

Food and Drug Administration

INFORMATION SHEETS

for Institutional Review Boards and
Clinical Investigators

Food and Drug Administration
Office of the Associate Commissioner for Health Affairs
5600 Fishers Lane
Rockville, Maryland, 20857

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Errata

Due to re-organizations the following changes are immediately effective:

The Document Management Reporting Branch, Center for Drug Evaluation and Research no longer exists. The new organization name and telephone number is: Document Requirements and Services Branch (HFD-53) at 301-827-1501. Please make this correction on pages 3 (question #4), 57, 62, 66, and 154.

The names of two FDA District Offices have changed. The Orlando District is now the Florida District and the Newark District is now the New Jersey District. Please make these corrections on page 147.

The CDER Institutional Review Branch no longer exists. Please substitute the Division of Scientific Investigations on page 150.

The CDER Executive Secretariat has been renamed to Communications Management. Please make this correction on page 150.



October 1995

FDA INFORMATION SHEETS FOR IRBs AND CLINICAL INVESTIGATORS

In 1984, the Office of Health Affairs published a series of Information Sheets to help Institutional Review Boards (IRBs) carry out their responsibilities for protection of research subjects. These were revised in 1989 and a separate set of Clinical Investigator Information Sheets was also developed in the same year. The attached set of information sheets is a major revision of those 1989 publications.

This revision (10/95) combines the two sets of information sheets into one, groups related topics together, adds several new sheets, expands the information content of the revised sheets and adds an index of significant terms. Users will soon be able to obtain direct access to current and updated sheets through an automated fax system and at the FDA home page on the Internet World Wide Web (<http://www.fda.gov>).

An Appendix has been included and contains resource materials such as the Agency's human subject regulations and the Belmont Report. Also included in the Appendix is contact information for key FDA offices.

These information sheets incorporate many comments and suggestions made by users, and we thank you for the support in making them more suited to your needs. We hope that you find these changes helpful, and that the FDA information sheets continue to be a valuable resource to you in discharging your responsibilities for protecting human subjects who participate in clinical research. We invite you to assist us in future enhancements by providing any suggestions you may have for improvements or additions which would make the information sheets more useful to you. Please send any comments to: Health Assessment Policy Staff, Office of Health Affairs, 5600 Fishers Lane, Room 15-22 (HFY-20), Rockville, MD 20857 [telephone (301) 827-1685].

Stuart L. Nightingale, M.D.
Associate Commissioner
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FREQUENTLY ASKED QUESTIONS

The following is a compilation of frequently asked questions about human subject protection and compliance with Food and Drug Administration (FDA) regulations. These questions are organized as follows.

- I. Institutional Review Board regulations
- II. Informed Consent regulations
- III. Clinical investigations
- IV. Other

I. Institutional Review Board Regulations

1. What is an Institutional Review Board (IRB)?

Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure the following [21 CFR 56.111].

- Risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- Risks to subjects are reasonable in relation to anticipated benefits (if any) to subjects, and the importance of the knowledge that may be expected to result.
- Selection of subjects is equitable.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative and will be documented in accordance with, and to the extent required, by the Agency's informed consent regulations.
- Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- Appropriate additional safeguards have been included in the study to protect the rights and welfare of subjects who are members of a vulnerable group.

2. Do IRBs have to be formally called by that name?

No, "IRB" is a generic term used by FDA (and HHS) to refer to a group whose function is to review research to assure the protection of the rights and welfare of the human subjects. Each institution may use whatever name it chooses. Regardless of the name chosen, the IRB is subject to the Agency's IRB regulations when studies of FDA regulated products are reviewed and approved.

3. Does an IRB need to register with FDA before approving studies?

Currently, FDA does not require IRB registration. The form FDA-1572 "Statement of Investigator" for a study conducted under an IND requires the name and address of the IRB that will be responsible for review of the study. IRBs that approve FDA regulated studies must be established and operated in compliance with 21 CFR part 56.

4. Which FDA office may an IRB contact to determine whether an investigational new drug application (IND) or investigational device exemption (IDE) is required for a study of a test article?

For drugs, the IRB may contact the Document Management and Reporting Branch, Center for Drug Evaluation and Research (CDER), at (301) 827-0531.

For a biological product, contact the Division of Congressional and Public Affairs, Center for Biologics Evaluation and Research (CBER), at (800) 835-4709.

For a medical device, contact the Program Operation Staff, Office of Device Evaluation, Center for Devices and Radiological Health (CDRH), at (301) 594-1190.

If the IRB is unsure about whether a test article is a "drug," a "biologic" or a "device," the IRB may contact the Health Assessment Policy Staff, Office of Health Affairs, at (301) 827-1685.

5. May a clinical investigator be an IRB member?

Yes, however, the IRB regulations [21 CFR 56.107(e)] prohibit any member from participating in the IRB's initial or continuing review of any study in which the member has a conflicting interest, except to provide information requested by the IRB. When selecting IRB members, the potential for conflicts of interest should be considered. When members frequently have conflicts and must absent themselves from deliberation and abstain from voting, their contributions to the group review process are diminished and can hinder the review procedure. Even greater disruptions may result if this person is chairperson of the IRB.

6. The IRB regulations require an IRB to have a diverse membership. May one member satisfy more than one membership category?

Yes. For example, one member could be otherwise unaffiliated with the institution and have a primary concern in a non-scientific area. This individual would satisfy two of the membership requirements of the regulations. IRBs should strive, however, for a membership that has a diversity of representative capacities and disciplines. In fact, the FDA regulations [21 CFR 56.107(a)] require that, as part of being qualified as an IRB, the IRB must have "diversity of members, including consideration of race, gender, cultural backgrounds and sensitivity to such issues as community attitudes...."

7. Must an institution establish its own IRB?

No. Although institutions engaged in research involving human subjects will usually have their own IRBs to oversee research conducted within the institution or by the staff of the institution, this is not required by FDA regulations. An institution without an IRB may allow another IRB to be responsible for studies conducted at the non-IRB institution. Such arrangements should be agreed to in writing. Individuals conducting research in a non-institutional setting often use established IRBs (independent or institutional) rather than form their own IRBs. Also, see the information sheets entitled "Non-local IRB Review" and "Cooperative Research."

8. May a hospital IRB review a study that will be conducted outside of the hospital?

Yes. IRBs may agree to review research from affiliated or unaffiliated investigators, however, FDA does not require IRBs to assume this responsibility. If the IRB conducts these reviews, the IRB policies should authorize such reviews and the process should be described in the IRB's written procedures.

9. May IRB members be paid for their services?

There is nothing in FDA regulations to preclude a member from being compensated for services rendered. Payment to IRB members should have no inducement for favorable decisions. Expenses, such as travel costs, may also be reimbursed.

10. What is the FDA role in IRB liability in malpractice suits?

FDA regulations do not address the question of IRB or institutional liability in the case of malpractice suits. FDA does not have authority to limit liability of IRBs or their members. Compliance with FDA regulations may help minimize an IRB's exposure to liability.

11. What happens during an FDA inspection of an IRB?

FDA field investigators interview institutional officials and examine the IRB records to determine compliance with FDA regulations. Also, see the information sheet entitled "FDA Institutional Review Board Inspections" for a complete description of the inspection process.

12. The FDA regulations [21 CFR 56.104(c)] exempt an emergency use of a test article from prospective IRB review, however, “[a]ny subsequent use of the test article at the institution is subject to IRB review.” What does the phrase “subsequent use” mean?

FDA regulations allow for one emergency use of a test article in an institution without prospective IRB review, provided that such emergency use is reported to the IRB within five working days after such use. An emergency use is defined as a single use (or single course of treatment, e.g., multiple doses of antibiotic) with one subject. “Subsequent use” would be a second use with that subject or the use with another subject.

In its review of the emergency use, if it is anticipated that the test article may again be used, the IRB should request a protocol and consent document(s) be developed so that an approved protocol would be in place when the next need arises. In spite of the best efforts of the clinical investigator and the IRB, a situation may occur where a second emergency use needs to be considered. FDA believes it is inappropriate to deny emergency treatment to an individual when the only obstacle is lack of time for the IRB to convene, review the use and give approval.

13. What is expedited review?

Expedited review is a procedure through which certain kinds of research may be reviewed and approved without convening a meeting of the IRB. The Agency’s IRB regulations [21 CFR 56.110] permit, but do not require, an IRB to review certain categories of research through an expedited procedure if the research involves no more than minimal risk. A list of categories was last published in the Federal Register on January 27, 1981 [46 FR 8980].

The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period covered by the original approval. Under an expedited review procedure, review of research may be carried out by the IRB chairperson or by one or more experienced members of the IRB designated by the chairperson. The reviewer(s) may exercise all the authorities of the IRB, except disapproval. Research may only be disapproved following review by the full committee. The IRB is required to adopt a method of keeping all members advised of research studies that have been approved by expedited review.

14. 21 CFR 56.115(a)(1) requires that the IRB maintain copies of "research proposals reviewed." Is the "research proposal" the same as the formal study protocol that the investigator receives from the sponsor of the research?

The IRB should receive and review sufficient information upon which to base approval/disapproval of the study (see the criteria required for IRB approval in 21 CFR 56.111). Some institutions only require the investigator to submit the formal study protocol for review and, in the case of investigational new drug studies, the investigator's brochure. Others also require the investigator to submit an institutionally-developed protocol summary form. A copy of all documentation reviewed is to be maintained for at least three years after completion of the research at that institution [21 CFR 56.115(b)].

15. If an IRB member cannot attend a meeting, may they send someone from their department to vote for them?

No. Ad hoc substitutes are not permissible as members of an IRB. If allowed by IRB procedures, representatives may attend as consultants and gather information for the absent member, but they may not participate in either deliberation or voting with the board. If such persons have an expertise similar to the absent member, the IRB may, of course, ask questions of this representative just as they could of any non-member consultant. Also, votes submitted prior to a convened meeting by mail, telephone, telefax or e-mail are not permissible. Opinions of the absent members may be transmitted and considered by the attending IRB members. A member who is unable to attend the convened meeting may also participate by video-conference, conference telephone call, or using other technologies that allow the member to interact with the assembled members.

16. May the IRB use alternate members?

The use of formally appointed alternate IRB members is acceptable to the FDA, provided that the IRB's written procedures describe the appointment and function of alternate members. The IRB roster should identify the primary member(s) for whom each alternate member may substitute. To ensure maintaining an appropriate quorum, the alternate's qualifications should be comparable to the primary member to be replaced. The IRB minutes should document when an alternate member replaces a primary member. When alternates substitute for a primary member, the alternate member should have received and reviewed the same material that the primary member received or would have received.

17. Does a non-affiliated member need to attend every IRB meeting?

No. Although 21 CFR 56.108(c) does not specifically require the presence of a member not otherwise affiliated with the institution to constitute a quorum, FDA considers the presence of such members an important element of the IRB's diversity. Frequent absence of non-affiliated member representation is not an acceptable practice. Acknowledging their important role, many IRBs have appointed more than one member who is not otherwise affiliated with the institution. FDA encourages IRBs to appoint members in accordance with 21 CFR 56.107(a) who will be able to participate fully in the IRB process.

18. The number of studies we review has increased, and the size of the package of review materials we send to IRB members is becoming formidable. Must we send the full package to all IRB members?

The IRB system was designed to foster open discussion and debate at convened meetings of the full IRB membership. While it is preferable for every IRB member to have personal copies of all study materials, each member must be provided with sufficient information to be able to actively and constructively participate. Some institutions have developed a "primary reviewer" system to promote a thorough review. Under this system, studies are assigned to one or more IRB members for a full review of all materials. Then, at the convened IRB meeting the study is presented by the primary reviewer(s) and, after discussion by IRB members, a vote for an action is taken.

The "primary reviewer" procedure is acceptable to the FDA if each member receives, at a minimum; a copy of consent documents and a summary of the protocol in sufficient detail to determine the appropriateness of the study-specific statements in the consent documents. In addition, the complete documentation should be available to all members for their review, both before and at the meeting. The materials for review should be received by the membership sufficiently in advance of the meeting date to allow for adequate review of the materials.

Some IRBs are also exploring the use of electronic submissions and computer access for IRB members. Whatever system the IRB develops and uses, it must ensure that each study receives an adequate review and that the rights and welfare of the subjects are protected.

19. Must an investigator's brochure be included in the documentation when an IRB reviews an investigational drug study?

For studies conducted under an investigational new drug application, an investigator's brochure is usually required by FDA [21 CFR 312.23(a)(5) and 312.55]. Even though 21 CFR part 56 does not mention the investigator's brochure by name, information contained in such brochures is clearly required to be reviewed by the IRB. The regulations do outline the criteria for IRB approval of research. 21 CFR 56.111(a)(1) requires the IRB to assure that risks to the subjects are minimized. 21 CFR 56.111(a)(2) requires the IRB to assure that the risks to subjects are reasonable in relation to the anticipated benefits. The risks cannot be determined without review of the results of previous animal and human studies, which are summarized in the investigator's brochure.

20. Are there any regulations that require clinical investigators to report to the IRB when a study has been completed?

IRBs are required to function under written procedures. One of these procedural requirements [21 CFR 56.108(a)(3)] requires ensuring "prompt reporting to the IRB of changes in a research activity." The completion of the study is a change in activity and should be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report/notice to the IRB allows it to close its files as well as providing information that may be used in the evaluation and approval of related studies by that investigator.

II. Informed Consent Regulations

1. Is the purpose of the IRB review of informed consent to protect the institution or the subject?

The fundamental purpose of IRB review of informed consent is to assure that the rights and welfare of subjects are protected. A signed informed consent document is evidence that the document has been provided to a prospective subject (and presumably, explained) and that the subject has agreed to participate in the research. IRB review of informed consent documents also ensures that the institution has complied with applicable regulations.

2. Is getting the subject to sign a consent all that is required by the regulations?

No. The consent document itself is a written summary of the information that should be provided to the subject. Many clinical investigators use the consent document as a guide for the verbal explanation of the study. The subject's signature provides documentation of consent to participate in a study, but is only one part of the consent process. The entire informed consent process involves giving a subject adequate information concerning the study, providing adequate opportunity for the subject to consider all options, responding to the subject's questions, ensuring that the subject has comprehended this information, obtaining the subject's voluntary agreement to participate and, continuing to provide information as the subject or situation requires. To be effective, the process should provide ample opportunity for the investigator and the subject to exchange information and ask questions.

3. 21 CFR 50.27(a) of the FDA informed consent regulation requires that a copy of the consent document be given to the person signing the form. Does this copy have to be a photocopy of the form with the subject's signature affixed?

No. The copy of the form given to the subject need not be a copy of the document that the subject signed. It must, however, be a copy of the IRB approved document that was given to the subject to obtain consent [21 CFR 50.27(a) or 21 CFR 50.27(b)(2)]. One purpose of providing the person signing the form with a copy of the consent document is to allow the subject to review the information with others, both before and after making a decision, as well as providing a continuing reference for items such as emergency contacts.

4. If an IRB uses a standard "fill-in-the-blank" consent format, does the IRB need to review the filled out form for each study?

Yes. A fill-in-the-blank format provides only some standard wording and a framework for organizing the relevant study information. The IRB should review a completed sample form, individualized for each study, to ensure that the consent document, in its entirety, contains all the information required by 21 CFR 50.25 in language the subject can understand. The completed sample form should be typed to enhance its readability by the subjects. The form finally approved by the IRB should be an exact copy of the form that will be presented to the research subject. The IRB should also review the "process" for consent interviews, i.e., the circumstances under which consent will be obtained, who will obtain consent, and so forth.

5. The informed consent regulations [21 CFR 50.25 (a)(5)] require the consent document to include a statement that notes the possibility that FDA may inspect the records. Is this statement a waiver of the subject's legal right to privacy?

No. FDA does not require any subject to "waive" a legal right. Rather, FDA requires that subjects be informed that complete privacy does not apply in the context of research involving FDA regulated products. Under the authority of the Federal Food, Drug, and Cosmetic Act, FDA may inspect and copy clinical records to verify information submitted by a sponsor. Ordinarily it is not necessary that a subject's name be revealed to FDA unless a more detailed study of the case is required or there is reason to believe that the records do not represent the actual cases studied or results obtained.

The consent should not state or imply that FDA needs clearance or permission from the clinical investigator, the subject or the IRB for such access. When clinical investigators conduct studies for submission to FDA, they agree to allow FDA access to the study records, as outlined in 21 CFR 312.68 and 812.145. Informed consent documents should make it clear that, by participating in research, the subject's records automatically become part of the research database. Subjects do not have the option to keep their records from being audited/reviewed by FDA.

When an individually identifiable medical record (usually kept by the clinical investigator, not by the IRB) is copied and reviewed by the Agency, proper confidentiality procedures are followed within FDA. Consistent with laws relating to public disclosure of information and the law enforcement responsibilities of the Agency, however, absolute confidentiality cannot be guaranteed.

6. Does an IRB or institution have to compensate subjects if injury occurs as a result of participation in a research study?

Institutional policy, not FDA regulation, determines whether compensation and medical treatment(s) will be offered and the conditions that might be placed on subject eligibility for compensation or treatment(s). The FDA informed consent regulation on compensation [21 CFR 50.25(a)(6)] requires that, for research involving more than minimal risk, the subject must be told whether any compensation and any medical treatment(s) are available if injury occurs and, if so, what they are, or where further information may be obtained. Any statement that compensation is not offered must avoid waiving or appearing to waive any of the subject's rights or releasing or appearing to release the investigator, sponsor, or institution from liability for negligence [21 CFR 50.20].

7. May an IRB require that the sponsor of the study and/or the clinical investigator be identified on the study's consent document?

Yes. The FDA requirements for informed consent are the minimum basic elements of informed consent that must be presented to a research subject [21 CFR 50.25]. An IRB may require inclusion of any additional information which it considers important to a subject's decision to participate in a research study [21 CFR 56.109(b)].

8. Must the informed consent document contain a space for assent by children?

No, however, many investigators and IRBs consider it standard practice to obtain the agreement of older children who can understand the circumstances before enrolling them in research. While the FDA regulations do not specifically address enrollment of children (other than to include them as a class of vulnerable subjects), the basic requirement of 21 CFR 50.20 applies, i.e., the legally effective informed consent of the subject or the subject's legally authorized representative must be obtained before enrollment. Parents, legal guardians and/or others may have the ability to give permission to enroll children in research, depending on applicable state and local law of the jurisdiction in which the research is conducted. (Note: permission to enroll in research is not the same as permission to provide medical treatment.) IRBs generally require investigators to obtain the permission of one or both of the parents or guardian (as appropriate) and the assent of children who possess the intellectual and emotional ability to comprehend the concepts involved. Some IRBs require two documents, a fully detailed explanation for parents and older children to read and sign, and a shorter, simpler one for younger children.

9. Should children be required to sign consent documents?

As indicated above, researchers may seek assent of children of various ages. Older children may be well acquainted with signing documents through prior experience with testing, licensing and/or other procedures normally encountered in their lives. Signing a form to give their assent for research would not be perceived as unusual and would be reasonable. Younger children, however, may never have had the experience of signing a document. For these children requiring a signature may not be appropriate, and some other technique to verify assent could be used. For example, a third party may verify, by signature, that the assent of the child was obtained.

10. Must informed consent documents be translated into the written language native to study subjects who do not understand English?

21 CFR 50.20, requires that "the information that is given to the subject or the representative shall be in language understandable to [them]." Study subjects are given a copy of the consent that may be used as a reference document to reinforce their understanding of the study and, if subjects desire, used to consult with their personal physician and/or family members about the study. Another purpose is to provide a continuing reference for items such as emergency contacts. Therefore, when the prospective subject is fluent in English, and the consent interview is conducted in English, the consent document should be in English. When the study subject population will include people who do not understand English, and the clinical investigator or the IRB anticipates that consent interviews are likely to be conducted in a language other than English, the IRB should assure that a translated consent document is prepared and that the translation accurately conveys the information as approved by the IRB. Ad hoc oral translation of the English consent document should not be routinely substituted for a written translation. In unanticipated circumstances, however, this may be acceptable.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Informed Consent and the Clinical Investigator"

III. Clinical Investigations

1. Does a physician, in private practice, conducting research with an FDA regulated product, need to obtain IRB approval?

The FDA regulations require IRB review and approval of regulated clinical investigations, whether or not the study involves institutionalized subjects. FDA has included non-institutionalized subjects because it is inappropriate to apply a double standard for the protection of research subjects based on whether or not they are institutionalized.

An investigator may be able to obtain IRB review by submitting the research proposal to a community hospital, a university/medical school, an independent IRB, a local or state government health agency or other organizations. If IRB review cannot be accomplished by one of these means, investigators may contact the FDA for assistance (Health Assessment Policy Staff 301-827-1685.).

2. Does a clinical investigation involving a marketed product require IRB review and approval?

Yes, if the investigation is governed by FDA regulations [see 21 CFR 56.101, 56.102(c), 312.2, 361.1, 601.2, 812.2, and 813.2]. Also, see the information sheet entitled "Investigational and 'Off-label' Use of Marketed Drugs and Biologics" for more information.

3. Does a treatment IND [21 CFR 312.34] require prior IRB approval?

Test articles given to human subjects under a treatment IND require prior IRB approval, with two exceptions. If a life-threatening emergency exists, as defined by 21 CFR 56.102(d), the procedures described in 56.104(c) ("Exemptions from IRB Requirement") may be followed. In addition, FDA may grant the sponsor or sponsor/investigator a waiver of the IRB requirement in accord with 21 CFR 56.105. An IRB may still choose to review a study even if FDA has granted a waiver. For further information see the information sheets entitled "Emergency Use of an Investigational Drug or Biologic," "Emergency Use of Unapproved Medical Devices," "Waiver of IRB Requirements" and "Treatment use of Investigational Drugs and Biologics."

4. How have the FDA policies on enrolment of special populations changed?

On July 22, 1993, the FDA published the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, in the Federal Register [58 FR 39406]. The guideline was developed to ensure that the drug development process provides adequate information about the effects of drugs and biological products in women. For further information, see the information sheet entitled "Evaluation of Gender Differences in Clinical Investigations."

On December 13, 1994, FDA published a final rule on the labeling of prescription drugs for pediatric populations [59 FR 64240]. The rule [21 CFR 201.57] encourages sponsors to include pediatric subjects in clinical trials so that more complete information about the use of drugs and biological products in the pediatric population can be developed.

5. What is a medical device?

A medical device is any instrument, apparatus, or other similar or related article, including component, part, or accessory, which is

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them;
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals; or
- intended to affect the structure or any function of the human body or in animals; and
- does not achieve any of its principal intended purposes through chemical action within or on the human body or in animals and is not dependent upon being metabolized for the achievement of its principal intended purposes.

Approximately 1,700 types of medical devices are regulated by FDA. The range of devices is broad and diverse, including bandages, thermometers, ECG electrodes, IUDs, cardiac pacemakers, and hemodialysis machines. For further information, see the information sheets entitled "Medical Devices" and "Significant Risk and Nonsignificant Risk Medical Device Studies."

6. Are *in vitro* diagnostic products medical devices?

The definition of a "device" includes *in vitro* diagnostic products — devices that aid in the diagnosis of disease or medical/physiological conditions (e.g., pregnancy) by using human or animal components to cause chemical reactions, fermentation, and the like. A few diagnostic products are intended for use in controlling other regulated products (such as those used to screen the blood supply for transfusion-transmitted diseases) and are regulated as biological products.

7. What are the IRB's general obligations towards IOL clinical investigations?

An IRB is responsible for the initial and continuing review of all IOL clinical investigations. Each individual IOL style is subject to a separate review by the IRB. This does not, however, preclude the IRB from using prior experience with other IOL investigations in considering the comparative merits of a new lens style. All IOL studies are also subject to FDA approval

8. Considering the large number of intraocular lens (IOL) studies, how does an IRB approach the review of a new IOL style?

Full IRB review is required for all new IOLs that exhibit major departures from available lenses. Minor changes to existing lenses may be approved through expedited review. FDA designates new IOL styles as either major or minor changes based upon a predetermined classification scheme and advises the sponsor of its determination. The sponsor, through the investigator, should provide the IRB with the investigational plan which indicates the FDA study requirements, as well as the informed consent document and other comparative information on the proposed lens that describes its characteristics. It is the IRB's prerogative to request any relevant information on a new IOL to arrive at a decision or to be more rigorous in its evaluation than FDA considers minimally required.

IV. Other

1. What is an "assurance" or a "multiple project assurance?"

An "assurance," is a document negotiated between an institution and the Department of Health and Human Services (HHS) in accordance with HHS regulations. For research involving human subjects conducted by HHS or supported in whole or in part by HHS, the HHS regulations require a written assurance from the performance-site institution that the institution will comply with the HHS protection of human subjects regulations [45 CFR part 46]. The assurance mechanism is described in 45 CFR 46.103. Once an institution's assurance has been approved by HHS, a number is assigned to the assurance. The assurance may be for a single grant or contract (a "single project assurance"); for multiple grants ("multiple project assurances" — formerly called "general assurances"); or for certain types of studies such as oncology group studies and AIDS research group studies ("cooperative assurances"). The Office for Protection from Research Risks (OPRR), is responsible for implementing the HHS regulations. The address and telephone number for OPRR are: 6100 Executive Boulevard, Suite 3B01 (MSC-7507), Rockville, MD 20892-7507; (301) 496-7041.

2. Is an "assurance" required by FDA?

Currently, FDA regulations do not require an assurance. FDA regulations [21 CFR parts 50 and 56] apply to research involving products regulated by FDA—federal funds and/or support do not need to be involved for the FDA regulations to apply. When research studies involving products regulated by FDA are funded/supported by HHS, the research institution must comply with both the HHS and FDA regulations. Also, see "Significant Differences in HHS and FDA Regulations for the protection of Human Subjects."

COOPERATIVE RESEARCH

Cooperative research studies involve more than one institution. The Food and Drug Administration (FDA) and Department of Health and Human Services (HHS) regulations permit institutions involved in multi-institutional studies to use reasonable methods of joint or cooperative review [21 CFR 56.114 and 45 CFR 46.114, respectively]. This provision is intended to assure Institutional Review Boards (IRBs) that FDA will accept reasonable methods of joint review. While the IRB assumes responsibility for oversight and continuing review, the clinical investigator and the research site retain the responsibility for the conduct of the study.

Scope of Cooperative Research Activities

The regulatory provision for cooperative review arrangements may be applied to different types of cooperative clinical investigations. Examples include research coordinated by cooperative oncology groups and participation by investigators and subjects in a clinical study primarily conducted at or administered by another institution. Often, one institution has the primary responsibility for the conduct of the study and the responsibility for administrative or coordinating functions. At other times, multi-centered trials may be coordinated by an office or organization that does not actually conduct the clinical study or have an IRB.

Written Cooperative Review Agreements

The cooperative research arrangements between institutions may apply to the review of one study, to certain specific categories of studies or to all studies. A single cooperative IRB may provide review for several participating institutions, but the respective responsibilities of the IRB and each institution should be agreed to in writing.

An institution may agree to delegate the responsibility for initial and continuing review to another institution's IRB. In turn, the IRB agrees to assume responsibility for initial and continuing review. The institution delegating the responsibility for review should understand that it is agreeing to abide by the reviewing IRB's decisions. The delegating institution remains responsible for ensuring that the research conducted within its own institution is in full accordance with the determinations of the IRB providing the review and oversight.

The IRB which agrees to review studies conducted at another institution has responsibility for initial and continuing review of the research. Such an IRB, in initially reviewing the study, should take into account the required criteria for approval, the facilities and capabilities of the other institution, and the measures taken by the other institution to ensure compliance with the IRB's determinations. The reviewing IRB needs to be sensitive to factors such as community attitudes.

The agreement for IRB review of cooperative research should be documented. Depending upon the scope of the agreement, documentation may be simple, in the form of a letter, or more complex such as a formal memorandum of understanding. In the case of studies supported or conducted by HHS, arrangements or agreements may be subject to approval by HHS through the Office for Protection from Research Risks (OPRR) and should be executed in accordance with OPRR's instructions. Whatever form of documentation is used, copies should be furnished to all parties to the agreement, and to those responsible for ensuring compliance with the regulations and the IRB's determinations. The IRB's records should include documentation of such agreements.

When an IRB approves a study, it notifies (in writing) the clinical investigator and the institution at each location for which the IRB has assumed responsibility [21 CFR 56.109(d)]. All required reports from the clinical investigators should be sent directly to the responsible IRB with copies to the investigator's institution, as appropriate.

Multi-institutional IRB

Another form of cooperative research activity is a multi-institutional IRB, that oversees the research activities of more than one institution in a defined area, such as a city or county. Such an IRB is formed by separate but cooperating institutions and eliminates the need for each facility to organize and staff its own IRB. A variation of this is an IRB that is established by a corporate entity to oversee research at its operating components, for example, a hospital system with facilities at several locations.

Also see FDA Information Sheet: "Non-Local IRB Review"

NON-LOCAL IRB REVIEW

Under certain circumstances, local review by an Institutional Review Board (IRB) may not be available, e.g., research conducted by investigators unaffiliated with an institution with an IRB. Although conceptually modeled for local IRB review, the Food and Drug Administration (FDA) regulations do not prohibit review of research by IRBs in locations other than where the research is to be performed (e.g., independent IRB or national IRB). Therefore, an IRB may review studies that are not performed on-site as long as the 21 CFR parts 50 and 56 requirements are met.

When non-local IRB review takes place, the reviewing IRB must document its role and responsibility. A written agreement should be executed between the performance site where the research is to be conducted (e.g., private practitioner's office, clinic, etc.) and the IRB or its institution. The agreement should confirm the authority of the IRB to oversee the study. While the IRB assumes responsibility for oversight and continuing review, the clinical investigator and the research site retain the responsibility for the conduct of the study.

Community Attitudes

The non-local IRB should have adequate knowledge of community attitudes, information on conditions surrounding the conduct of the research, and the continuing status of the research to assure fulfilling the requirements of 21 CFR 56.107, 56.111(a)(3), (a)(7) and (b). The non-local IRB needs to ensure these requirements are met for each location for which it has assumed IRB oversight responsibility.

The FDA regulations require all IRBs to have membership sufficiently qualified to promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects [21 CFR 56.107]. IRBs conducting non-local review need to be knowledgeable about the community from which the subjects are drawn to ensure that subject rights will be protected and that the consent process is appropriate for the subject population involved. The IRB should be sensitive to community laws and mores because state and local laws and community attitudes pertaining to research may be more restrictive than Federal regulations or the prevailing standards of the community where the IRB is located.

IRBs can obtain knowledge of community attitudes by having an IRB member drawn from that community, or by having a consultant from the community participate in the IRB's deliberations. If travel is not feasible, participation in the IRB meeting can be by video-conference, conference telephone call, or by using other technologies that allow for the consultant to interact with the assembled members. The minutes of the meeting, during which non-local research is reviewed, should document the procedures used to assure that community attitudes were adequately taken into consideration.

IRB Information Needs

IRBs should have access to a variety of information to properly conduct initial and continuing reviews. Knowledge of the conditions surrounding the conduct of the research is needed to ensure that risks to subjects are minimized [21 CFR 56.111]. An IRB should have sufficient information to judge the qualifications of the researcher conducting the study in question. The researcher's curriculum vitae, a listing of other studies conducted, letters of reference, information from the sponsor of the research, and information from licensing boards and professional societies are examples of information a non-local IRB may want to review. If the research is to be conducted in an institution, the clinical investigator should provide a description of that institution and associated medical facilities. The acknowledgment and/or the permission of the institution should also be provided. If the research is to be conducted outside an institutional setting, the IRB may request a plan for emergency medical care. Depending upon the degree of risk inherent in the study, a hospital should certify that its facilities are available.

The IRB should explicitly detail the information it needs in written reports from the researcher. In addition to scheduled continuing review of progress reports, an IRB may use other methods of obtaining information on the conduct of the study. All IRBs should have procedures that assure the IRB becomes aware of unexpected problems in ongoing studies in a timely manner. Fulfilling this requirement may call for additional efforts for non-local IRBs, such as visiting the study site, contacting the sponsor's research monitor for information on the monitor's site visits, or arranging for other oversight of the study.

IRB Contact

The FDA informed consent regulations [21 CFR 50.25(a)(7)] require that the subject be given the name of a person to contact "... for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject." Non-local IRBs should include, in the consent document, an IRB contact person and a telephone number (toll-free if long-distance). The non-local IRB may also designate an individual at the research site to be the contact and to relay reports to the IRB.

Also see FDA Information Sheet: "Cooperative Research"

CONTINUING REVIEW AFTER STUDY APPROVAL

Institutional Review Boards (IRBs) are responsible for continuing review of ongoing research to ensure that the rights and welfare of human subjects are protected. The Food and Drug Administration (FDA) regulations regarding continuing review require an IRB to develop and follow written procedures

- for conducting continuing review of research at intervals appropriate to the degree of risk, but not less than once per year [21 CFR 56.108(a)(1) and 56.109(e)];
- for determining which studies need verification from sources other than the investigator that no material changes in the research have occurred since the previous IRB review [21 CFR 56.108(a)(2)];
- for ensuring that changes in approved research are promptly reported to, and approved by, the IRB [21 CFR 56.108(a)(3-4)]; and
- for suspending or terminating approval of research that is not being conducted in accordance with the IRB's requirements [21 CFR 56.108(b)(2) and 56.113].

The FDA continuing review regulations outline minimum requirements; they do not provide specific instructions to IRBs on how to set up their own rules for continuing review within the framework of the regulations. Therefore, the regulations allow institutions or IRBs to impose greater and more detailed standards of protection for human subjects than those specified by the regulations and permit each IRB to develop procedures appropriate to its needs. By regulation, the IRB has the authority and the responsibility to take appropriate steps such as terminating or suspending approval of research that is not being conducted in accordance with the IRB's requirements.

1. Criteria for Conducting Continuing Review

FDA regulations set forth the criteria to be satisfied if an IRB is to approve research [21 CFR 56.111]. These criteria are the same for initial review and continuing review and include a determination by the IRB that

- risks to subjects are minimized;
- risks to subjects are reasonable in relation to anticipated benefits;
- selection of subjects is equitable;
- informed consent is adequate and appropriately documented;

- where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and
- appropriate safeguards have been included to protect vulnerable subjects.

2. Process for Conducting Continuing Review

Routine continuing review should include IRB review of a written progress report(s) from the clinical investigator. Progress reports include information such as: the number of subjects entered into the research study; a summary description of subject experiences (benefits, adverse reactions); numbers of withdrawals from the research; reasons for withdrawals; the research results obtained thus far; a current risk-benefit assessment based on study results; and any new information since the IRB's last review. Special attention should be paid to determining whether new information or unanticipated risks were discovered during the research. Any significant new findings which may relate to the subjects' willingness to continue participation should be provided to the subjects in accordance with 21 CFR 50.25(b)(5).

The IRB should obtain a copy of the consent document currently in use and determine whether the information contained in it is still accurate and complete, including whether new information that may have been obtained during the course of the study needs to be added. Obtaining the consent document also provides a check on whether the document being used by the clinical investigator has current IRB approval.

The purpose of continuing review is to review the entire study, not just changes in it. Continuing review of a study may not be conducted through an expedited review procedure, unless 1) the study was eligible for, and initially reviewed by, an expedited review procedure, or 2) the study has changed such that the only activities remaining are eligible for expedited review.

The IRB should determine that the frequency and extent of continuing review for each study is adequate to ensure the continued protection of the rights and welfare of research subjects. IRBs should grant approval for each study for a definite period of time, not in excess of one year [21 CFR 56.109(e)]. This limitation must be documented in IRB records and communicated to the investigator. The factors considered in setting the frequency of review may include: the nature of the study; the degree of risk involved; and the vulnerability of the study subject population. Note that 21 CFR 56.108(a)(2) requires IRBs to follow written procedures for determining the frequency and extent of continuing review.

The continuation of research after expiration of IRB approval is a violation of the regulations [21 CFR 56.103(a)]. If the IRB has not reviewed and approved a research study by the study's current expiration date, i.e., IRB approval has expired, research activities should stop. No new subjects may be enrolled in the study. If the investigator is actively pursuing renewal with the IRB and the IRB believes that an over-riding safety concern or ethical issue is involved, some IRBs have permitted some flexibility for currently enrolled subjects for the brief time required to complete the review process.

When study approval is terminated by the IRB (for one example, due to lack of compliance with continuing review requirements), in addition to stopping all research activities, any subjects currently participating should be notified that the study has been terminated. Procedures for withdrawal of enrolled subjects should consider the rights and welfare of subjects. If follow-up of subjects for safety reasons is permitted/required by the IRB (e.g., device studies), the subjects should be so informed and any adverse events/outcomes should be reported to the IRB and the sponsor.

3. Process for Dealing with Reports of Serious Adverse Reactions, Unexpected Events and Changes in the Study

IRB continuing review responsibilities include reviewing reports of adverse reactions and unexpected events involving risks to subjects or others. The IRB should establish a procedure for receiving and reviewing these reports.

Researchers should be made aware of the IRB's policies and procedures concerning reporting and continuing review requirements. This can be accomplished by notifying the investigator, in the IRB's letter of approval, of the requirement to report changes and unanticipated problems in research activities. The IRB's written procedures pertaining to continuing review and reporting requirements should be distributed to ensure that all individuals involved in research activities understand their obligations.

Unanticipated risks are sometimes discovered during the course of research. Information that may impact on the risk/benefit ratio should be promptly reported to, and reviewed by, the IRB to ensure adequate protection of the welfare of the subjects. Based upon such information, the IRB may need to reconsider its approval of the study, require modifications to the study or, revise the continuing review timetable. IRBs are also responsible for ensuring that reports of unanticipated problems involving risks to human subjects or others are reported to the FDA [21 CFR 56.108(b)(1)]. Usually, this reporting is accomplished through the normal reporting channel, i.e., the investigator to the sponsor to FDA.

4. Process for Reviewing Changes in Ongoing Research During the Approval Period

In accord with 21 CFR 56.110(b), an IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB.

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects [21 CFR 56.108(a)(4)]. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

SPONSOR - INVESTIGATOR - IRB INTERRELATIONSHIP

The interrelationship and interaction between the research sponsor (e.g., drug, biologic and device manufacturers), the clinical investigator and the Institutional Review Board (IRB) may be very complex. The regulations do not prohibit direct sponsor-IRB contacts, although, the sponsor-IRB interaction customarily occurs through the investigator who conducts the clinical study. The clinical investigator provides the communication link between the IRB and the sponsor. Such linkage is agreed to by the sponsors and investigators when they sign forms FDA-1571 and FDA-1572, respectively, for drug and biologic studies or an investigator agreement for device studies. There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The clinical investigator should be kept apprised of the discussion.

Sponsor Assurance that IRBs Operate in Compliance with 21 CFR Part 56

FDA regulations [21 CFR 312.23(a)(1)(iv)] require that a sponsor assure the FDA that a study will be conducted in compliance with the informed consent and IRB regulations [21 CFR parts 50 and 56]. This requirement has been misinterpreted to mean that it is a sponsor's obligation to determine IRB compliance with the regulations. This is not the case. Sponsors should rely on the clinical investigator, who assures the sponsor on form FDA-1572 for drugs and biologics or the investigator agreement for devices that the study will be reviewed by an IRB. Because clinical investigators work directly with IRBs, it is appropriate that they assure the sponsor that the IRB is functioning in compliance with the regulations.

An IRB must notify an investigator in writing of its decision to approve, disapprove or request modifications in a proposed research activity [21 CFR 56.109(d)]. This correspondence should be made available to the sponsor by the clinical investigator. In the Agency's view, reviewing required documents provides a reasonable basis for confirming that an IRB complies with 21 CFR part 56 and that it will be responsible for initial and continuing review of each of the studies. Also, the sponsor and, in fact, anyone who is interested, may obtain an Establishment Inspection Report from an FDA inspection of an IRB. These reports summarize the conditions observed during the IRB inspection. FDA, however, does not certify IRBs.

Sponsor Access to Medical Records

The IRB is responsible for ensuring that informed consent documents include the extent to which the confidentiality of medical records will be maintained [21 CFR 50.25(a)(5)]. FDA has encouraged sponsors (or research monitors hired by them) to monitor the accuracy of the data submitted to FDA in accordance with regulatory requirements. These data are generally in the possession of the clinical investigator. Each subject must be advised during the informed consent process of the extent to which confidentiality of records identifying the subject will be maintained and of the possibility that the FDA may inspect the records. While FDA access to

medical records is a regulatory requirement, subject names are not usually requested by FDA unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied or actual results obtained. The consent document should list all other entities (e.g., the sponsor) who will have access to records identifying the subject. The extent to which confidentiality will be maintained may affect a subject's decision to participate in a clinical investigation.

Confidentiality of Sponsor Information

The IRB's primary responsibility with respect to protecting confidentiality is to the research subject. IRBs should, however, respect the sponsor's need to maintain confidentiality of certain information about products under development. IRB members and staff should be aware that information submitted for review may be confidential, trade secret, and of commercial interest and should recognize the need for maintaining the confidentiality of the review materials and IRB records. It is advisable for IRBs to have policies that address this issue.

Nonsignificant Risk Device Studies

The determination that a medical device study presents a nonsignificant risk (NSR) is delegated by FDA to the IRB [21 CFR 812.2(b)]. The effect of the IRB's NSR decision is important to research sponsors and investigators because significant risk (SR) studies require sponsors to file an Investigational Device Exemption (IDE) with FDA before they may begin. NSR studies, however, may begin as soon as the IRB approves the study. The sponsor, usually through the clinical investigator, provides the IRB with information necessary to make a judgment on the risk of a device study. While the investigational plan and supporting materials usually contain sufficient information to make a determination, the IRB can request additional information if needed [21 CFR 812.150(b)(10)]. If the IRB believes that additional information is needed, it may contact the sponsor directly, but it should keep the clinical investigator apprised of the request. While making the SR/NSR determination, any of the three parties may ask FDA to provide a risk assessment. See FDA Information Sheet: "Significant Risk and Nonsignificant Risk Medical Device Studies" for further information.

Disagreements

The sponsor may choose not to conduct, to terminate, or to discontinue studies that do not conform with the sponsor's wishes. For example, the sponsor, clinical investigator, and IRB may reach an impasse about study procedures or specific wording in an informed consent document. The FDA will not mediate such disagreements. The Agency's policy of decentralized ethical review of clinical investigations allows such decisions to be made by local IRBs, and any disagreements between a sponsor, IRB, and clinical investigator should be resolved through appropriate communication among those parties.

RECORDKEEPING IN CLINICAL INVESTIGATIONS

The Food and Drug Administration (FDA) assesses compliance with the regulations governing clinical investigations, reviews the progress and conduct of these studies, and ultimately evaluates safety and effectiveness of the test article by reviewing a variety of documents. For these purposes, accurate and complete study documentation is important. This information sheet describes certain clinical investigator documentation requirements contained in 21 CFR parts 312 (drugs and biologics) and 812 (devices). The recordkeeping requirements for devices apply to significant risk devices, not to devices determined to be nonsignificant risk devices.

Records of Receipt and Disposition of Test Articles

Certain FDA regulations focus on those records that the Agency considers necessary to ensure strict control over distribution of test articles used in clinical investigations. Clinical investigators are required to maintain records pertaining to the test articles received from the sponsor, the date the test articles were received, and the disposition of the test articles, e.g., their use by subjects. When the study is terminated, discontinued, or completed, the investigator is required to return the unused supplies of the drug, biologic or device to the sponsor or, if authorized by the sponsor, the investigator may dispose of the test article(s) in some mutually agreeable way.

Generally, accountability records do not include details on each subject's use of a drug or biologic product. For device studies, however, the investigator must maintain a record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy. Such records may also be useful in the event of product recall. Records on the amount of product returned by a subject can serve as a check of subject compliance with the testing regimen.

Investigators are not permitted to supply an investigational drug, biologic or device to any unauthorized person and should maintain an inventory that reflects overall disposition of test articles to ensure that the articles are distributed only to those authorized to receive them [21 CFR 312.61, 812.110(c), and 813.107(a)]. Investigators are expected to maintain records to assure proper control of the investigational product.

If test articles are sent directly to the pharmacy department or other appropriate department in the institution rather than to the investigator, the pharmacy or other department may distribute the test article to the investigator or the subject and maintain the accountability records. When the test article is distributed in this manner, the investigator still remains responsible for ensuring that adequate records are maintained.

Clinical Investigation Records

There are two basic types of records that are kept regarding a clinical investigation: (1) case history records and (2) the study protocol and related documentation.

Case History Records

Investigators are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the study about each subject treated with the investigational article or enrolled as a control. Investigators are to maintain these records even though the research sponsor may also have such records.

Case history records, which include both case report forms and documents that support data in those forms, should contain: (1) basic subject identification information; (2) information showing that each subject meets the subject selection criteria or justification for otherwise enrolling the subject; (3) sufficient information to support data in the case report form as submitted to the sponsor; (4) information on each subject's exposure to the test or control article, including the date (and time, if relevant) of each administration and the quantity administered; and (5) copies of case report forms submitted to the sponsor. Case history records should be retrievable in such a fashion that all information regarding each individual in a study is attributable to that individual.

Case history records also include information obtained from tests and examinations, such as physical examinations; lab results; x-rays; progress notes; consultations; correspondence; information and data on the subject's condition before, during, and after the clinical investigation; all diagnostic tests results; diagnoses made; concomitant or concurrent therapy; and factors that might alter the test article's effects (e.g., development of an intercurrent illness).

To substantiate that each subject meets the subject selection criteria, the investigator should maintain records of the subject's medical history before entry into the study (if these records exist in the investigator's own files or hospital files). In most cases, the investigator is not obliged to seek past medical history records from other physicians who may have treated the subject or who referred the subject to the investigator. If the subject has had no previous contact with the investigator, the medical history taken when the subject enters the study should demonstrate that the subject meets the study inclusion criteria.

Additionally, investigators should maintain correspondence sent to or received from the study sponsor and the monitor, including the protocol or investigational plan, materials to be used in obtaining informed consent, protocol modifications, and records of Institutional Review Board (IRB) approval and of other communications/actions pertaining to the study.

FDA assesses study results through a scientific evaluation of the data contained in case report tables summarizing the data in case report forms. The case report format and content often varies from investigation to investigation. Case report forms are a critical part of the investigation records, but in most cases they cannot serve as the complete investigation record. The case report should contain all data required by the protocol but need not duplicate all the investigator's records on the subjects' medical histories. Likewise, everything in the case report forms need not be duplicated in the medical records. FDA does not require that special medical records be established to meet its requirements.

When FDA needs to verify the validity and completeness of the case report data submitted to the Agency, FDA may audit case history records in the possession of the investigator or investigator's institution [21 CFR 312.68 and 812.145].

Study Protocol and Related Documentation

All study protocols are required to contain

- (1) A statement of the study's objectives and purpose.
- (2) For studies of drugs (including biologics, medical foods and food additives), each investigator's name, address and statement of the qualifications, as well as each subinvestigator's name; the research facility's name and address; and each reviewing IRB's name and address. For device studies, this information is contained in the Investigational Device Exemption (IDE) investigational plan, rather than in the protocol.
- (3) Subject selection and exclusion criteria and the estimated number of subjects to be studied. For device studies, the actual number of subjects must be given.
- (4) A description of the study design, including any controls to be used, and a description of methods to minimize bias on the part of subjects, investigators, and analysts.
- (5) For drug and biologic studies, the method for determining the doses to be administered, the planned maximum dosage, and the duration of subject exposure to the drug. For device studies, the method for determining the treatment parameters, including administration and duration of subject exposure to the medical device.
- (6) A description of the observations and measurements to be made to fulfill the study's objectives.
- (7) A description of clinical procedures, laboratory tests, and other measures to be taken to minimize risk and to monitor the effects of the test and control articles.

The investigator must maintain a current study protocol with any amendments. The investigator must submit any changes to, or deviations from, the protocol to the IRB for review and approval before they are initiated unless the changes or deviations are necessary to eliminate apparent immediate hazards to the human subjects. For device studies, the research sponsor must also approve of changes before they are instituted. In drug and biologic studies, however, the investigator is only required to notify the sponsor of proposed changes in a protocol, FDA does not require the sponsor to explicitly approve the change. For significant risk devices, except when the deviations are necessary to protect the life or physical well-being of a subject in an emergency, FDA must approve all changes or deviations from the investigational plan that may affect the plan's scientific soundness or subject rights, safety, or welfare. Deviations that are necessary to prevent harm should be reported to the IRB and to the sponsor, who should report the deviations to FDA.

Records Retention

FDA regulations require investigators to retain records for a specified time period. [Note: these time periods are different from those required for IRB records.] For investigational new drug (IND) studies (and medical food and food additive studies), records are to be maintained for two years following the date of marketing application approval for the drug for the indication for which it was being investigated. If no application is filed, or if the application is not approved for the indication, the records are to be retained for two years after the investigation (i.e., the IND) is discontinued, and FDA is notified of that fact. For device studies, records are to be maintained for two years after the later of the following dates: the date on which the investigation is terminated or completed or; the date that the records are no longer required to support a premarket approval application or a notice of completion of a product development protocol.

To comply with FDA record retention requirements, clinical investigators should arrange with study sponsors to be kept informed of the status of the application for their respective studies. To illustrate, for an IND study, FDA regulations require sponsors to notify each investigator if FDA approves the new drug application (NDA) or product license application (PLA), or if the investigation is discontinued. Therefore, FDA recommends that all investigators insist that their contract with a sponsor include a provision requiring the sponsor to notify the investigator of any action with regard to the test article, e.g., submission or approval of an NDA or PLA, withdrawal of an IND, or the placement of the IND on inactive status.

Retention of accurate and complete records is essential to establish the validity and completeness of a report on a clinical investigation that is submitted to FDA in support of an application for a research or marketing permit. The investigator, not the sponsor, is responsible for the accuracy and completeness of his or her study records, and the investigator is responsible for any discrepancies found in these records during an inspection.

The investigator may maintain all the study records or, in those cases where the subject is a patient in a hospital or other facility, the records may be maintained as part of the patient's hospital or clinical records. If a hospital or clinic keeps the records, the investigator must still ensure that the records are retained at least for the length of time set forth by the regulations.

An investigator may retain records either in their original form or by means of microfilm, microfiche, photocopies, or other accurate reproductions of the original records. If copies are used, however, they must be legible and the investigator is required to assure that such reproductions are true and accurate copies of the original. When reproduction techniques (e.g., microfilming) are used, a reader and photocopying equipment should be readily available. If written notes, erasure marks, or other changes are not apparent on the reproduction, a notation of this fact should be clear on the reproduction of the record, and the original record should be retained for the time required.

Raw data, entered directly into a computer system, is considered to be the original or true copy of the data whether it is printed out as a hard copy or stored as computer files. An acceptable computerized data collection system would be one that (1) allows data entry only by authorized individuals; (2) controls the ability to delete or alter previously entered data and provides an audit trail for such data changes (e.g., modification file); (3) protects the data base from tampering; and (4) ensures data preservation. If records are retained in a computer data system, suitable equipment should be readily available to produce a hard copy of the data. Data should be retrievable in such a fashion that all information regarding each individual in a study is attributable to that individual, i.e., case report equivalents must be available.

FDA may audit any and all records that might support microfilm, microfiche, or other stored data. These records must be maintained just as paper case report forms must be maintained.

Privacy of Records

FDA understands the need to protect the privacy of research subjects. Study records need not identify subjects by name but they do need to provide some type of identifier to permit cross-indexing a subject's study record. Identifying information must be available to respond to allegations that may arise, such as the claim that a subject's consent was not obtained, or that the study records do not represent actual studies or do not present the actual results. When an individually identifiable medical record is copied and reviewed by the Agency, FDA safeguards the information and uses or disseminates the information only under conditions that protect the individual's privacy to the fullest possible extent consistent with laws relating to public disclosure and the Agency's law enforcement responsibilities.

Research subjects' expectations concerning confidentiality will vary depending upon the study and the subject's relationship to the clinical investigator. Because FDA oversight responsibilities may compromise subject confidentiality, the Agency requires consent documents to note that FDA may inspect the records and to describe the extent to which confidentiality will be maintained by the investigator [21 CFR 50.25(a)(5)]. The subjects must be informed if anyone other than authorized hospital or office personnel will have access to records containing their identities. Although FDA regulations neither require nor prohibit sponsor access to study records, subjects must be made aware of the extent to which such access will be allowed.

When clinical investigators conduct a study for submission to FDA, they agree to allow FDA access to the study records. The investigator is responsible for making subject's records available to FDA for inspection and copying. The Agency will inspect and copy records regardless of whether or not the subject has agreed to such review [21 CFR 312.68 and 812.145].

ACCEPTANCE OF FOREIGN CLINICAL STUDIES

The Food and Drug Administration (FDA) may accept foreign clinical studies in support of safety and efficacy claims for drugs, biologics and devices. Whether such a clinical investigation is subject to the FDA informed consent and Institutional Review Board (IRB) regulations [21 CFR parts 50 and 56, respectively] depends on whether the clinical investigation is conducted under the Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations.

IND or IDE Studies

All drug, biologic and device studies conducted under an IND or IDE, are governed by the FDA informed consent and IRB requirements, regardless of the location of the research. [See 21 CFR part 312 IND regulations and 21 CFR part 812 IDE regulations.] Because IND and IDE studies are intended, from the outset, to be reported to FDA to support marketing in the United States, the Agency requires that all such studies meet the regulations which have been established under standards of this country. FDA does not accept a lesser level of human subject protection for studies solely because they are to be conducted at foreign sites.

Studies not requiring an IND or IDE

In general, FDA accepts foreign safety and efficacy studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. FDA recognizes that standards for protection of human subjects vary from country to country. Meeting at least minimum standards for assuring human subject protection is required, however, if the FDA is to accept the data. Therefore, for studies submitted to FDA which were conducted outside the United States, the Agency requires demonstration that such studies conformed with the ethical principles outlined in the Declaration of Helsinki (as amended) or with the laws and regulations of the country in which the research is conducted, whichever provides greater protection of the human subjects.

21 CFR 312.120(c)(4) contains the text of the Declaration of Helsinki. 21 CFR 312.120 addresses the acceptability of clinical data from investigational drug studies conducted outside of the United States that were not conducted under an IND. 21 CFR 814.15(b) and (c) address device studies conducted outside the United States that were not conducted under an IDE.

Also see FDA Information Sheets: "Non-Local IRB Review," "Waiver of IRB Requirements for Drug and Biologic Studies" and "Informed Consent and the Clinical Investigator"

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CHARGING FOR INVESTIGATIONAL PRODUCTS

This information sheet discusses FDA policy on allowing charges for the test articles in clinical investigations and advises Institutional Review Boards (IRBs) of ethical issues that may need to be considered.

Decisions concerning charging subjects for investigational products are guided by professional ethics, institutional policies, and FDA regulations. IRBs must ensure that subjects are fully informed if they will be charged for the costs of the investigational product and/or associated treatment. IRBs must also ensure that any such charges are appropriate and equitable.

IRBs reviewing studies in which charges are proposed may wish to consider several ethical questions: Should the subject be charged for a product that is investigational, i.e., when its safety and effectiveness have not been established by the FDA? Does charging for an investigational product preclude the economically disadvantaged or the uninsured from participating in a clinical trial?

If an investigator proposes to charge subjects for the investigational drug, biologic, or device, the IRB should review and approve the charge. The FDA informed consent regulations require the consent document to include a description of any additional costs to the subject that may result from participation in the research [21 CFR 50.25(b)(3)].

An IRB reviewing proposed charges to subjects should ask whether or not FDA approved the sponsor charging the investigator for the product. Because the regulations governing drugs and biologics vary from those governing medical devices, the Agency's position on charging for investigational products will be discussed separately. Investigators may charge the subject for related treatment or for services.

1. Charging for Investigational Medical Devices and Radiological Health Products

The Investigational Device Exemption (IDE) regulations allow sponsors to charge for an investigational device, however, the charge should not exceed an amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [21 CFR 812.7(b)]. A sponsor justifies the proposed charges for the device in the IDE application, states the amount to be charged, and explains why the charge does not constitute commercialization [21 CFR 812.20(b)(8)]. FDA generally allows sponsors to charge investigators for investigational devices, and this cost usually is passed on to the subjects.

2. Charging for Investigational Drugs and Biologics

Under the Investigational New Drug (IND) regulations [21 CFR 312.7(d)], FDA will permit a sponsor to charge investigators for an investigational drug or biologic depending upon whether the charge is for an investigation in a clinical trial under an IND or is for an investigation for a treatment use under a treatment protocol or treatment IND. In both a clinical trial and a treatment IND, the charge should not exceed an amount that is necessary to recover the costs associated with the manufacture, research, development, and handling of the investigational drug or biologic. FDA may withdraw authorization to charge if the Agency finds that the conditions underlying the authorization are no longer satisfied. FDA does not prohibit charging for marketed products that are used in clinical investigations.

(a) Clinical Trials Under an IND

A sponsor may not charge for an investigational drug or biologic in a clinical trial under an IND without the Agency's prior written approval. In requesting such approval, the sponsor must explain why a charge is necessary, i.e., why providing the product without charge should not be considered part of the normal cost of conducting a clinical trial. When charges are authorized by FDA, whether they are passed on to subjects of research is a matter that clinical investigators and IRBs should carefully consider.

(b) Treatment Protocol or Treatment IND

A sponsor or investigator may charge for an investigational drug or biologic for a treatment use under a treatment protocol or treatment IND provided: (1) there is adequate enrollment in the ongoing clinical investigations under the authorized IND; (2) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (3) the drug or biologic is not being commercially promoted or advertised; and (4) the sponsor is actively pursuing marketing approval with due diligence. FDA must be notified in writing prior to commencing any such charges. Authorization for charging goes into effect automatically 30 days after receipt of the information by FDA, unless FDA notifies the sponsor to the contrary.

RECRUITING STUDY SUBJECTS

FDA requires that an Institutional Review Board (IRB) review and have authority to approve, require modifications in, or disapprove all research activities covered by the IRB regulations [21 CFR 56.109(a)]. An IRB is required to ensure that appropriate safeguards exist to protect the rights and welfare of research subjects [21 CFR 56.107(a) and 56.111]. In fulfilling these responsibilities, an IRB is expected to review all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. The protocol, the consent document, and, for studies conducted under the Investigational New Drug (IND) regulations, the investigator's brochure are examples of documents that the IRB should review. The IRB should also review the methods that investigators propose to use to recruit subjects.

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects, is not in and of itself an objectionable recruitment practice. Direct recruiting advertisements are seen as part of the informed consent and subject selection processes. [21 CFR 50.20, 50.25, 56.111(a)(3) and 812.20(b)(11).] IRB review is necessary to ensure that the information is not misleading to subjects. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence.

When direct advertising is to be used, the IRB should review the information contained in the advertisement and the mode of its communication, to determine that the procedure for recruiting subjects is not coercive and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. The IRB should review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB should review the final audio/video tape. The IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate content. The review of a taped message prepared from IRB approved text may be accomplished through expedited procedures.

No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to subjects but would also be a violation of the Agency's regulations concerning the promotion of investigational drugs [21 CFR 312.7(a)] and of investigational devices [21 CFR 812.7(d)].

Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" implies that all study subjects will be receiving newly marketed products of proven worth.

Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. IRBs should consider if the promise of treatment without charge is coercive to financially constrained subjects. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid.

If a clinical investigator decides to begin advertising for subjects after the study has received IRB approval, the advertising may be considered as an amendment to the ongoing study. When such advertisements are easily compared to the consent, the IRB may choose to review and approve the advertisement using expedited procedures. When the comparison is not obvious or other complicating issues are involved, the advertisement should be reviewed at a convened meeting.

Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of the listed items.

1. the name and address of the clinical investigator and/or research facility;
2. the condition under study and/or the purpose of the research;
3. in summary form, the criteria that will be used to determine eligibility for the study;
4. a brief list of participation benefits, if any (e.g., a no-cost health examination);
5. the time or other commitment required of the subjects; and
6. the location of the research and the person or office to contact for further information.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Payment to Research Subjects."

PAYMENT TO RESEARCH SUBJECTS

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when benefit to subjects is remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

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 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.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Recruiting Study Subjects."

SCREENING TESTS PRIOR TO STUDY ENROLLMENT

For some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that screening tests performed solely for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

Screening procedures for research eligibility are considered part of the subject selection and recruitment process and, therefore, require IRB oversight. IRB review and approval should not be too burdensome for either IRBs or investigators, as screening may qualify as a minimal risk procedure [21 CFR 56.102(i)] and the IRB may choose to use expedited review procedures [21 CFR 56.110] to approve such screening. The IRB should receive a written outline of the screening procedure to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing the tests including a brief summary description of the study in which they may be asked to participate. Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a consent document [21 CFR 56.109(c)]. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would be followed.

Also see FDA Information Sheet: "Recruiting Study Subjects"

A GUIDE TO INFORMED CONSENT DOCUMENTS

The Food and Drug Administration (FDA) has regulations [21 CFR part 50] that govern informed consent for research with products regulated by the Agency. This information sheet was developed to help clinical investigators and Institutional Review Boards (IRBs) ensure that informed consent documents comply with the FDA requirements. For studies that are subject to the requirements of the FDA regulations, the informed consent documents should meet the requirements of 21 CFR 50.20 and contain the information required by each of the eight elements of 21 CFR 50.25(a), and each of the elements of 21 CFR 50.25(b) that are appropriate to the study. Informed consent is more than just a signature on a form, it is a process of information exchange that includes, recruitment materials, written materials, verbal instructions, question/answer sessions and measures of subject understanding.

Sample or draft consent documents may be developed by a sponsor or cooperative study group, however, it is the responsibility of the approving IRB to review such consent documents and assure that the required elements are adequately addressed, that no exculpatory language is used and that the language is understandable to the subjects. The IRB should review and approve the finalized informed consent document developed from the sample. When a short form consent document is to be used [21 CFR 50.27(b)(2)], the IRB should review and approve the written summary of the full information to be presented orally to the subject. The IRB should inform the investigator that only IRB approved documents may be used.

[Note: the wording of the regulations below are provided in *italics*, with explanatory comments following.]

21 CFR 50.20 General requirements for informed consent

Except as provided in §50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

In informed consent documents, the use of the wording, "I understand..." may be inappropriate as many prospective subjects will not "understand" the scientific and medical significance of all the statements. Consent documents are more understandable if they are written just as the clinical investigator would give an oral explanation to the subject, that is, the subject is addressed as "you" and the clinical investigator as "I/we." This second person writing style also helps to communicate that there is a choice to be made by the prospective subject. Use of first person may be interpreted as presumption of subject consent, i.e., the subject has no choice. Also, the tone of the first person "I understand" style seems to misplace emphasis on legal statements rather than on explanatory wording enhancing the subject's comprehension.

Subjects are not in a position to judge whether the information provided is complete. Subjects may certify that they understand the statements in the consent document and are satisfied with the explanation provided by the consent process. They should not be required to certify completeness of disclosure (e.g., "This study has been fully explained to me," or, "I fully understand the study.")

Consent documents should not contain claims of effectiveness, explicit or implicit, that may unduly influence potential subjects. Overly optimistic representations are misleading and violate FDA regulations concerning the promotion of investigational drugs [21 CFR 312.7] or investigational devices [21 CFR 812.7(d)].

If subjects are paid for their participation in studies, the payment should accrue as the study progresses and 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 amounts paid are reasonable and the amount of any payment based upon completion should not be so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. Therefore, the amount and schedule of all payments should be presented to the IRB at the time of initial review and the IRB should determine their acceptability. The consent document should outline the schedule and conditions of earning payment.

Investigational drug and biologic studies are not officially approved by FDA. Subjects are likely to impute a greater involvement by the Agency in a research study than actually exists if phrases such as, "FDA has given permission..." or "FDA has approved..." are used in consent documents. When a sponsor submits a study to FDA as part of the initial application for an investigational new drug (IND), FDA has thirty days to review the application and place the study on "hold" if there are any obvious reasons why the proposed study should not be conducted. If FDA does not stop the sponsor within the thirty day period, they may begin the study (with IRB approval).

FDA also believes that an explicit statement that an IRB has approved solicitation of subjects to participate in research could mislead or unduly induce subjects. Subjects might think that, because the IRB had approved the research, there is no need to evaluate the study for themselves to determine whether or not they should participate.

To meet the requirements of 21 CFR 50.20, the informed consent document should be in language understandable to the subject (or authorized representative). When the consent interview is conducted in English, the consent document should be in English. When the study subject population includes non-English speaking people or the clinical investigator or the IRB anticipates that the consent interviews will be conducted in a language other than English, the IRB should require a translated consent document to be prepared and assure that the translation is accurate. As required by 21 CFR 50.27, a copy of the consent document must be given to each subject. In the case of non-English speaking subjects, this would be the translated document. While a translator may be helpful in facilitating conversation with a non-English speaking subject, routine ad hoc translation of the consent document should not be substituted for a written translation.

If a non-English speaking subject is unexpectedly encountered, investigators will not have a written translation of the consent document and must rely on oral translation. Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective. If investigators enroll subjects without an IRB approved written translation, a "short form" written consent document, in a language the subject understands, should be used to document that the elements of informed consent required by 21 CFR 50.25 were presented orally. The required signatures on a short form are stated in 21 CFR 50.27(b)(2).

Even when all the subjects speak English, the IRB should ensure that technical and scientific terms are adequately explained or that common terms are substituted. The IRB should ensure that the informed consent document properly translates complex scientific concepts into simple words that the typical subject can read and comprehend.

A person who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the consent document. Development of a short form or a narrative statement is not required, but there should be an impartial witness to attest to the adequacy of the consent process and to the subject's voluntary agreement. The signatures required by 21 CFR 50.27(b)(2) are necessary.

Although not addressed in the regulations, FDA believes that IRBs should consider whether to require the approval of older children before they are enrolled in a research study. For research with children, some IRBs have required that two consent documents be developed. One for obtaining the parents permission and one, which outlines the study in simplified language, for obtaining the assent of children who can understand the concepts involved.

21 CFR 50.25 Elements of informed consent

(a) *Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:*

(1) *A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.*

The statement that the study involves research is important because the relationship between patient-physician is different than that between subject-investigator. Any procedures relating solely to research (e.g., randomization and placebo control) should be explained to the subjects. The procedures subjects will encounter should be outlined in the consent document, or an explanation of the procedures may be attached to and referenced in the consent document.

Consent documents for studies of investigational articles should include a statement that a purpose of the study includes an evaluation of the safety of the test article. Statements that test articles are safe or statements that the safety has been established in other studies, are not appropriate when the purpose of the study includes determination of safety. In studies that also evaluate the effectiveness of the test article, consent documents should include that purpose, but should not contain claims of effectiveness.

(2) *A description of any reasonably foreseeable risks or discomforts to the subject.*

The risks of procedures relating solely to research should be explained in the consent document. The risks of the tests required in the study protocol should be explained, especially for tests that carry significant risk of morbidity/mortality themselves. The explanation of risks should be reasonable and should not minimize reported adverse effects.

The explanation of risks of the test article should be based upon information presented in documents such as the protocol and/or investigator's brochure, package labeling, and previous research study reports. For IND studies, the IRB should assure that the clinical investigator submits the investigator's brochure (when one exists) with the other study materials for review.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

The description of benefits to the subject should be clear and not overstated. If no direct benefit is anticipated, that should be stated. The IRB should be aware that this element includes a description not only of the benefits to the subject, but to "others" as well. This may be an issue when benefits accruing to the investigator, the sponsor, or others are different than that normally expected to result from conducting research. Thus, if these benefits may be materially relevant to the subject's decision to participate, they should be disclosed in the informed consent document.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

To enable a rational choice to participate in the research study, subjects should be aware of the full range of options available to them. Consent documents should briefly explain any pertinent alternatives to entering the study. While this should be more than just a list of alternatives, a full risk/benefit explanation of alternatives may not be appropriate to include in the written document. The person(s) obtaining the subjects' consent, however, should be able to discuss available alternatives and answer questions that the subject may raise about them. As with other required elements, the consent document should contain sufficient information to ensure an informed decision.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

Study subjects should be informed of the extent to which the institution intends to maintain confidentiality of records identifying the subjects. In addition, they should be informed that FDA may inspect study records (which include individual medical records). If any other entity, such as the sponsor of the study, may gain access to the study records, the subjects should be so informed. The consent document may, at the option of the IRB, state that subjects' names are not routinely required to be divulged to FDA. When FDA requires subject names, FDA will treat such information as confidential, but on rare occasions, disclosure to third parties may be required. Therefore, absolute protection of confidentiality by FDA should not be promised or implied. Also, consent documents should not state or imply that FDA needs clearance or permission from the subject for access. When clinical investigators conduct a study for submission to FDA, they agree to allow FDA access to the study records. Informed consent documents should make it clear that, by participating in research, the subject's records automatically become part of the research database. Subjects do not have the option to keep their records from being audited/reviewed by FDA.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

Informed consent documents should describe any compensation or medical treatments that will be provided if injury occurs. If specific statements cannot be made (e.g., each case is likely to require a different response), the subjects should be informed where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

This requirement contains three components, each of which should be specifically addressed. The consent document should provide the name of a specific office or person and the telephone number to contact for answers to questions about: 1) the research subjects' rights; 2) a research-related injury; and 3) the research study itself. It is as important for the subject to know why an individual should be contacted as it is for the subject to know whom to contact. Although a single contact might be able to fulfill this requirement, IRBs should consider requiring that the person(s) named for questions about research subjects' rights not be part of the research team as this may tend to inhibit subjects from reporting concerns and discovering possible problems.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

This element requires that subjects be informed that they may decline to participate or to discontinue participation at any time without penalty or loss of benefits. Language limiting the subject's right to withdraw from the study should not be permitted in consent documents. Subjects may be informed that they may be asked to permit follow-up if they withdraw.

(b) *Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:*

(1) *A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.*

A statement that there may be unforeseen risks to the embryo or fetus may not be sufficient if animal data are not available to help predict the risk to a human fetus. Informed consent documents should explain that mutagenicity (the capability to induce genetic mutations) and teratogenicity (the capability to induce fetal malformations) studies have not yet been conducted/completed in animals. [Note: The lack of animal data does not constitute a valid reason for restricting entry of women of childbearing potential into a clinical trial.] Subjects, both women and men, need to understand the danger of taking a drug whose effects on the fetus are unknown. If relevant animal data are available, however, the significance should be explained to potential subjects. Investigators should ensure that subjects who agree to enter a study fully understand the potential risks that the study poses. If measures to prevent pregnancy should be taken while in the study, that should be explained.

FDA guidance on the inclusion of women in clinical trials [58 FR 39406] now gives IRBs broader discretion to encourage the entry of a wide range of individuals into the early phases of clinical trials. FDA urges IRBs to question any study that appears to limit enrollment based on gender and/or minority status. Statements such as, "you may not participate in this research study if you are a woman who could become pregnant" should not routinely be included in informed consent documents.

(2) *Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.*

When applicable, subjects should be informed of circumstances under which their participation may be terminated by the investigator without the subject's consent. An unexplained statement that the investigator and/or sponsor may withdraw subjects at any time, does not adequately inform the subjects of anticipated circumstances for such withdrawal.

A statement that the investigator may withdraw subjects if they do not "follow study procedures" is not appropriate. Subjects are not in a position to know all the study procedures. Subjects may be informed, however, that they may be withdrawn if they do not follow the instructions given to them by the investigator.

(3) Any additional costs to the subject that may result from participation in the research.

If the subjects may incur an expense because they are participating in the research, the costs should be explained. IRBs should consider that some insurance and/or other reimbursement mechanisms may not fund care that is delivered in a research context.

(4) The consequences of a subjects' decision to withdraw from the research and procedures for orderly termination of participation by the subject.

When withdrawal from a research study may have deleterious effects on the subject's health or welfare, the informed consent should explain any withdrawal procedures that are necessary for the subject's safety and specifically state why they are important to the subject's welfare. An unexplained statement that the subject will be asked to submit to tests prior to withdrawal, does not adequately inform the subjects why the tests are necessary for the subject's welfare.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

When it is anticipated that significant new findings that would be pertinent to subject's continued participation are likely, the IRB should determine that a system, or a reasonable plan, exists to make such notification to subjects.

(6) The approximate number of subjects involved in the study.

If the numbers of subjects in a study is material to the subjects' decision to participate, the subjects should be told not only the approximate number of subjects involved in the study, but also why the number of participants is important (e.g., a small number may compromise confidentiality).

Also see FDA information sheets: "A Informed Consent and the Clinical Investigator," "Evaluation of Gender Differences in Clinical Investigations," and "Significant Differences in HHS and FDA Regulations for the Protection of Human Subjects."

INFORMED CONSENT AND THE CLINICAL INVESTIGATOR

Respect for human subjects' rights and dignity requires that informed consent be obtained before a subject participates in any clinical investigation, and this principle forms the basis for the Agency's informed consent regulations [21 CFR part 50]. Institutional Review Boards (IRBs), clinical investigators, and research sponsors all share responsibility for ensuring that the informed consent process is adequate.

1. General Informed Consent Requirements

The informed consent process is designed to give subjects all the information that they need to decide about participating in a study; to ensure that subjects understand the information; and to give subjects an opportunity to consider participation in the study (initially and ongoing). The process should permit the subject to ask questions and to exchange information freely with investigator. Thus, rather than an endpoint, the consent document should be the basis for a meaningful exchange between the investigator and the subject.

The general informed consent requirements are contained in 21 CFR 50.20 and are summarized below.

- Informed consent must be obtained from the subject (or the subject's legally authorized representative) before a subject can be involved in research.
- The investigator must seek consent under circumstances that give a subject sufficient opportunity to consider whether to participate and that minimize possible coercion or undue influence. Circumstances surrounding the consent process (timing, setting, who obtains the informed consent and other details) are important to the subject's ability to comprehend the information provided.
- The information given to subjects must be understandable to them. Technical and medical terminology should be avoided or must be explained, and non-English speaking subjects must have the information presented in a language that they understand.
- The informed consent document may not include exculpatory language through which the subject is made to waive or appear to waive any legal rights or releases or appears to release the investigator, the sponsor, the institution, or their agents from liability for negligence.

2. Exception from General Requirements

As described in 21 CFR 50.23, informed consent is required unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify, in writing, all of the following:

- The subject is confronted by a life-threatening situation necessitating the test article's use.
- Informed consent cannot be obtained from the subject because of an inability to communicate with or to obtain legally effective consent from, the subject. For clarification, an "inability to communicate with the subject" exists where the subject is in a coma or a state of confusion. In contrast, a subject's inability to speak a particular language would not be considered to be an "inability to communicate."
- Time is insufficient to obtain consent from the subject's legal representative.
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If the investigator believes that immediate use of the test article is required to preserve the subject's life and it is not possible to obtain timely certification from a physician who is not participating in the study, the clinical investigator may proceed with its use. Following such emergency test article use, a physician who is not otherwise participating in the study must review and evaluate, in writing, the use.

When an emergency use without informed consent has occurred, the investigator must submit the certification or the evaluation to the IRB within 5 working days after the test article's use. The IRB Chair should review this documentation and, at the next convened meeting, the full IRB should be made aware of the use.

3. Documentation of Informed Consent

The informed consent documentation requirements [21 CFR 50.27] permit the use of either a written consent document that embodies the elements of informed consent or a "short form" stating that the elements of informed consent have been presented orally to the subject. Whichever document is used, a copy must be given to the person signing the document. While not specifically mentioned in the FDA regulations, the signature on the consent document should be dated at the time the subject signs, to permit verification that consent was actually obtained before the subject's participation in the study.

When the "short form" method is used, the regulations require an IRB review and approval of a written summary of the information to be presented to subjects. A witness is required to attest to the adequacy of the consent process and to the subject's voluntary consent. The subject or the subject's legally authorized representative must sign the short form. The witness must sign both the short form and a copy of the summary, and the person actually obtaining the consent must sign a copy of the summary. The subject or the representative must be given a copy of the summary as well as a copy of the short form.

21 CFR 56.109 permits the IRB to waive, for some or all subjects, the requirement that the subject sign a written consent document if the IRB finds that:

- the research presents no more than minimal risk of harm to subjects, as defined by 21 CFR 56.102(i), and
- involves only procedures for which written consent is not normally required outside the research context.

The Agency's regulations do not permit the waiver or alteration of any of the elements of informed consent. In cases where the documentation requirement is waived, the IRB may require that the investigator provide subjects with a written statement regarding the research.

Many IRBs have developed standard language and/or a standard format to be used in portions of all consent documents. Standard language is typically developed for those elements that deal with confidentiality, compensation, answers to questions, and the voluntary nature of participation. Each investigator should determine the local IRB's requirements before submitting a study for initial review. Where changes are needed from the standard paragraphs or format, the investigator can save time by anticipating the local IRB's concerns and explaining in the submission to the IRB why the changes are necessary.

While the regulations do not prohibit the use of multiple consent documents, FDA suggests that they be used with caution. The Agency has no objection to the process of "re-consenting" subjects over time, which may be appropriate for certain types of studies. Multiple consent documents may be confusing to a research subject and if, inadvertently, one document is not presented, critical information may not be relayed to the research subject. For some studies, however, the use of multiple documents may improve subject understanding by "staging" information in the consent process. This process may be useful for studies with separate and distinct, but linked, phases through which the subject may proceed. If this technique is used, the initial document should explain that subjects will be asked to participate in the additional phases. It should be clear whether the phases are steps in one study or separate but interrelated studies.

4. Responsibility for the Consent Document Information

The elements of informed consent are listed in 21 CFR part 50.25. Clinical investigators should ensure that consent documents include information that either reflects or refers to all the basic elements of informed consent. The additional elements of informed consent must be included when they are appropriate to the study being described. IRBs are responsible for ensuring the adequacy of the information in the informed consent document.

Investigational New Drug Applications (IND) submitted to FDA are not required to contain a copy of the consent document. If the sponsor submits a copy, or if FDA requests a copy, the Agency will review the document and may comment on the document's adequacy.

For significant risk medical devices, the consent document is considered to be a part of the investigational plan in the Application for an Investigational Device Exemption (IDE). FDA always reviews these consent documents. The Agency's review is generally limited to ensuring the presence of the required elements of informed consent and the absence of exculpatory language. Any substantive changes to the document made by an IRB must be submitted to FDA (by the sponsor) for review and approval.

5. Common Problems with the Consent Document

FDA expects that consent documents will reflect, in language that is understandable to subjects all relevant information about the study. Common problems with documents are that they:

- fail to include all the required elements specified in 21 CFR 50.25
- fail to explain technical/scientific language
- fail to state that the drug, biologic or device is experimental
- fail to state all the purposes of the research, e.g., they include only those purposes that would be considered by the subject to be "most beneficial"
- fail to state the expected duration of the subject's participation
- overstate facts or are overly optimistic in tone or wording (e.g., "this product has been extensively and safely used")
- fail to completely describe the procedures to be followed
- fail to adequately describe the treatment alternatives available to the subject or the risks or benefits of the alternatives

- fail to describe accurately the extent to which confidentiality will be maintained or they fail to advise the subject that FDA may inspect the records
- fail to describe the manner of payment, if any, to subjects
- fail to provide a contact for answers to questions about the research, research subjects' rights, and research-related injury to the subject (a general offer to answer questions is not adequate). The contact names, telephone numbers, and addresses (when appropriate) should be included.
- fail to include "additional elements of informed consent" when those elements are appropriate, or include certain elements when they are inappropriate
- omit a written summary of what is to be said to the subject for IRB review when "short form" written consent documents are to be presented orally to subjects, or fail to provide the written summary to research subjects
- do not contain study-specific information (e.g., they are non-specific "boiler-plate" forms)
- fail to obtain IRB review and approval before use.

6. The Consent Process

The clinical investigator is responsible for ensuring that informed consent is obtained from each research subject before that subject participates in the research study. FDA does not require the investigator to personally obtain the informed consent. Investigators may ensure that an individual knowledgeable about the research presents the information to each subject, that each subject understands the information, and that subjects sign a consent document. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent. Dated signatures permit verification that consent was obtained before the subject's participation in the study. A copy of the consent document must be provided to the subject and the investigator should retain the signed consent document in the study records. Note, that the subject's copy does not need to be a signed copy.

The IRB should be aware of who will obtain informed consent. The IRB should also be informed of such matters as the timing of obtaining informed consent and of any waiting period (between informing the subject and obtaining the consent) that will be observed.

The consent process begins when a potential research subject is initially contacted. Although an investigator may not recruit subjects to participate in a research study before the IRB reviews and approves the study, an investigator may query potential subjects to determine if an adequate number of potentially eligible subjects is available.

7. Requirements for Foreign Studies

Studies conducted under an IND or IDE in a foreign country are required to conform to the requirements of 21 CFR parts 50 and 56. Foreign studies that are not intended for submission to FDA, i.e., not conducted under an IND or IDE, may not have conformed to these requirements. If the results from such studies are later submitted to FDA in support of a marketing permit or a premarket approval application, the Agency will require that the study conformed, at least, with the Declaration of Helsinki and/or the laws of the foreign country in which the research was conducted, whichever affords the greater protection of the human subjects. [See 21 CFR 312.120 and 21 CFR 814.15.]

The Declaration of Helsinki sets forth twelve basic principles. Two are especially relevant to informed consent:

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

Although the Declaration of Helsinki does not require IRB review of research by name, it does state that:

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

Also see FDA information sheets: "A Guide to Informed Consent Documents," "Sponsor-Investigator-IRB Interrelationship," "Acceptance of Foreign Clinical Studies," "Emergency Use of an Investigational Drug or Biologic," "Emergency Use of Unapproved Medical Devices," "Screening Tests Prior to Study Enrollment," "Recruiting Study Subjects," "Payment to Research Subjects," and "Significant Differences in HHS and FDA Regulations for the Protection of Human Subjects."

USE OF INVESTIGATIONAL PRODUCTS WHEN SUBJECTS ENTER A SECOND INSTITUTION

Several issues are raised when a subject who is participating in a research study at one institution is admitted to another facility. To help illustrate, the following will serve as the model for this information sheet: Regional Medical Center (RMC) has developed a research protocol; the study has been reviewed and approved by the RMC institutional review board (RMC-IRB); each subject receives a test drug for a 16 week period (4 weeks inpatient, 12 weeks outpatient); some research subjects will live in a distant town with a local health care facility, Memorial General Hospital (MGH). For these subjects, participation at RMC will involve considerable travel time and costs. While several examples can be imagined, the three scenarios below may help to illustrate some key points.

The least complex scenario is when treatment/hospitalization is incidental to the research. Procedures should be in place for rapidly identifying test drugs and devices (e.g., an emergency contact number and unblinding procedure). For this example, we will assume that hospitalization at MGH is medically necessary and that the local physician has determined that it is appropriate to continue the subject (now patient) on the test drug. In this case, MGH is providing incidental medical care and is not participating as a research site. Therefore, MGH staff are not investigators and the MGH-IRB does not need to review the protocol. The usual procedures for dealing with drugs prescribed out-of-facility would be followed (often, this is a pharmacy department policy). The investigator at RMC remains responsible for test drug administration and follow-up and therefore, should be aware of the hospitalization and may even need to report the event as an unexpected adverse incident. The RMC-IRB remains the IRB of record.

For the next scenario, the involvement of MGH is reasonably foreseen and is an anticipated part of the study protocol (e.g., the need for inpatient care is anticipated for the condition under study, or the need for subjects to return home and receive medical follow-up). The RMC-IRB should be aware that other institutions and/or providers will be providing medical care/follow-up and should ensure that adequate reporting and safety systems are in place before approving the study. In this example, the protocol allows the test drug to be sent to subjects' regular health care providers. Even though the test article is being given at MGH, only routine medical monitoring is conducted by the local provider with little or no reporting to the RMC investigator, who remains responsible for the test drug administration and collects research data when the subject returns to RMC. The involvement of MGH is incidental to the study (i.e., research data is not collected) and thus, it is not participating as a research site.

In both examples above, prior to continuing the investigational drug, the local physician should obtain the information necessary to safely continue the investigational drug from the clinical investigator. The information conveyed might include a description of treatment procedures, warnings of possible adverse reactions, emergency procedures, a copy of the signed informed consent document (which is a research summary as well as documentation of consent).

For the final scenario, MGH is designated as an extension of the research milieu. In this instance, the second institution is responsible for a portion of the research protocol. For this example, a physician at MGH has been identified in the protocol as a sub-investigator for subjects residing in that local catchment area. As sub-investigator, this physician is responsible for conducting examinations of subjects to monitor status and measure effects of the test drug (data collection). These research data are systematically reported to the RMC investigator

Because MGH is conducting research, it is responsible for complying with the applicable research regulations. The MGH-IRB may review, approve and be responsible for monitoring the portion of the research conducted at MGH just as it would for any other research in the facility or, MGH may agree to accept the RMC-IRB as the responsible IRB. If the RMC-IRB is to accept responsibility for other sites, it should consider the rationale for transferring or referring subjects to another institution; the circumstances under which responsibility will be shared; the instructions that will be given to the sub-investigators; the monitoring procedures that will be followed; and the informed consent process.

Informed Consent

In these examples, FDA regulations would not ordinarily require the subject to sign a second consent document for the other facility. In the first case, research is not being conducted at MGH and therefore, no research consent is needed for the second facility (obviously, consent for medical treatment may be required). The informed consent document would not be expected to discuss such involvement (i.e., providing routine and/or emergency medical care). In the second example, because research is not being conducted at MGH and a separate research consent is not needed. When the need for involvement of other facilities/providers is predicted, however, the investigator and the IRB should consider whether any additional information, such as an emergency contact number, needs to be included in the informed consent document.

The final example, is the most complex. Because the second facility is involved in research, the informed consent process should include a description of this activity. As appropriate, this could be included in the document presented to all subjects, or a separate informed consent document could be prepared for those subjects entering a secondary facility. If the RMC-IRB is accepting responsibility for other sites, it would review and approve the informed consent document(s). If MGH does not agree to cooperative review, however, MGH-IRB may accept the RMC informed consent document if it adequately describes the involvement of MGH (i.e., not require a second document). MGH-IRB may also decide to develop its own informed consent document. In this case it is important that the subject not receive conflicting information and the two IRBs should work to resolve such issues. Generally, the RMC document would cover the overall study and the MGH document would only detail the specific procedures involved while at that facility.

Also see FDA Information Sheet: "Cooperative Research"

EMERGENCY USE OF AN INVESTIGATIONAL DRUG OR BIOLOGIC

The emergency use of test articles frequently prompts questions from Institutional Review Boards (IRBs) and investigators. This information sheet addresses three areas of concern: emergency Investigational New Drug (IND) requirements; IRB procedures; and informed consent requirements.

Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means [21 CFR 312.36].

FDA contacts for obtaining an emergency IND:

For drug products contact:

Document Management Reporting Branch
(HFD-53)
(301) 827-0531

For biologic products contact:

Division of Congressional and Public
Affairs (HFM-11)
(800) 835-4709

Nights and weekends:

Division of Emergency and Epidemiological Operations
(HFC-160)
(202) 857-8400

Emergency Exemption from Prospective IRB Approval

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the

investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Institutional procedures may require that the IRB be notified prior to such use, however, this notification should not be construed as an IRB approval. Notification should be used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, some IRBs have sent to the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although, this is not an "IRB approval," the acknowledgement letter has been acceptable to manufacturers and has allowed the shipment to proceed.

Exception From Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

- (1) The subject is confronted by a life-threatening situation necessitating the use of the test article.
- (2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- (3) Time is not sufficient to obtain consent from the subject's legal representative.
- (4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

Also see FDA Information Sheets: "Emergency Use of Unapproved Medical Devices" and "Treatment Use of Investigational Drugs."

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INVESTIGATIONAL AND "OFF-LABEL" USE OF MARKETED DRUGS AND BIOLOGICS

"Off-Label" Use of Marketed Drugs and Biologics

Good medical practice and patient interest require that physicians use commercially available drugs, and biologics according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a product in this manner as part of the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND) or review by an Institutional Review Board (IRB), unless such review is required by the institution at which the product will be used.

FDA encourages the submission of applications containing the relevant safety and effectiveness information on drugs and biologics being prescribed for "off-label" uses. The Agency believes that it is important for appropriate uses to become part of the approved labeling so that patients may benefit from reliable and up-to-date information about the safe and effective uses of such drugs and biologics.

Investigational Use of Marketed Drugs and Biologics

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND is generally required. According to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug, however, does not require an IND if:

- (1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
- (2) it is not intended to support a significant change in the advertising for the product;
- (3) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- (4) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and

- (5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7].

For additional information on whether or not an IND is required in a specific situation, contact:

For DRUG PRODUCTS contact:

Product Information Coordination Staff
Document Management Reporting (HFD-53)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827-0531

For BIOLOGIC PRODUCTS contact:

Division of Congressional and Public Affairs
(HFM-11)
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852
(800) 835-4709

TREATMENT USE OF INVESTIGATIONAL DRUGS

Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the Food and Drug Administration (FDA) that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval.

OPEN LABEL PROTOCOL OR OPEN PROTOCOL IND

These are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective Institutional Review Board (IRB) review and informed consent.

TREATMENT IND

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued: 1) the drug is intended to treat a serious or immediately life-threatening disease; 2) there is no satisfactory alternative treatment available; 3) the drug is already under investigation, or trials have been completed; and 4) the trial sponsor is actively pursuing marketing approval.

Treatment IND studies require prospective IRB review and informed consent. A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.

GROUP C TREATMENT IND

The "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the compassionate distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. Because administration of Group C drugs is not done with research intent, FDA has generally granted a waiver from the IRB review requirements [21 CFR 56.105]. Even though FDA has granted a waiver for these drugs, an IRB may still choose to conduct a review under its policies and procedures. The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains an FDA-approved informed consent document which must be used if there has been no local IRB review.

PARALLEL TRACK

The Agency's Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS and HIV-related diseases under a separate "treatment" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating acquired immunodeficiency syndrome (AIDS) and other HIV-related diseases. These studies require prospective IRB review and informed consent.

EMERGENCY USE IND

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use [21 CFR 312.36]. Such authorization is usually conditioned upon the sponsor making an appropriate application as soon as practicable. These studies often meet the requirement for exception from prior IRB. Informed consent is required unless it cannot be obtained as outlined in 21 CFR 50.23.

Also see FDA Information Sheet "Emergency Use of an Investigational Drug or Biologic."

**WAIVER OF IRB REQUIREMENTS
FOR DRUG AND BIOLOGIC STUDIES**

In accordance with 21 CFR 56.105, FDA may waive any of the requirements contained in the Institutional Review Board (IRB) regulations [21 CFR part 56] if requested by the sponsor or sponsor-investigator. A waiver can be granted for specific research activities or for classes of research activities otherwise covered by the IRB regulations. Note that the waiver provision does not apply to the informed consent requirements [21 CFR part 50]. An institution may still require IRB review on the local level even if a waiver from FDA is granted.

FDA uses the waiver provision only where it would be in the best interest of the subjects and where alternative mechanisms for assuring the protection of the subjects are adequate. Circumstances which FDA will consider for a waiver include "treatment INDs," i.e., the use of an investigational drug or biologic primarily for the treatment of a subject with a serious or immediately life-threatening disease for whom comparable or satisfactory alternate therapy is unavailable. [See 21 CFR 312.34.] The waiver provision is not needed for an emergency use because the regulations contain a provision for exemption from prospective IRB review in an emergency, provided that such use is reported to the IRB within 5 working days [21 CFR 56.104(c)].

FDA will handle waiver requests expeditiously. A request for waiver should contain the following information:

- (1) The specific requirement or requirements in the IRB regulations for which a waiver is requested.
- (2) The specific research activity for which the waiver will be applied and why this is a special situation.
- (3) Why a waiver would be in the interest of subjects.
- (4) What alternate mechanism(s) for assuring the protection of human subjects is available and would be utilized.
- (5) A copy of the proposed consent document.

The sponsor or sponsor-investigator should submit a request for a waiver associated with an IND (to the Review Division in the Center for Drug Evaluation and Research (CDER) or to the Review Division in the Center for Biologic Evaluation and Research (CBER) responsible for reviewing the IND. If the identity of the responsible Review Division is unknown, the waiver request may be sent to:

For DRUG PRODUCTS:

Product Information Coordination Staff
Document Management Reporting (HFD-53)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827-0531

For BIOLOGIC PRODUCTS:

Division of Congressional and Public Affairs
(HFM-11)
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852
(800) 835-4709

Also see FDA Information Sheets: "Emergency Use of an Investigational Drug or Biologic" and "Treatment Use of Investigational Drugs."

DRUG STUDY DESIGNS

Before a new drug or biologic can be marketed, its sponsor must show, through adequate and well-controlled clinical studies, that it is effective. A well-controlled study permits a comparison of subjects treated with the new agent with a suitable control population, so that the effect of the new agent can be determined and distinguished from other influences, such as spontaneous change, "placebo" effects, concomitant therapy, or observer expectations. FDA regulations [21 CFR 312.126] cite five different kinds of controls that can be useful in particular circumstances:

- (1) placebo concurrent control
- (2) dose-comparison concurrent control
- (3) no-treatment concurrent control
- (4) active-treatment concurrent control, and
- (5) historical control

No general preference is expressed for any one type, but the study design chosen must be adequate to the task. Thus, in discussing historical controls, the regulation notes that, because it is relatively difficult to be sure that historical control groups are comparable to the treated subjects with respect to variables that could effect outcome, use of historical control studies has been reserved for special circumstances, notably cases where the disease treated has high and predictable mortality (a large difference from this usual course would be easy to detect) and those in which the effect is self-evident (e.g., a general anesthetic).

Placebo control, no-treatment control (suitable where objective measurements are felt to make blinding unnecessary), and dose-comparison control studies are all study designs in which a difference is intended to be shown between the test article and some control. The alternative study design generally proposed to these kinds of studies is an active-treatment concurrent control in which a finding of no difference between the test article and the recognized effective agent (active-control) would be considered evidence of effectiveness of the new agent. There are circumstances in which this is a fully valid design. Active-controls are usually used in antibiotic trials, for example, because it is easy to tell the difference between antibiotics that have the expected effect on specific infections and those that do not. In many cases, however, the active-control design may be simply incapable of allowing any conclusion as to whether or not the test article is having an effect.

There are three principal difficulties in interpreting active-control trials. First, active-control trials are often too small to show that a clinically meaningful difference between the two treatments, if present, could have been detected with reasonable assurance; i.e., the trials have a high "beta-error." In part, this can be overcome by increasing sample size, but two other problems remain even if studies are large. One problem is that there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diagnostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of

observers. As a general statement, carelessness of all kinds will tend to obscure differences between treatments. Where the objective of a study is to show a difference, investigators have powerful stimuli toward assuring study excellence. Active-control studies, however, which are intended to show no significant difference between treatments, do not provide the same incentives toward study excellence, and it is difficult to detect or assess the kinds-of poor study quality that can arise. The other problem is that a finding of no difference between a test article and an effective treatment may not be meaningful. Even where all the incentives toward study excellence are present, i.e., in placebo-controlled trials, effective drugs are not necessarily demonstrably effective (i.e., superior to placebo) every time they are studied. In the absence of a placebo group, a finding of no difference in an active-control study therefore can mean that both agents are effective, that neither agent was effective in that study, or that the study was simply unable to tell effective from ineffective agents. In other words, to draw the conclusion that the test article was effective, one has to know with assurance that the active-control would have shown superior results to a placebo, had a placebo group been included in the study.

For certain drug classes, such as analgesics, antidepressants or antianxiety drugs, failure to show superiority to placebo in a given study is common. This is also often seen with antihypertensives, anti-angina drugs, anti-heart failure treatments, antihistamines, and drugs for asthma prophylaxis. In these situations, active-control trials showing no difference between the new drug and control are of little value as primary evidence of effectiveness and the active-control design (the study design most often proposed as an alternative to use of a placebo) is not credible.

In many situations, deciding whether an active-control design is likely to be a useful basis for providing data for marketing approval is a matter of judgment influenced by available evidence. If, for example, examination of prior studies of a proposed active-control reveals that the test article can very regularly (almost always) be distinguished from placebo in a particular setting (subject population, dose, and other defined parameters), an active-control design may be reasonable if it reproduces the setting in which the active-control has been regularly effective.

It is often possible to design a successful placebo-controlled trial that does not cause investigator discomfort nor raise ethical issues. Treatment periods can be kept short; early "escape" mechanisms can be built into the study so that subjects will not undergo prolonged placebo-treatment if they are not doing well. In some cases randomized placebo-controlled therapy withdrawal studies have been used to minimize exposure to placebo or unsuccessful therapy; in such studies apparent responders to a treatment in an open study are randomly assigned to continued treatment or to placebo. Subjects who fail (e.g., blood pressure rises, angina worsens) can be removed promptly, with such failure representing a study endpoint.

IRBs may face difficult issues in deciding on the acceptability of placebo-controlled and active-control trials. Placebo-controlled trials, regardless of any advantages in interpretation of results, are obviously not ethically acceptable where existing treatment is life-prolonging. A placebo-controlled study that exposes subjects to a documented serious risk is not acceptable, but it is critical to review the evidence that harm would result from denial of active treatment, because alternative study designs, especially active-control studies, may not be informative, exposing subjects to risk but without being able to collect useful information.

For additional information, contact:

For DRUG PRODUCTS:

Office of the Executive Secretary (HFD-8)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 594-1012

For BIOLOGIC PRODUCTS:

Associate Director for Medical and
International Affairs (HFM-30)
Center for Biologic Evaluation and Research
Food and Drug Administration
9200 Rockville Pike
Rockville, MD 20852
(301) 827-0641

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EVALUATION OF GENDER DIFFERENCES IN CLINICAL INVESTIGATIONS

FDA Guideline

On July 22, 1993, the FDA published the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, in the Federal Register [58 FR 39406]. The guideline was developed amidst growing concerns that the drug development process did not provide adequate information about the effects of drugs or biological products in women and a general consensus that women should be allowed to determine for themselves the appropriateness of participating in early clinical trials.

Many aspects of the guideline may be important to an Institutional Review Board (IRB) as part of its initial deliberations about protocols and ongoing surveillance of research. While the guideline specifically addresses drug and biologic testing, the Agency suggests that when reviewing medical device studies, IRBs consider whether the principles of the guideline apply to the device under investigation and, if so, whether to include these principles in their review of the protocol. IRBs should be aware that the FDA guideline represents current policy and describes the Agency's expectations regarding the inclusion of subjects in drug development.

The guideline presents the following critical changes that should be reflected in drug and biologic product protocols presented to IRBs:

- First, the guideline lifts a restriction on participation by most women with childbearing potential from entering Phase 1 and early Phase 2 trials, and now encourages their participation. FDA believes that early drug and biologic trials can be safely conducted in women even before completion of all animal reproduction studies through protocol designs that include monitoring for pregnancy as well as measures to prevent pregnancy during exposure to investigational agents. Pregnancy testing is recommended, and women must be counseled about the reliable use of contraception or abstinence from intercourse while participating in the clinical trial. The guideline does not, however, specify the type of contraception to be used because FDA believes that decisions of this nature are best left to the woman in consultation with her health care provider. It is important that investigators have access to gynecologic consultants who can provide information about contraceptives and advice for study participants.

- Second, the guideline states that sponsors should collect gender-related data during research and development and should analyze the data for gender effects in addition to other variables such as age and race. FDA requires sponsors to include a fair representation of both genders as participants in clinical trials so that clinically significant gender-related differences in response can be detected. The guideline also underscores the importance of collecting pharmacokinetics data on demographic differences beginning in the Phase 1 and 2 studies, so that relevant study designs are developed for later trials.
- In addition, the guideline identifies three specific pharmacokinetics issues to be considered when feasible: (1) effect of the stages of the menstrual cycle; (2) effect of exogenous hormonal therapy including oral contraceptives; and (3) effect of the drug or biologic on the pharmacokinetics of oral contraceptives.

Informed Consent Issues

A critical responsibility of the investigator and the IRB has always included ensuring that there is an adequate informed consent process for study subjects. When preclinical teratology and reproductive toxicology studies are not completed prior to the initial studies in humans, male and female study subjects should be informed about lack of full characterization of the test article and the potential effects of the test agent on conception and fetal development. All study subjects should be provided with new pertinent information arising from preclinical studies as it becomes available, and informed consent documents should be updated when appropriate. Study subjects should also be informed about any new clinical data that emerge regarding general safety and effectiveness, including relevant gender effects.

Summary

IRBs now have broader discretion to encourage the entry of a wide range of individuals into the early phases of clinical trials. FDA appreciates the cooperation of IRBs in assisting the Agency to foster changes in product development that will promote the overall health of all people. FDA urges IRBs not to needlessly exclude women or other groups.

MEDICAL DEVICES

A medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for *in vitro* diagnosis (IVD) of disease and other medical conditions such as pregnancy.

Clinical investigations of medical devices must comply with the Food and Drug Administration (FDA) informed consent and Institutional Review Board (IRB) regulations [21 CFR parts 50 and 56, respectively]. Federal requirements governing investigations involving medical devices were enacted as part of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990. These amendments to the Federal Food, Drug, and Cosmetic Act (the Act) define the regulatory framework for medical device development, testing, approval, and marketing.

Except for certain low risk devices, each manufacturer who wishes to introduce a new medical device to the market must submit a premarket notification to FDA. FDA reviews these notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (i.e., a "pre-amendments device"). If the new device is deemed substantially equivalent to a pre-amendments device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. (The premarket notification requirement for new devices and devices that are significant modifications of already marketed devices is set forth in section 510(k) of the Act. Devices determined by FDA to be "substantially equivalent" are often referred to as "510(k) devices". If the new device is deemed not to be substantially equivalent to a pre-amendments device, it must undergo clinical testing and premarket approval before it can be marketed unless it is reclassified into a lower regulatory class.

Investigational Device Exemption (IDE)

An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21 CFR part 812]. Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations [21 CFR 812.2(c)]. Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "nonsignificant risk" (NSR). The determination that a device presents a nonsignificant or significant risk is initially made by the sponsor. The proposed study is then submitted either to FDA (for SR studies) or to an IRB (for NSR studies).

The IRB's SR/NSR determination has significant consequences for the study sponsor, FDA, and prospective research subjects. SR device studies must be conducted in accordance with the full IDE requirements [21 CFR part 812], and may not commence until 30 days following the sponsor's submission of an IDE application to FDA. Submission of the IDE application enables FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal and human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations [21 CFR 812.2(b)]. Unless otherwise notified by FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, recordkeeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

IRB Review of the Protocol and Informed Consent

Once the final SR/NSR decision has been rendered by the IRB (or FDA), the IRB must consider whether or not the study should be approved. In considering whether a study should be approved, the IRB should use the same criteria it would use in considering approval of any research involving an FDA regulated product [21 CFR 56.111]. Some NSR studies may also qualify as "minimal risk" studies, and thus may be reviewed through an expedited review procedure [21 CFR 56.110]. FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

Also see FDA Information Sheets: "Significant Risk and Nonsignificant Risk Medical Device Studies" and "Sponsor-Investigator-IRB Interrelationship"

SIGNIFICANT RISK AND NONSIGNIFICANT RISK MEDICAL DEVICE STUDIES

The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

Distinguishing Between SR and NSR Device Studies

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations [21 CFR part 812]. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA.

If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA. If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

SR/NSR Studies and the IRB

The NSR/SR Decision

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The IRB may ask the sponsor for information such as a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The IRB should ask the sponsor whether other IRBs have reviewed the proposed study and what determination was made. The sponsor should inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor must notify FDA that a SR determination has been made. The study can be conducted at that institution as a SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses a SR, an IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. Two examples follow:

- ° The study of a pacemaker that is a modification of a commercially-available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated with the investigational pacemaker should only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.
- ° The study of an extended wear contact lens is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the Agency does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

IRB and Sponsor Responsibilities Following SR/NSR Determination

If IRB decides the study is Significant Risk:

1. IRB Responsibilities:

- Notify sponsor and investigator of SR decision
- After IDE obtained by sponsor, proceed to review study applying requisite criteria [21 CFR 56.111]

2. Sponsor Responsibilities:

- Submit IDE to FDA or, if electing not to proceed with study, notify FDA (CDRH Program Operations Staff 301-594-1190) of the SR determination;
- Study may not begin until FDA approves IDE and IRB approves the study.
- Sponsor and investigator(s) must comply with IDE regulations [21 CFR part 812], as well as informed consent and IRB regulations [21 CFR parts 50 and 56].

If the IRB decides the study is Nonsignificant Risk:

1. IRB proceeds to review study applying requisite criteria [21 CFR 56.111]
2. If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements" [21 CFR 812.2(b)], and informed consent and IRB regulations [21 CFR parts 50 and 56].

The Decision to Approve or Disapprove

Once the SR/NSR decision has been reached, the IRB should consider whether the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study [21 CFR 56.111]. The IRB should assure that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of subjects are acceptable. To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device. Minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, IRB review at a convened meeting is also required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk [21 CFR 56.102(i)] and the IRB may choose to review those studies under its expedited review procedures [21 CFR 56.110].

Examples of NSR/SR Devices

The following examples are provided to assist sponsors and IRBs in making SR/NSR determinations. The list includes many commonly used medical devices. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

NONSIGNIFICANT RISK DEVICES

Low Power Lasers for treatment of pain [Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.]

Caries Removal Solution

Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)

Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use

Conventional Gastroenterology and Urology Endoscopes and/or Accessories

Conventional Laparoscopes, Culdoscopes, and Hysteroscopes

Dental Filling Materials, Cushions or Pads made from traditional materials and designs

Denture Repair Kits and Realigners

Digital Mammography [Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.]

Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities)

Externally Worn Monitors for Insulin Reactions

Functional Electrical Neuromuscular Stimulators

General Biliary Catheters

General Urological Catheters (e.g., Foley and diagnostic catheters)

Jaundice Monitors for Infants

Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters

Menstrual Pads (Cotton or Rayon, only)

Menstrual Tampons (Cotton or Rayon, only)

Nonimplantable Electrical Incontinence Devices

Nonimplantable Male Reproductive Aids with no components that enter the vagina

Ob/Gyn Diagnostic Ultrasound within FDA approved parameters

Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain

Wound Dressings, excluding absorbable hemostatic devices and dressings
(also excluding Interactive Wound and Burn Dressings)

SIGNIFICANT RISK DEVICES

GENERAL MEDICAL USE

Catheters:

Urology - urologic with anti-infective coatings

General Hospital - long-term percutaneous, implanted, subcutaneous and intravascular

Neurological - cerebrovascular, occlusion balloon

Cardiology - transluminal coronary angioplasty, intra-aortic balloon with control system

Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery, urological and dental applications

Surgical Lasers for use in various medical specialties

Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology

ANESTHESIOLOGY

Breathing Gas Mixers

Bronchial Tubes

Electroanesthesia Apparatus

Epidural and Spinal Catheters

Epidural and Spinal Needles

Esophageal Obturators

Gas Machines for anesthesia or analgesia

High Frequency Jet Ventilators greater than 150 BPM

Rebreathing Devices

Respiratory Ventilators

Tracheal Tubes

CARDIOVASCULAR

Aortic and Mitral Valvoplasty Catheters

Arterial Embolization Devices

Cardiac Assist Devices: artificial heart (permanent implant and short term use), cardiomyoplasty devices, intra-aortic balloon pumps, ventricular assist devices

Cardiac Bypass Devices: oxygenators, cardiopulmonary non-roller blood pumps, closed chest devices

Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable

Cardiopulmonary Resuscitation (CPR) Devices

Cardiovascular/Intravascular Filters

Coronary Artery Retroperfusion Systems
Coronary Occluders for ductus arteriosus, atrial and septal defects
Coronary and Peripheral Arthrectomy Devices
Extracorporeal Membrane Oxygenators (ECMO)
Implantable Cardioverters/Defibrillators
Laser Coronary and Peripheral Angioplasty Devices
Myoplasty Laser Catheters
Organ Storage/Transport Units
Pacing Leads
Percutaneous Conduction Tissue Ablation Electrodes
Peripheral, Coronary, Pulmonary, Renal, Vena Caval and Peripheral Stents
Replacement Heart Valves
RF Catheter Ablation and Mapping Systems
Ultrasonic Angioplasty Catheters
Vascular and Arterial Graft Prostheses
Vascular Hemostasis Devices

DENTAL

Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications
Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA)
Dental Lasers for hard tissue applications
Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants
Subperiosteal Implants
Temporomandibular Joint (TMJ) Prostheses

EAR, NOSE AND THROAT

Auditory Brainstem Implants
Cochlear Implants
Laryngeal Implants
Total Ossicular Prosthesis Replacements

GASTROENTEROLOGY AND UROLOGY

Anastomosis Devices
Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)
Biliary Stents
Components of Water Treatment Systems for Hemodialysis
Dialysis Delivery Systems
Electrical Stimulation Devices for sperm collection
Embolization Devices for general urological use
Extracorporeal Circulation Systems
Extracorporeal Hyperthermia Systems
Extracorporeal Photopheresis Systems
Femoral, Jugular and Subclavian Catheters
Hemodialyzers
Hemofilters
Implantable Electrical Urinary Incontinence Systems
Implantable Penile Prostheses
Injectable Bulking Agents for incontinence
Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic)
Mechanical/Hydraulic Urinary Incontinence Devices
Penetrating External Penile Rigidity Devices with components that enter the vagina
Peritoneal Dialysis Devices
Peritoneal Shunt
Plasmapheresis Systems
Prostatic Hyperthermia Devices
Urethral Occlusion Devices
Urethral Sphincter Prostheses
Urological Stents (e.g., ureteral, prostatG)

GENERAL AND PLASTIC SURGERY

Absorbable Adhesion Barrier Devices
Absorbable Hemostatic Agents
Artificial Skin and Interactive Wound and Burn Dressings
Injectable Collagen
Implantable Craniofacial Prostheses
Repeat Access Devices for surgical procedures
Sutures

GENERAL HOSPITAL

Implantable Vascular Access Devices
Infusion Pumps (implantable and closed-loop — depending on the infused drug)

NEUROLOGICAL

Electroconvulsive Therapy (ECT) Devices
Hydrocephalus Shunts
Implanted Intracerebral/Subcortical Stimulators
Implanted Intracranial Pressure Monitors
Implanted Spinal Cord and Nerve Stimulators and Electrodes

OBSTETRICS AND GYNECOLOGY

Antepartum Home Monitors for Non-Stress Tests
Antepartum Home Uterine Activity Monitors
Catheters for Chorionic Villus Sampling (CVS)
Catheters Introduced into the Fallopian Tubes
Cervical Dilation Devices
Contraceptive Devices:
 Cervical Caps
 Condoms (for men) made from new materials (e.g., polyurethane)
 Contraceptive *In Vitro* Diagnostics (IVDs)
 Diaphragms
 Female Condoms
 Intrauterine Devices (IUDs)
 New Electrosurgical Instruments for Tubal Coagulation
 New Devices for Occlusion of the Vas Deferens
 Sponges
 Tubal Occlusion Devices (Bands or Clips)
Devices to Prevent Post-op Pelvic Adhesions
Embryoscopes and Devices intended for fetal surgery
Falloposcopes and Falloposcopic Delivery Systems
Intrapartum Fetal Monitors using new physiological markers
New Devices to Facilitate Assisted Vaginal Delivery
Thermal Systems for Endometrial Ablation

OPHTHALMICS

Class III Ophthalmic Lasers

Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use

Corneal Implants

Corneal Storage Media

Epikeratophakia Lenticules

Extended Wear Contact Lens

Eye Valve Implants (glaucoma implant)

Intraocular Lenses (IOLs) [21 CFR part 813]

Keratoprotheses

Retinal Reattachment Systems: fluids, gases, perfluorocarbons, perfluoropropane, silicone oil, sulfur hexafluoride, tacks

Viscosurgical Fluids

ORTHOPEDICS AND RESTORATIVE

Bone Growth Stimulators

Calcium Tri-Phosphate Hydroxyapatite Ceramics

Collagen and Bone Morphogenic Protein Meniscus Replacements

Implantable Protheses (ligament, tendon, hip, knee, finger)

RADIOLOGY

Boron Neutron Capture Therapy

Hyperthermia Systems and Applicators

Image Guided Surgery

Your comments and suggestions for additional examples are welcome and should be sent to:

Program Operation Staff (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850
(301) 594-1190

EMERGENCY USE OF UNAPPROVED MEDICAL DEVICES

For the purpose of this information sheet, an unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 360(e)]. An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an Investigational Device Exemption (IDE) under section 520(g) of the Act [21 U.S.C. 360(j)(g)] and 21 CFR part 812.

The Food and Drug Administration (FDA) recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed.

Requirements for Emergency Use

Each of the following conditions must exist to justify emergency use:

1. the patient is in a life-threatening condition that needs immediate treatment;
2. no generally acceptable alternative for treating the patient is available; and
3. because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-594-1190) immediately after shipment is made. [Note: an unapproved device may not be shipped in anticipation of an emergency.] Nights and weekends, contact the Division of Emergency and Epidemiological Operations (202-857-8400).

FDA would expect the physician to follow as many subject protection procedures as possible. These include:

1. obtaining an independent assessment by an uninvolved physician;
2. obtaining informed consent from the patient or a legal representative;
3. notifying institutional officials as specified by institutional policies;
4. notifying the Institutional Review Board (IRB); and
5. obtaining authorization from the IDE holder, if an approved IDE for the device exists.

After-use Procedures

After an unapproved device is used in an emergency, the physician should:

1. report to the IRB within five days [21 CFR 56.104(c)] and otherwise comply with provisions of the IRB regulations [21 CFR part 56];
2. evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use; and
3. if an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use (CDRH Program Operation Staff 301-594-1190) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

Also see FDA Information Sheet: "Emergency Use of an Investigational Drug or Biologic"

FDA INSTITUTIONAL REVIEW BOARD INSPECTIONS

Background

Since 1971, FDA regulations have required that studies involving investigational new drugs and biologics performed on human subjects in institutions (including hospitals, nursing homes, mental institutions, and prisons) receive review and approval by an Institutional Review Board (IRB). Medical devices have required IRB review since 1976.

FDA developed the Bioresearch Monitoring Program and began an expanded review of IRB operations in April 1977. The Bioresearch Monitoring Program, which encompasses not only IRBs, but also clinical investigators, research sponsors, monitors, and non-clinical (animal) laboratories, is primarily intended to ensure the quality and integrity of data submitted to FDA for regulatory decisions, as well as to protect human subjects of research. For this reason, the IRB regulations note that FDA may inspect IRBs and review and copy IRB records [21 CFR 56.115(b)].

IRB Review Program

Under the Bioresearch Monitoring Program, FDA conducts on-site procedural reviews of IRBs. These reviews are conducted to determine whether an IRB is operating in accordance with its own written procedures as well as in compliance with current FDA regulations affecting IRBs. These regulations include 21 CFR part 50 (Informed Consent), part 56 (Standards for IRBs), part 312 (Investigational New Drugs), and part 812 (Investigational Devices).

When an IRB is selected for a procedural review, an investigator from one of the Agency's District Offices will contact a responsible individual at the institution, usually the IRB chairperson, and arrange a mutually acceptable time for the visit. When the field investigators arrive at the institution, they will show FDA credentials (photo ID) and present a "Notice of Inspection" form to the responsible official. This is done simply to let those persons at the institution know that the investigators are duly authorized representatives of FDA conducting official business. The investigator will interview appropriate persons and obtain information about the IRB's policies and procedures. Then, using one or more studies which are subject to FDA regulations, the investigator will examine the IRB's performance by tracking these studies through the review process used by the IRB. The IRB procedures and membership rosters will be examined to see whether they conform to current Agency regulations. The FDA investigator may request copies of records of IRB membership, IRB procedures and guidelines, minutes of meetings at which the studies were reviewed and discussed, material on the studies submitted by the clinical investigator to the IRB, and any other materials pertaining to these studies. Copies of these materials become part of the field investigator's report to FDA Headquarters.

After the inspection has been completed, the investigator will conduct an "exit interview" with a responsible institutional representative and/or the IRB chairperson. At this interview, the investigator will review the findings, clarify any misunderstandings that might exist, describe any deviations from the current regulations, and may suggest corrective actions. A written Form FDA-483 (Notice of Observations) may be left with the institution.

After the investigator returns to the District Office, a written report is prepared. This report is forwarded to FDA Headquarters for evaluation. When the evaluation is completed, a letter may be sent to the IRB chairperson or other responsible institutional official. If the regulations have not been followed, the letter may suggest methods to achieve compliance and ask the IRB to correct its procedures. If serious deviations were observed, a written response assuring adequate correction is usually required. A follow-up inspection may be also conducted. FDA may take administrative actions against IRBs and/or their institutions for noncompliance with the regulations [21 CFR part 56 subpart E].

Additional Information

A copy of the FDA Compliance Program Guidance Manual for IRB Inspections (Program 7348.809) is available to the public by writing to:

Freedom of Information Staff (HFI-30)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Contact Person for Inspection Problems

If, during the course of an inspection, questions arise that the FDA field investigator has not answered, the Director of the District Office may be contacted. The name and telephone number of the District Director is available from the field investigator and is also on the Notice of Inspection (Form FDA-482).

FDA INSPECTIONS OF CLINICAL INVESTIGATORS

Background

The FDA Bioresearch Monitoring Program involves site visits to clinical investigators, research sponsors, contract research organizations, Institutional Review Boards (IRBs), and nonclinical (animal) laboratories. All FDA product areas, i.e., drugs, biologics, medical devices, radiological products, foods, and veterinary drugs, are involved in the Bioresearch Monitoring Program. While program procedures differ slightly depending upon product type, all inspections have as their objective ensuring the quality and integrity of data and information submitted to FDA as well as the protection of human research subjects.

Clinical Investigator Inspection Programs

FDA carries out three distinct types of clinical investigator inspections: (1) study-oriented inspections; (2) investigator-oriented inspections; and (3) bioequivalence study inspections. Bioequivalence study inspections are conducted because one study may be the sole basis for a drug's marketing approval. The bioequivalence study inspection differs from the other inspections in that it requires participation by an FDA chemist or an investigator knowledgeable about analytical evaluations. The other two types of inspections are discussed in more detail below.

Study-oriented Inspections

FDA field offices conduct study-oriented inspections on the basis of assignments developed by headquarters staff. Assignments are based almost exclusively on studies that are important to product evaluation, such as new drug applications and product license applications pending before the Agency.

When a clinical investigator, who has participated in the study being examined, is selected for an inspection, the FDA investigator from the FDA District Office will contact the clinical investigator to arrange a mutually acceptable time for the visit. Upon arrival, the FDA investigator will show FDA credentials (photo ID) and present a "Notice of Inspection" form to the clinical investigator. FDA credentials let the clinical investigator know that the FDA investigator is a duly authorized FDA representative.

If, during the course of an FDA inspection, a clinical investigator has any questions that the FDA investigator has not answered, either the Director of the District Office or the Center that initiated the inspection may be contacted. The name and telephone number of the District Director and the specific Center contact person are available from the FDA investigator.

The investigation consists of two basic parts. First, determining the facts surrounding the conduct of the study:

- who did what,
- the degree of delegation of authority,
- where specific aspects of the study were performed,
- how and where data were recorded,
- how test article accountability was maintained,
- how the monitor communicated with the clinical investigator, and
- how the monitor evaluated the study's progress.

Second, the study data is audited. The FDA investigator compares the data submitted to the Agency and/or the sponsor with all available records that might support the data. These records may come from the physician's office, hospital, nursing home, laboratories and other sources. FDA may also examine patient records that predate the study to determine whether the medical condition being studied was, in fact, properly diagnosed and whether a possibly interfering medication had been given before the study began. The FDA investigator may also review records covering a reasonable period after completion of the study to determine if there was proper follow-up, and if all signs and symptoms reasonably attributable to the product's use had been reported.

Investigator-oriented Inspections

An investigator-oriented inspection may be initiated because an investigator conducted a pivotal study that merits in-depth examination because of its singular importance in product approval or its effect on medical practice. An inspection may also be initiated because representatives of the sponsor have reported to FDA that they are having difficulty getting case reports from the investigator, or that they have some other concern with the investigator's work. In addition, the Agency may initiate an inspection, if a subject in a study complains about protocol or subject rights violations. Investigator-oriented inspections may also be initiated because clinical investigators have participated in a large number of studies or have done work outside their specialty areas. Other reasons include safety or effectiveness findings that are inconsistent with those of other investigators studying the same test article; too many subjects with a specific disease given the locale of the investigation are claimed; or laboratory results that are outside the range of expected biological variation.

Once the Agency has determined that a investigator-oriented inspection should be conducted, the procedures are essentially the same as in the study-oriented inspection except that the data audit goes into greater depth, covers more case reports, and may cover more than one study. If the investigator has repeatedly or deliberately violated FDA regulations or has submitted false information to the sponsor in a required report, FDA will initiate actions that may ultimately determine that the clinical investigator is not to receive investigational products in the future.

Inspection Findings

At the end of an inspection, the FDA investigator will conduct an "exit interview" with the clinical investigator. At this interview, the FDA investigator will discuss the findings from the inspection, clarify any misunderstandings that might exist, and may issue a written Form FDA-483 (Notice of Observations) to the clinical investigator. Following the inspection, the FDA field investigator prepares a written report and submits it to headquarters for evaluation.

After the report has been evaluated, FDA headquarters usually issues a letter to the clinical investigator. The letter is usually one of three types:

- (1) a notice that no significant deviations from the regulations were observed. This letter does not require any response from the clinical investigator.
- (2) an informational letter that identifies deviations from regulations and good investigational practice. This letter may, or may not require a response from the clinical investigator. If a response is requested, the letter will describe what is necessary and give a contact person for questions.
- (3) a "Warning Letter" identifying serious deviations from regulations requiring prompt correction by the clinical investigator. The letter will give a contact person for questions. In these cases, FDA may inform both the study sponsor and the reviewing IRB of the deficiencies. The Agency may also inform the sponsor if the clinical investigator's procedural deficiencies indicate ineffective monitoring by the sponsor. In addition to issuing these letters, FDA may take other courses of action, i.e., regulatory and/or administrative sanctions.

Additional Information

A copy of the FDA Compliance Program Guidance Manual for Clinical Investigator Inspections (Program 7348.811), the document used by the FDA investigator to conduct the inspection, is available by writing to:

Freedom of Information Staff (HFI-30)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857.

Also see FDA Information Sheet: "Clinical Investigator Regulatory Sanctions"

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CLINICAL INVESTIGATOR REGULATORY SANCTIONS

This information sheet focuses on the applicability of regulatory sanctions to clinical investigators participating in studies involving investigational new drugs, antibiotics, biologics, medical foods or food additives. Currently, the Food and Drug Administration (FDA) has other compliance mechanisms for medical devices, but disqualification will also be added to these in the near future. [Note: Although this information sheet refers to human subjects in the context of an Investigational New Drug Application (IND), analogous principles apply to animal subjects in an Investigational New Animal Drug Application (INAD).]

The Disqualification Process

Informal Conference or Written Explanation

FDA may disqualify clinical investigators from receiving investigational drugs only when the investigator has repeatedly or deliberately violated the Agency's regulations, or has submitted false information to the sponsor in a required report. The appropriate FDA Center will send the investigator a written notice (Warning Letter) describing the noncompliance or false submission and offer the investigator an opportunity to respond to the notice at an informal conference or in writing. The Agency will specify a time period within which the investigator must respond. While the conference is informal, a transcript may be made, and the investigator may have legal representation. Because the invitation to the informal conference is a Warning Letter, it is available to the public under the Freedom of Information (FOI) Act and is placed on public display in the Agency's FOI office.

If the investigator offers a timely and satisfactory explanation for the noncompliance, and the Center accepts, the process is terminated and the investigator is so notified in writing. If, however, the investigator offers an explanation that the Center rejects, or if the investigator fails to respond within the specified time period, FDA will offer the investigator an opportunity for an informal regulatory "Part 16" hearing under the Agency's regulations [21 CFR part 16] to determine whether the investigator should remain eligible to receive investigational new drugs.

Notice of an Opportunity for Hearing on Proposed Disqualifications

FDA initiates a Part 16 hearing when it sends the investigator a written Notice of Opportunity for Hearing. The Notice specifies the allegations and other relevant information that is the subject of the hearing. An investigator must respond to the notice within a specified time. If the investigator does not respond within that time period, FDA considers the offer to have been refused, and no informal hearing will be held. The Commissioner will then consider the information available to FDA to determine whether the investigator should be disqualified.

If a hearing is requested, the Commissioner will designate a presiding officer from the Office of Health Affairs (OHA), and the hearing will take place at a mutually agreeable time at FDA headquarters. If agreement cannot be reached, however, the presiding officer will designate a hearing date acceptable to FDA.

Part 16 Hearing and Final Order on Disqualification

Before the hearing, FDA gives the investigator notice of the matters to be considered at the hearing which includes a comprehensive statement of the basis for the proposal to disqualify the investigator and a general summary of the information that the Center will present. The Center and the investigator exchange written notice of any published articles or written information to be presented or relied on at the hearing. If it seems unreasonable to expect the other party to have, or to be able to obtain, a copy of a particular document, a copy of the document is provided.

Part 16 hearings are informal, and the rules of evidence do not apply. Any participant may comment upon or rebut all data, information, and views presented. The presiding officer conducts the hearing. The hearing begins with Center staff giving a complete statement of the action that is the subject of the hearing and describing the information and reasons supporting disqualification. They may present any oral or written information relevant to the hearing. The investigator, who may be represented by legal counsel, then may present any oral or written information relevant to the hearing.

After the hearing, the OHA presiding officer prepares a written report. This report includes a recommended decision and the reasons for the recommendation. The administrative record of the hearing includes all written material presented at the hearing and the hearing transcript. The parties are given the opportunity to review and comment on the presiding officer's report. The report and the comments of the parties are transmitted to the Commissioner who considers them along with the administrative record to determine whether the investigator should be disqualified. The Commissioner issues a written decision giving the basis for the action taken.

Actions Upon Disqualification

If the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the regulatory requirements, or has deliberately or repeatedly submitted false information to the sponsor in any required report, the Commissioner will:

- (1) Notify the investigator and the sponsor(s) of any investigation(s) in which the investigator has participated that the investigator is not entitled to receive investigational drugs. The notification will include a statement explaining the basis for this determination.

(2) Notify the sponsors of studies conducted under each IND, INAD, or each approved application containing data reported by the investigator that the Agency will not accept the investigator's work in support of claims of safety and efficacy without validating information establishing that the study results were unaffected by the investigator's misconduct.

(3) After the investigator's data are eliminated from consideration, determine whether the data remaining can support a conclusion that studies under the IND may continue. If the Commissioner determines that the remaining data are inadequate, the sponsor will be notified and will have an opportunity for a regulatory hearing under 21 CFR part 16. If a danger to public health exists, however, the Commissioner will terminate the IND immediately and notify the sponsor of the determination. The sponsor will then have an opportunity for a Part 16 regulatory hearing to determine whether the IND should be reinstated.

(4) After the investigator's data are eliminated from consideration, determine, whether the continued approval of the product is justified. If it is not, the Commissioner will move to withdraw approval in accordance with the applicable provisions of the Federal Food, Drug, and Cosmetic Act.

The action to be taken with regard to an ongoing clinical investigation conducted by a disqualified investigator is made on a case-by-case basis. FDA considers the nature of the clinical investigation, the number of subjects involved, the risks to the subjects from discontinuation of the study, and the need for involvement of an acceptable investigator. If another investigator accepts responsibility for the investigation, FDA may allow an investigation to continue. If not, further use of the test article is deferred until another investigator is identified. If this deferment could create a life-threatening situation, FDA may permit a subject to continue to receive or use a test article without a further written statement from the disqualified investigator. The investigator can bring such cases to the Agency's attention during the regulatory hearing, so that the Commissioner may consider this option.

Public Disclosure of Information Regarding Disqualification

Notification of impending or contemplated action is limited to those persons who have a legitimate interest in knowing that the clinical investigator may be disqualified (e.g., the sponsors of the investigator's studies, the investigator's Institutional Review Board(s), federal, state or local agencies, and institutions in which the investigator practices or teaches). Similar notification also may be provided at the time of a consent agreement (see below).

Notification generally will be made when FDA sends a Notice of Opportunity for a Hearing under Part 16 to the investigator. However, when safety considerations warrant earlier notification, the Agency will act accordingly. These "safety considerations" include not only the subjects' safety in any study in question, but also the safety of subjects in other studies in which

the investigator is involved. FDA will notify other government agencies of a proposed disqualification whenever the Agency deems such notification to be appropriate.

If the Agency notifies other parties of its preliminary findings prior to final disqualification, FDA will provide a description of these findings, state that the Agency has yet to reach a final decision on whether the investigator should be disqualified, and will not recommend that action be taken by the third party. If the disqualification proceeding does not result in a disqualification or a consent agreement, FDA will so advise those third parties that had been contacted. A copy of each notification will be sent to the investigator.

If the Agency gives notice of the disqualification of a specific investigator to a third party, FDA will provide a copy of the final disqualification order, explain its legal meaning, and state that FDA is not advising or recommending that the person notified take any action upon the matter. A copy of each notification will be sent to the investigator. The list of investigators who are ineligible to receive investigational new drugs or who have agreed to some restriction of investigational drug use (see below) is not considered to be a "notice" as discussed above.

Reinstatement of a Disqualified Investigator

Investigators who have been disqualified may be reinstated if the Commissioner determines that the investigators have presented adequate assurances that they will employ investigational drugs in compliance with FDA regulations. The Agency's reinstatement guidelines, entitled "Procedures for Reinstating Eligibility of Disqualified Clinical Investigators to Receive Investigational Articles" are available by writing to the FOI Staff at the address given below.

Consent Agreements

In addition to an opportunity for an informal conference or to respond in writing to Center allegations, the Center for Drug Evaluation and Research and the Center for Biologic Evaluation and Research offer investigators the opportunity to enter into a consent agreement whereby the investigator agrees to meet certain conditions mutually acceptable to both FDA and the investigator. This agreement obviates the need to proceed further with the disqualification process. Consent agreements generally take one of two forms: (1) the individual agrees to refrain from further studies with FDA regulated test articles or (2) the individual agrees to specific restrictions in the use of investigational products, such as oversight by an individual acceptable to both the investigator and to the Agency. The consent agreement option remains available to the clinical investigator at all stages of the disqualification process. Most actions have been settled by consent agreements.

Criminal Prosecutions

After a Part 16 proceeding, a final order or entry into a consent agreement constitutes final Agency administrative action. This, however, does not preclude institution of criminal proceedings against an investigator. Those investigators referred for criminal prosecution are generally clinical investigators who have knowingly or willingly submitted false information to a research sponsor.

Additional Information

FDA maintains a list of investigators who are ineligible to receive investigational new drugs or who have agreed to some restriction of investigational drug use. This list is regularly updated and is not considered to be a "notice" of disqualification (see above). The list is available to the public by writing to the following FDA office.

Freedom of Information Staff (HFI-30)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857.

[Note: The FDA cumulative list of investigators ineligible to receive investigational new drugs, is not considered a "notice of the disqualification."]

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**A List of Selected FDA Regulations
Relating to the Protection of Human Subjects**

This list contains Food and Drug Administration (FDA) regulations that specifically relate to the protection of human subjects in clinical investigations. The citations selected below are only a few of the FDA regulations (contained in nine volumes) that apply to clinical investigations and govern the development and approval of drugs, biologics, and devices. The regulations are contained in Title 21 of the Code of Federal Regulations (CFR), which can be purchased from the Superintendent of Documents, Attn: New Orders, P.O. Box 371954, Pittsburgh, PA 15250-7954; (202-512-1800, fax: 202-512-2233)

I. FDA HUMAN SUBJECT PROTECTIONS

Part 50 - Protection of Human Subjects (Informed Consent)
Part 56 - Institutional Review Boards

II. SUBSTANCES AND ARTICLES REGULATED BY FDA

Foods

Part 71 - Color Additives
Part 171 - Food Additive Petitions
Part 180 - Food Additives (Interim)

Drugs

Part 312 - Investigational New Drug Application
Part 320 - Bioavailability and Bioequivalence Requirements
Part 330 - Over-the-Counter Human Drugs
Part 361.1 - Radioactive Drugs for Certain Research Uses

Biologics

Part 312 - Investigational New Drug Application
Part 601 - Licensing
Part 630 - Additional Standards for Viral Vaccines

Medical Devices

Part 812 - Investigational Device Exemptions
Part 813 - Investigational Device Exemptions for Intraocular Lenses
Part 814 - Premarket Approval of Medical Devices

Radiological Health

Part 361.1 - Radioactive Drugs for Certain Research Uses
Part 1010 - Performance Standards for Electronic Products

III. RELATED FDA PROCEDURES

Part 10 - General Agency Administrative Procedures
Part 16 - Regulatory Hearings before the FDA
Part 20 - Public Information

IV. STATUTES PROVIDING AUTHORITY FOR REGULATIONS LISTED ABOVE:

Biological Control Act of 1902/Virus, Serum and Toxin Act of 1902
Food, Drug and Cosmetic Act of 1938 (as ammended)
Public Health Service Act of 1944 (as ammended)
Food Additive Amendments of 1958
Color Additives Amendment of 1960
New Drug Amendments of 1962
Radiation Control for Public Health and Safety Act of 1968
National Research Act of 1974
Medical Device Amendments of 1976
Safe Medical Devices Act of 1990
Device Amendments of 1992

21 CFR PART 50 — PROTECTION OF HUMAN SUBJECTS

Subpart A General Provisions

- 50.1 Scope.
- 50.3 Definitions.

Subpart B Informed Consent of Human Subjects

- 50.20 General requirements for informed consent.
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Subpart C Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects

- 50.40 Applicability.
- 50.42 Purpose.
- 50.44 Restrictions on clinical investigations involving prisoners.
- 50.46 Composition of institutional review boards where prisoners are involved.
- 50.48 Additional duties of the institutional review boards where prisoners are involved.

[Source: 45 FR 36390, May 30, 1980, unless otherwise noted.]

Subpart A — General Provisions

§ 50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) 507(d), and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., 21 CFR parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 406, 409, 502, 503, 505, 506, 507, 510, 513-516, 518 520, 706, and 801 of the Federal Food, Drug and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981]

§ 50.3 Definitions.

As used in this part:

(a) **Act** means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq. as amended (21 U.S.C. 321-392)).

(b) **Application** for research or marketing permit includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) Data and information about an antibiotic drug submitted as part of the procedures for issuing, amending or repealing regulations for these drugs, described in § 314.300 of this chapter.

(12) An application for a biological product license, described in part 601.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an *in vitro* diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) An "Application for an Investigational Device Exemption," described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(c) **Clinical investigation** means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) **Investigator** means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) **Sponsor** means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator) and the employees are considered to be investigators.

(f) **Sponsor-investigator** means an individual who both initiates and actually conducts, alone or with others a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) **Human subject** means an individual who is or becomes a participant in research, either as a recipient of the test article as a control. A subject may be either a healthy human or a patient.

(h) **Institution** means any public or private entity or Agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(i) **Institutional review board (IRB)** means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(j) **Prisoner** means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(k) **Test article** means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

(l) **Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(m) **Legally authorized representative** means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

[45 FR.36390, May 30, 1980, as amended at 46 FR 8950 Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991]

Subpart B — Informed Consent of Human Subjects

§ 50.20 General requirements for informed consent.

Except as provided in § 50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

§ 50.21 Effective date.

The requirements for informed consent set out in this part apply to all human subjects entering a clinical investigation that commences on or after July 27, 1981.

§ 50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- (1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.
- (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
- (3) Time is not sufficient to obtain consent from the subject's legal representative.
- (4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d)(1) The Commissioner may also determine that obtaining informed consent is not feasible when the Assistant Secretary of Defense (Health Affairs) requests such a determination in connection with the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD). DOD's request for a determination that obtaining informed consent from military personnel is not feasible must be limited to a specific military operation involving combat or the immediate threat of combat. The request must also include a written justification supporting the conclusions of the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) identified in the IND that a military combat exigency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate the accomplishment of the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel without regard to what might be any individual's personal preference for no treatment or for some alternative treatment. The written request must also include a statement that a duly constituted institutional review board has reviewed and approved the use of the investigational drug without informed consent. The Commissioner may find that informed consent is not feasible only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy.

(2) In reaching a determination under paragraph (d)(1) of this section that obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel, the Commissioner will review the request submitted under paragraph (d)(1) of this section and take into account all pertinent factors, including, but not limited to:

(i) The extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use;

(ii) The context in which the drug will be administered, e.g., whether it is intended for use in a battlefield or hospital setting or whether it will be self-administered or will be administered by a health professional;

(iii) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(iv) The nature of the information to be provided to the recipients of the drug concerning the potential benefits and risks of taking or not taking the drug.

(3) The Commissioner may request a recommendation from appropriate experts before reaching a determination on a request submitted under paragraph (d)(1) of this section.

(4) A determination by the Commissioner that obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel will expire at the end of 1 year, unless renewed at DOD's request, or when DOD informs the Commissioner that the specific military operation creating the need for the use of the investigational drug has ended whichever is earlier. The Commissioner may also revoke this determination based on changed circumstances.

§ 50.25 Elements of informed consent.

(a) Basic elements of informed consent.

In seeking informed consent, the following information shall be provided to each subject:

- (1) A statement that the study involves research an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- (5) A statement describing the extent if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
- (6) For research involving more than minimal risk an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent.

When appropriate one or more of the following elements of information shall also be provided to each subject:

- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- (3) Any additional costs to the subject that may result from participation in the research.
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- (6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

§ 50.27 Documentation of informed consent.

(a) Except as provided in § 56.109(c) informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in § 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A short form written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

Subpart C — Protections pertaining to Clinical Investigations Involving Prisoners as Subjects

Effective Date Note: At 46 FR 35085, July 7, 1981, the effective date of Subpart C was stayed until further notice.

50.40 Applicability.

50.42 Purpose.

50.44 Restrictions on clinical investigations involving prisoners.

50.46 Composition of institutional review boards where prisoners are involved.

50.48 Additional duties of the institutional review boards where prisoners are involved.

21 CFR PART 56 — INSTITUTIONAL REVIEW BOARDS

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[Source: 46 FR 8975, Jan 27, 1981, unless otherwise noted.]

Subpart A — General Provisions

§ 56.101 Scope.

(a) This part contains the general standards for the composition operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration including food and color additives, drugs for human use medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21, unless otherwise noted.

§ 56.102 Definitions.

As used in this part:

(a) **Act** means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392)).

(b) **Application** for research or marketing permit includes:

- (1) A color additive petition, described in part 71.
- (2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in § 170.35.
- (3) A food additive petition, described in part 171.
- (4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1.
- (5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials described in section 406 of the act.
- (6) An investigational new drug application, described in part 312 of this chapter.
- (7) A new drug application, described in part 314.
- (8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in § 314.300 of this chapter.

(11) An application for a biological product license, described in part 601.

(12) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in part 601.

(13) An Application for an Investigational Device Exemption, described in parts 812 and 813.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860.

(15) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861.

(16) An application for premarket approval of a medical device for human use, described in section 515 of the act.

(17) A product development protocol for a medical device for human use, described in section 515 of the act.

(18) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.

(19) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4.

(20) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard as described in § 1010.5.

(21) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(c) Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

(d) **Emergency use** means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) **Human subject** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) **Institution** means any public or private entity or Agency (including Federal State, and other agencies). The term facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(g) **Institutional Review Board (IRB)** means any board committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(h) **Investigator** means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(i) **Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) **Sponsor** means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator) and the employees are considered to be investigators.

(k) **Sponsor-investigator** means an individual who both initiates and actually conducts, alone or with others a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) **Test article** means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

(m) **IRB approval** means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

[46 FR 8975, Jan. 27, 1981, as amended at 54 FR 9038 Mar. 3, 1989; 56 FR 28028, June 18, 1991]

§ 56.103 Circumstances in which IRB review is required.

(a) Except as provided in §§ 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in §§ 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

[46 FR 8975, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981]

§ 56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[46 FR 8975, Jan. 27 1981, as amended at 56 FR 28028, June 18, 1991]

§ 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations including the requirements for IRB review, for specific research activities or for classes of research activities otherwise covered by these regulations.

SUBPART B — ORGANIZATION AND PERSONNEL

§ 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

[46 FR 8975, Jan 27 1981, as amended at 56 FR 28028, June 18, 1991; 56 FR 29756 June 28, 1991]

Subpart C — IRB Functions and Operations

§ 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see § 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved it shall receive the approval of a majority of those members present at the meeting.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

§ 56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 50.25. The IRB may require that information in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with § 50.27, except that the IRB may, for some or all subjects, waive the requirement that the subject or the subject's legally authorized representative sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

§ 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate through periodic republication in the Federal Register.

(b) An IRB may use the expedited review procedure to review either or both of the following:
(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not

disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited review procedure set forth in § 56.108(c).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

§ 56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by § 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

§ 56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator appropriate institutional officials, and the Food and Drug Administration.

§ 56.114 Cooperative research.

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D — Records and Reports.

§ 56.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by § 56.108(a) and (b).

(7) Statements of significant new findings provided to subjects, as required by § 50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

Subpart E — Administrative Actions for Noncompliance

§ 56.120 Lesser administrative actions.

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The Agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the Agency may:

- (1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;
- (2) Direct that no new subjects be added to ongoing studies subject to this part;
- (3) Terminate ongoing studies subject to this part when doing so would not subjects; or
- (4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

§ 56.121 Disqualification of an IRB or an institution.

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the Agency under § 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.

(b) The Commissioner may disqualify an IRB or the parent if the Commissioner determines that:

- (1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and;

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the Agency may elect to publish a notice of its action in the Federal Register.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution unless the IRB or the parent institution is reinstated as provided in § 56.123.

§ 56.122 Public disclosure of information regarding revocation.

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

§ 56.123 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Commissioner determines upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under § 56.121(c).

§ 56.124 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The Agency may also refer pertinent matters to another Federal State, or local government Agency for any action that Agency determines to be appropriate.

Clinical Investigations Which May Be Reviewed Through Expedited Review Procedures Set Forth in FDA Regulations

This notice contains a list of research activities which institutional review boards may review through the expedited review procedures set forth in FDA regulations for the protection of human research subjects. This list will be amended as appropriate and current list will be published periodically in the Federal Register.

Research activities with human subjects involving no more than minimal risk **and** involving one or more of the following categories (carried out through standard methods), may be reviewed by an IRB through the expedited review procedures authorized in 21 CFR 56.110.

(1) Collection of hair and nail clippings in a non-disfiguring manner; of deciduous teeth; and of permanent teeth if patient care indicates a need for extraction.

(2) Collection of excreta and external secretions including sweet and uncannulated saliva; of placenta at delivery; and of amniotic fluid at the time of rupture of the membrane before or during labor.

(3) Recording of data from subjects who are 18 years of age or older using non-invasive procedures routinely employed in clinical practice. This category includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, electrocardiography, electroencephalography, thermography detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. This category does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays or microwaves).

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight week period and no more often than two times per week from subjects who are 18 years of age or older and who are in good health and not pregnant.

(5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth, and the process is accomplished in accordance with accepted prophylactic techniques.

(6) Voice recordings made for research purposes such as investigations of speech defects.

(7) Moderate exercise by healthy volunteers.

(8) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

(9) Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

[Federal Register Vol 46, No. 17 Tuesday, January 27, 1981, 46 FR 8960]

**Significant Differences in FDA and HHS Regulations
for Protection of Human Subjects**

The Department of Health and Human Services (HHS) regulations [45 CFR part 46] apply to research involving human subjects conducted by the HHS or funded in whole or in part by the HHS. The Food and Drug Administration (FDA) regulations [21 CFR parts 50 and 56] apply to research involving products regulated by the FDA. Federal support is not necessary for the FDA regulations to be applicable. When research involving products regulated by the FDA is funded, supported or conducted by FDA and/or HHS, both the HHS and FDA regulations apply.

IRB Regulations

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| <p>§ 56.102 (FDA)
§ 46.102 (HHS)</p> | <p>FDA definitions are included for terms specific to the type of research covered by the FDA regulations (test article, application for research or marketing permit, clinical investigation). A definition for emergency use is provided in the FDA regulations.</p> |
| <p>§ 56.104 (FDA)
§ 46.116 (HHS)</p> | <p>FDA provides exemption from the prospective IRB review requirement for "emergency use" of test article in specific situations. HHS regulations state that they are not intended to limit the provision of emergency medical care.</p> |
| <p>§ 56.105 (FDA)
§ 46.101 (HHS)</p> | <p>FDA provides for sponsors and sponsor-investigators to request a waiver of IRB review requirements (but not informed consent requirements). HHS exempts certain categories of research and provides for a Secretarial waiver.</p> |
| <p>§ 56.109 (FDA)
§ 46.109 (HHS)
§ 46.117(c)(HHS)</p> | <p>Unlike HHS, FDA does <u>not</u> provide that an IRB may waive the requirement for signed consent when the <u>principal</u> risk is a breach of confidentiality because FDA does not regulate studies which would fall into that category of research. (Both regulations allow for IRB waiver of <u>documentation</u> of informed consent in instances of minimal risk.)</p> |
| <p>§ 56.110 (FDA)
§ 46.110 (HHS)</p> | <p>The FDA list of investigations eligible for expedited review (published in the Federal Register) does not include the studies described in category 9 of the HHS list because these types of studies are not regulated by FDA</p> |
| <p>§ 56.114 (FDA)
§ 46.114 (HHS)</p> | <p>FDA does not discuss administrative matters dealing with grants and contracts because they are irrelevant to the scope of the Agency's regulation. (Both regulations make allowances for review of multi-institutional studies.)</p> |

§ 56.115 (FDA) FDA has neither an assurance mechanism nor files of IRB membership.
§ 46.115 (HHS) Therefore, FDA does not require the IRB or institution to report changes in membership whereas HHS does require such notification.

§ 56.115(c) (FDA) FDA may refuse to consider a study in support of a research or marketing permit if the IRB or the institution refuses to allow FDA to inspect IRB records. HHS has no such provision because it does not issue research or marketing permits.

§ 56.120 — FDA regulations provide sanctions for non-compliance with regulations.
§ 56.124 (FDA)

Informed Consent Regulations

§ 50.23 (FDA) FDA, but not HHS, provides for an exception from the informed consent requirements in emergency situations. The provision is based on the Medical Device Amendments of 1976, but may be used in investigations involving drugs, devices, and other FDA regulated products in situations described in § 50.23.

§ 46.116(c)&(d) (HHS) HHS provides for waiving or altering elements of informed consent under certain conditions. FDA has no such provision because the types of studies which would qualify for such waivers are either not regulated by FDA or are covered by the emergency treatment provisions (§ 50.23).

§ 50.25(a)(5) (FDA) FDA explicitly requires that subjects be informed that FDA may inspect the records may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study. While HHS has the right to inspect records of studies it funds, it does not impose that same informed consent requirement.
§ 46.116(a)(5) (HHS)

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

**The National Commission
for the Protection of Human Subjects of
Biomedical and Behavioral Research**

April 18, 1979

Ethical Principles and Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and

statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethic of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. Respect for Persons. Respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to give forethought the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children — even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. *Justice.* Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be

scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conflict of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the

furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capabilities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited — for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence — especially where possible sanctions are involved — urge a course of action for a subject. A continuum of such announcing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk i benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons.

The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/ benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject — or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. *Selection of Subjects.* — Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/ benefit assessment, the

principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting. They can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

A Self-evaluation Checklist for IRBs

The Food and Drug Administration (FDA) has regulations that govern human subject protection aspects of research on products regulated by the Agency. In addition, other federal agencies and departments and some States have regulations that govern human subject protection. Each institution should be familiar with the laws and regulations that apply to research conducted at the institution. This checklist was developed to help institutions evaluate procedures for the protection of human subjects of research.

Through its review of IRB activities, FDA has been impressed by the variety of procedural systems that have been developed to protect human subjects. At the same time, successful IRBs make use of written procedures that, in one way or another, cover a common core of topics. This checklist is an effort to present these topics in a systematic way. Some of the items are not covered by FDA regulations (e.g., policy regarding place and time of meeting) but may be appropriate to consider when comprehensive procedures are being developed. FDA does not expect institutions to develop procedural statements responding to each item in the list. Rather, the checklist should be used to identify procedures that may be needed to meet an institution's particular situation.

Once an institution establishes its IRB structure and procedures, those procedures should be followed. FDA inspections assess compliance on both the regulatory requirements as well as on the institution's own written procedures. The institutional procedures should reflect the current processes. Therefore, policies and procedures should be reviewed on a regular basis and updated as necessary. FDA believes that when good procedures are developed, written, and followed, the rights and welfare of the subjects of research are likely to be adequately protected.

Tips on checklist use:

Three "response" columns are provided — "Yes," "No," and N/A." A "Yes" means that the institution has a policy/procedure and that it is current. A "No" may mean that a policy/procedure is lacking or needs to be updated. The "N/A" column indicates that a topic is not applicable or a procedure is not needed in the institution.

The columns may be completed by checking the appropriate box. Instead of a check-mark, some institutions record the date of issuance or revision date. Others have found it useful to record the policy/procedure number on the form. Any "No" responses indicate a need to write/revise policies and/or procedures.

References to the FDA regulations are given for additional guidance on requirements.

**A SELF-EVALUATION CHECKLIST FOR IRBs
REVIEWING STUDIES OF FDA REGULATED ARTICLES**

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE	YES	NO	N/A
I. THE INSTITUTIONAL AUTHORITY UNDER WHICH THE IRB IS ESTABLISHED AND EMPOWERED.			
II. THE DEFINITION OF THE PURPOSE OF THE IRB, i.e., THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH. ¹			
III. THE PRINCIPLES WHICH GOVERN THE IRB IN ASSURING THAT THE RIGHTS AND WELFARE OF SUBJECTS ARE PROTECTED.			
IV. THE AUTHORITY OF THE IRB.			
A. The scope of authority is defined, i.e., what types of studies must be reviewed.			
B. Authority to disapprove, modify or approve studies based upon consideration of human subject protection aspects. ²			
C. Authority to require progress reports from the investigators and oversee the conduct of the study. ³			
D. Authority to suspend or terminate a study. ⁴			
E. Authority to place restrictions on a study. ⁵			
V. THE IRB'S RELATIONSHIP TO			
A. The top administration of the institution.			
B. The other committees and department chairpersons within the institution.			
C. The research investigators.			
D. Other institutions.			
E. Regulatory agencies.			

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE

YES	NO	N/A
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VI. THE MEMBERSHIP OF THE IRB.		
A. Number of members. ⁶		
B. Qualification of members. ⁷		
C. Diversity of members (for example, representation from the community, and minority groups), including representation by ⁸		
— both men and women		
— multiple professions		
— non-scientific member(s)		
— non-affiliated member(s)		
D. Alternate members (if used).		
VII. MANAGEMENT OF THE IRB.		
A. The Chairperson		
— selection and appointment		
— length of term/service		
— duties		
— removal		
B. The IRB members.		
— selection and appointment		
— length of term/service and description of staggered rotation or overlapping of terms, if used		
— duties		
— attendance requirements		
— removal		

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE	YES	NO	N/A
C. Training of IRB Chair and members.			
— orientation			
— continuing education			
— reference materials (IRB library)			
D. Compensation of IRB members.			
E. Liability coverage for IRB members.			
F. Use of consultants. ⁹			
G. Secretarial/administrative support staff (duties).			
H. Resources (for example, meeting area, filing space, reproduction equipment, and computer access).			
I. Conflict of interest policy			
— no selection of IRB members by investigators			
— prohibition of participation in IRB deliberations and voting by investigators. ¹⁰			
VIII. FUNCTIONS OF THE IRB.			
A. Conducting initial and continuing review. ¹¹			
B. Reporting, in writing, findings and actions of the IRB to the investigator and the institution. ¹²			
C. Determining which studies require review more often than annually. ¹³			
D. Determining which studies need verification from sources other than the investigators that no material changes have occurred since previous IRB review. ¹⁴			
E. Ensuring prompt reporting to the IRB of changes in research activities. ¹⁵			
F. Ensuring that changes in approved research are not initiated without IRB review and approval except where necessary to eliminate immediate hazards. ¹⁶			

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE	YES	NO	N/A
G. Ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of			
— unanticipated problems involving risks to subjects or others ¹⁷			
— serious or continuing noncompliance with 21 CFR parts 50 and 56 or the requirements of the IRB ¹⁸			
— suspension or termination of IRB approval. ¹⁹			
H. Determining which device studies pose significant or non-significant risk.			
IX. OPERATIONS OF THE IRB.			
A. Scheduling of meetings.			
B. Pre-meeting distribution to members, for example, place and time of meeting, agenda, and study material to be reviewed.			
C. The review process			
— description of the process ensuring that 1) all members review complete study documentation (see XI.B); <u>or</u> 2) one or more "primary reviewers"/"secondary reviewers" review the complete study documentation, report to IRB and lead discussion; if other members review summary information only, these members must have access to complete study documentation			
— role of any subcommittees of the IRB			
— emergency use notification and reporting procedures ²⁰			

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE	YES	NO	N/A
<ul style="list-style-type: none"> — expedited review procedure²¹ — for approval of studies that are both minimal risk <u>and</u> on the FDA approved list (see Appendix A) — for approval of study modifications involving no more than minimal risk 			
D. Criteria for IRB approval contain all requirements of 21 CFR 56.111.			
E. Voting requirements ²²			
— quorum required to transact business			
— diversity requirements of quorum (for example requiring at least one physician when reviewing studies of FDA regulated articles)			
— percent needed to approve or disapprove a study			
— full voting rights of all members			
— no proxy votes (written or telephone)			
— prohibition against conflict-of-interest voting			
F. Further review/approval of IRB actions by others within the institution. (Override of disapprovals is prohibited.)			
G. Communication from the IRB.			
— to the investigator for additional information ²³			
— to the investigator conveying IRB decision ²⁴			
— to institution administration conveying IRB decision ²⁵			
— to sponsor of research conveying IRB decision			

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE	YES	NO	N/A
H. Appeal of IRB decisions.			
— criteria for appeal			
— to whom appeal is addressed			
— how appeal is resolved (Override of IRB disapprovals by external body/official is prohibited.)			
X. IRB RECORD REQUIREMENTS.			
A. IRB membership roster showing qualifications listed in 21 CFR 56.115(a)(5).			
B. Written procedures and guidelines. ²⁶			
C. Minutes of meetings. ²⁷			
— members present (any consultants/ guests/others shown separately)			
— summary of discussion on debated issues			
— record of IRB decisions			
— record of voting (showing votes for, against and abstentions)			
D. Retention of protocols reviewed and approved consent documents ²⁸			
E. Communications to and from the IRB. ²⁹			
F. 1) Adverse reactions reports, ³⁰ and			
2) documentation that the IRB reviews such reports.			
H. Records of continuing review. ³¹			
I. Record retention requirements. (at least 3 years after completion for FDA studies) ³²			
J. Budget and accounting records regarding acquisition and expenditure of resources.			

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE	YES	NO	N/A
K. Emergency use reports. ³³			
L. Statements of significant new findings provided to subjects. ³⁴			
XI. INFORMATION THE INVESTIGATOR PROVIDES TO THE IRB.			
A. Professional qualifications to do the research (including a description of necessary support services and facilities).			
B. Study protocol which includes/addresses ³⁵			
— title of the study.			
— purpose of the study (including the expected benefits obtained by doing the study).			
— sponsor of the study.			
— results of previous related research.			
— subject selection criteria.			
— subject exclusion criteria.			
— justification for use of any special/vulnerable subject populations (for example, the mentally impaired and children)			
— study design (including as needed, a discussion of the appropriateness of research methods).			
— description of procedures to be performed.			
— provisions for managing adverse reactions.			
— the circumstances surrounding consent procedure, including setting, subject autonomy concerns, language difficulties, vulnerable populations and other details.			
— the procedures for documentation of informed consent, including any procedures for obtaining assent from minors, using witnesses, translators and document storage.			

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE	YES	NO	N/A
— compensation to subjects for their participation.			
— any compensation for injured research subjects.			
— provisions for protection of subject's privacy.			
— extra costs to subjects for their participation in the study.			
— extra costs to third party payers because of subject's participation.			
C. Investigator's Brochure (when one exists) ³⁶			
D. The proposed informed consent document ³⁷			
— containing all requirements of 21 CFR 50.25(a)			
— containing requirements of 21 CFR 50.25(b), that are appropriate to the study.			
— meeting all requirements of 21 CFR 50.20			
— translated consent documents, as necessary considering likely subject population(s)			
E. Requests for changes in study after initiation. ³⁸			
F. Reports of unexpected adverse events. ³⁹			
G. Progress reports. ⁴⁰			
H. Final report.			
I. Institutional forms/reports			

Checklist References

1. § 56.101(a)
2. § 56.109(a)
3. § 56.108(a)(1) and § 56.109(e)
4. § 56.108(b)(3) and § 56.113
5. § 56.109(a) and § 56.113
6. § 56.107(a)
7. § 56.107(a—f)
8. § 56.107(a—f)
9. § 56.107(f)
10. § 56.107(e)
11. § 56.108(a)(1) and § 56.109(a and e)
12. § 56.108(a)(1) and § 56.109(d)
13. § 56.108(a)(2) and § 56.109(e)
14. § 56.108(a)(2)
15. § 56.108(a)(3)
16. § 56.108(a)(4) and § 56.115(a)(1)
17. § 56.108(b)(1) and § 56.115(a)(1)
18. § 56.108(b)(2)
19. § 56.108(b)(3) and § 56.113
20. § 56.104(c)
21. § 56.110(a—c)
22. § 56.108(c) and § 56.107(e—f)
23. § 56.109(a) and § 56.115(a) (4)
24. § 56.108(a)(1) and § 56.109(d)
25. § 56.109(d)
26. § 56.108(a—b) and § 56.115(a)(6)
27. § 56.115(a)(2)
28. § 56.115(a)(1)
29. § 56.115(a)(4)
30. § 56.108(a) and § 56.115(a)(1 and 4)
31. § 56.115(a)(3)
32. § 56.115(b)
33. § 56.115(a)(4) and § 56.104(c)
34. § 56.115(a)(7)
35. § 56.103(a) and § 56.115(a)(1)
36. § 56.111(a)(2) § 56.115(a)(1) and § 312.55
37. § 56.111(a)(4—5) and § 56.111(a)(1)
38. § 56.108(a)(4) and § 56.115(a)(3—4)
39. § 56.115(a)(3—4) § 56.115(b)(1) and § 56.113
40. § 56.115(a)(1 and 3—4)

FDA District Offices

Food and Drug Administration (FDA) District Offices are located throughout the country. IRB and other inspections are conducted by FDA District Office personnel. Problems or questions related to FDA regulated products or IRB inspections may be directed to the Director of the Investigations Branch (unless otherwise indicated), or the Bioresearch Monitoring Program Coordinator, in the appropriate District Office.

<u>District</u>	<u>States Served</u>
ATLANTA District 60 Eighth Street, N.E. Atlanta, Georgia 30309 (404) 347-3151	Alabama, Georgia, North Carolina, South Carolina
BALTIMORE District 900 Madison Avenue Baltimore, Maryland 21201 (410) 962-4099	District of Columbia, Maryland, Virginia, West Virginia
BOSTON District One Montvale Avenue Stoneham, Massachusetts 02180 (617) 279-1675, EXT 128	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont
NEW YORK District 850 Third Avenue Brooklyn, New York 11232 (516) 921-2035	New York (southern)
BUFFALO District 599 Delaware Avenue Buffalo, New York 14202 (716) 846-4467 EXT 3142	New York (upstate)

District

States Served

CHICAGO District
300 S. Riverside Plaza
5th Floor, Suite 550 South
Chicago, Illinois 60606
(312) 353-5863 EXT 132

Illinois

CINCINNATI District
1141 Central Parkway
Cincinnati, Ohio 45202-1097
(513) 684-3501 EXT 130

Ohio

DALLAS District
3310 Live Oak St.
Dallas, Texas 75204
(214) 655-5310 EXT 504

Oklahoma, Texas

DENVER District
P.O. Box 25087
6th and Kipling Sts.
Denver Federal Center
Denver, Colorado 80225-0087
(303) 236-3051

Colorado, Montana, New Mexico,
North Dakota, South Dakota,
Utah, Wyoming

DETROIT District
1560 East Jefferson
Detroit Michigan 48207
(313) 226-2253 EXT 105

Indiana, Michigan

KANSAS CITY District
11630 West 80th St.
Lenexa, Kansas 66214
(913) 752-2423

Iowa, Kansas, Missouri, Nebraska

<u>District</u>	<u>States Served</u>
<p>LOS ANGELES District 19900 MacArthur Blvd., Suite 300 Irvine, California 92715 (714) 798-7769</p>	<p>Arizona, California (southern)</p>
<p>MINNEAPOLIS District 240 Hennepin Avenue Minneapolis, Minnesota 55401 (612) 334-4100 EXT 162</p>	<p>Minnesota, Wisconsin</p>
<p>NASHVILLE District 297 Plus Park Boulevard Nashville, Tennessee 37217 (615) 781-5374 EXT. 111</p>	<p>Kentucky, Mississippi, Tennessee</p>
<p>NEWARK District Waterview Corp. Center 10 Waterway Bend, 3rd Floor Parsippany, New Jersey 07054 (201) 645-6230</p>	<p>New Jersey</p>
<p>NEW ORLEANS District 4298 Elysian Fields Avenue New Orleans, Louisiana 70122 (504) 589-7181 EXT 111</p>	<p>Arkansas, Louisiana</p>
<p>ORLANDO District 7200 Lake Ellenor Drive Suite 120 P. O. Box 118 Orlando, Florida 32809 (407)648-6913</p>	<p>Florida</p>
<p>PHILADELPHIA District 2nd and Chestnut Streets Room 900 Philadelphia, Pennsylvania 19106 (215) 362-0740</p>	<p>Delaware, Pennsylvania</p>

District

States Served

SEATTLE District
22201 23rd Drive S.E.
P.O. Box 3012
Bothell, Washington 98041
(206) 483-4941

Alaska, Idaho, Oregon, Washington

SAN FRANCISCO District
1431 Harbor Bay Pkwy.
Alameda, California 94502
(510) 337-6733

California (northern), Hawaii, Nevada

SAN JUAN District
#466 Fernandez Juncos Avenue
Stop 8 1/2
San Juan, Puerto Rico 00901-3223
(809) 729-6854

Puerto Rico

Important FDA Phone Numbers for IRBs and Clinical Investigators

GENERAL QUESTIONS

- Call **301-827-1699** (Health Assessment Policy Staff, Office of Health Affairs, Office of the Commissioner) for:
 - ▶ Questions about or suggestions for these Information Sheets
 - ▶ General questions about FDA human subject protection regulations [21 CFR parts 50 and 56]
 - ▶ Reports made pursuant to 21 CFR 56.108(b) and 56.113 including:
 - unanticipated problems involving risks to subjects 21 CFR 56.108(b)(1);
 - serious or continuing noncompliance (by an investigator) with FDA regulations or with the IRB's determinations 21 CFR 56.108(b)(2); or
 - suspension or termination of IRB approval of a protocol 21 CFR 56.108(b)(3).
- Call **301-827-1685** (Health Assessment Policy Staff) for:
 - ▶ Copies of the FDA human subject protection regulations [21 CFR parts 50 and 56] and general interpretative documents (e.g., Information Sheets).

BIOLOGICS QUESTIONS — Center for Biologics Evaluation and Research (CBER)

- Call **301-594-2000** (Office of Congressional and Public Affairs, CBER) for questions about:
 - ▶ Whether an investigational new drug application (IND) is required for a biological drug study
 - ▶ General questions about biological products and applications
- Call **301-594-1077** (Bioresearch Monitoring Branch, Office of Compliance, CBER) for questions about:
 - ▶ Human subject protection regulations pertaining to biologics [21 CFR parts 50, 56, 312]
 - ▶ CBER-assigned IRB Inspections (e.g., "483s" and "Warning Letters")
- Questions about specific products or classes of products should be directed to one of the following offices:
 - ▶ Office of Therapeutics Research and Review (301-594-5636)
 - ▶ Office of Vaccines Research and Review (301-594-2090)
 - ▶ Office of Blood Research and Review (301-594-2012)

DRUG QUESTIONS — Center for Drug Evaluation and Research (CDER)

- Call **301-594-1012** (Executive Secretariat, CDER) for questions about:
 - ▶ The legal status of a test article (e.g., whether an article is a "drug", or whether a drug is approved for marketing)
 - ▶ Whether research with a marketed drug in a particular study "significantly increases the risks (or decreases the acceptability of the risks)" and therefore requires an IND. [21 CFR 312.2(b)(iii)]
- Call **301-827-0577** or **800-342-2722** (Executive Secretariat, CDER automated fax system)
 - ▶ for copies of CDER documents (e.g., IND information).
- Call **301-827-0531** (Document Management and Reporting Branch, CDER) for questions about:
 - ▶ Whether an investigational new drug application (IND) is required for a drug study
- Call **301-594-1026** (Institutional Review Branch, Office of Compliance, CDER) for questions about:
 - ▶ Human subject protection regulations pertaining to drugs [21 CFR parts 50, 56, 312 and 361]
 - ▶ CDER-assigned IRB Inspections (e.g., "483s" and "Warning Letters")
 - ▶ Reports made pursuant to 21 CFR 56.108(b) and 56.113
- Call **301-594-1032** (Clinical Investigations Branch, Office of Compliance, CDER) for questions about:
 - ▶ FDA regulations pertaining to clinical investigators [21 CFR part 312]
 - ▶ Clinical Investigator Inspections (e.g., "483s" and "Warning Letters")

DEVICE QUESTIONS — Center for Device Evaluation and Radiologic Health (CDRH)

- Call **800-638-2041** (Division of Small Manufacturers Assistance, CDRH) for copies of publications pertaining to device studies.
- Call **301-594-1190** (Program Operation Staff, CDRH) for questions about:
 - ▶ Whether an investigational device exemption (IDE) is required for a device study
 - ▶ Whether a device is deemed "significant risk" or "non-significant risk"
 - ▶ Whether a device is approved for marketing
- Call **301-594-4718** (Bioresearch Monitoring Branch, Office of Compliance, CDRH) for questions about:
 - ▶ Human subject protection regulations pertaining to devices [21 CFR parts 50, 56, 812, 813 and 814]
 - ▶ CDRH-assigned IRB Inspections (e.g., "483s" and "Warning Letters")

OTHER

- Call (modem) **800-222-0185** (FDA computer Bulletin Board) for:
[settings=1200/2400 baud,8,N,1 login name = "BBS"]
 - ▶ FDA Federal Register notices, news releases, product approval lists, and selected consumer articles.

- Call **301-496-7041** (Office for Protection from Research Risks - OPRR) for:
 - ▶ Guidance about "Assurances" with the Department of Health and Human Services (HHS)
 - ▶ questions regarding 45 CFR part 46

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