's brochure.

5. Determine that each IRB member receives at a minimum a copy of the consent document and a summary of the protocol.

6. Determine that all IRB members have access to copies of the complete submission to the IRB.

7. Determine whether the IRB has reviewed proposed and continuing studies at convened meetings. A majority of the IRB members must be present, including at least one member whose primary concerns are in nonscientific areas, except when the expedited procedures described in section 56.110 apply.

8. Determine whether IRB approved research received the approval of a majority of the IRB members present at the meeting.

9. Determine that the written procedures describe how the IRB ensures that clinical investigators make all initially required modifications prior to enrollment of research subjects.

10. Determine whether the IRB has and follows written procedures for nonsignificant risks determination for investigational devices.

11. Determine that the review for ongoing studies is performed by the IRB at the assigned frequency.

12. Determine that the written procedures describe the IRB actions for determining which projects require review more often than once a year.

    Discussion: This requirement is easily fulfilled by a simple statement in the written procedures that the IRB will determine/set the review frequency concurrently with the decision to approve the proposed study. IRB's should avoid the use of terms "annual reviews" or "yearly reviews" to describe the progress reports. An IRB may determine that most or all of its progress reports should be submitted annually, however, IRB's should not allow the system to set all review frequency annually. It is recommended that the review frequency be recorded in the minutes and included in the notice of approval sent to the clinical investigator.

D. CONTINUING REVIEW OF RESEARCH

1. Determine whether the clinical investigator promptly submits progress reports.

2. Determine whether each member has access to the progress report.

3. Determine whether at least one member is assigned responsibility for appropriate review of each progress report.

4. Determine how progress reports are evaluated to determine whether the study should be amended, terminated or allowed to continue as originally approved.

5. Determine whether the protocols and consent forms approved by the IRB continue to be used by the clinical investigator.

6. Determine whether all amendments have been submitted to and approved by the IRB.

7. Determine whether all serious/unexpected reaction reports are promptly submitted and reviewed by the IRB.

8. Determine whether IRB files contain documentation that appropriate continuing review procedures were completed.

E. IRB REPORTING TO THE CLINICAL INVESTIGATORS AND THE INSTITUTION

1. Determine whether the IRB notifies: (a) the clinical investigators and the institution in writing of the IRB actions, and (b) the clinical investigators of their responsibility for providing subsequent reports to the IRB [Sections 56.108, (a)(3), (a)(4), and (b) and 56.109(d)].

Discussion: The IRB should insure that the clinical investigators are made aware of their responsibilities for complying with sections 56.108(a)(3) and (a)(4). Some methods for informing clinical investigators may include:

i. Handbooks or Informational Sheets for clinical investigators which describe their responsibilities.

ii. Letters of approval to clinical investigators which describe their responsibility. For the latter method, a sample copy of the approved letter should be referenced in and attached to the written procedures.

iii. A copy of IRB procedures is given to the clinical investigators.

Clinical investigators must be provided with an opportunity to respond in person or in writing to the IRB for any disapproval of their proposed research. IRB files should contain copies of both the IRB notifications and subsequent responses from the clinical investigator.

2. Determine whether the IRB maintains records to document that both the IRB and the clinical investigator have met their responsibilities.

Discussion: The IRB procedures should describe how the IRB reports its finding and actions to the clinical investigator and the institution. Notifications of IRB actions are to be in writing. IRB requests for additional information and/or modifications of the proposed research should be fully described in the notices to the clinical investigators.

F. EXPEDITED REVIEW

1. Determine whether the IRB's use of expedited review procedures meets the requirements of sections 56.110(a) and (b), and that these actions are documented in the IRB records.

Discussion: The list of categories of research that may be approved through expedited review is found in the Federal Register Notice published on January 27, 1981. This Notice is included as Appendix A in the IRB Information Sheets.

2. Determine that expedited review procedures are not used for circumventing the convened meeting requirements of section 56.108(b). Examples of such misuse can be any of the following actions:

a. Interim approval granted by the chairperson pending review of the proposed study at a later convened meeting.

b. Compassionate approval granted for the one-patient nonemergency use in a protocol which does not meet the requirements of section 56.110.

c. Expedited approval based on IRB approval of the protocol at another institution for which no cooperative agreement exists.

d. Expedited review of a so-called emergency use when the circumstances do not meet the requirements of 56.102(d).

G. EMERGENCY REVIEW*

1. Determine whether all uses of FDA regulated articles exempted from prior IRB review on the basis of "emergency use" meet the requirements of sections 56.102(d) and 56.104(c).

2. Determine whether subsequent use is subject to IRB review.

H. INFORMED CONSENT*

1. Determine that the consent form contains the required elements as noted in section 50.25(a) and any of the elements of section 50.25(b) that are relevant to the study.

2. Determine that the IRB has reviewed and approved the consent form used in the study.

   The IRB is responsible for ensuring that each consent document provides the required information, Part 50, in readily understandable wording. The Center will determine the adequacy and completeness of the elements.

3. Determine if the IRB has ever waived informed consent requirements for FDA regulated studies, i.e., permitted subjects to participate in a study prior to giving informed consent. If so, obtain the IRB's SOPs covering this procedure and document each instance where this occurred by collecting the minutes of the meeting at which the requirement was waived and the documents that the IRB reviewed to make its decision.

   Discussion: The exceptions from informed consent is only permitted under emergency circumstances. Refer to 21 CFR 50.23 for guidance. The FDA regulations have no provision for waiving informed consent.

Current Changes