



Guidance for Institutional Review Boards and Clinical Investigators 1998 Update

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This document represents the agency's current guidance on protection of human subjects of research. It is published as Level 2 guidance in accordance with the FDA "Good Guidance Practices." It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. However, in many places throughout this document, a specific regulation is cited and the requirements of the regulation are reiterated. The regulations are enforceable.

This guidance document represents an update of the October 1995 revision of the Information Sheets. Comments and suggestions may be submitted at any time for Agency consideration. Comments received after publication may not be acted upon by the Agency until the document is next revised.

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U.S. Food and Drug Administration

INFORMATION SHEETS

Guidance for Institutional Review Boards and Clinical Investigators 1998 Update

Frequently Asked Questions

The following is a compilation of answers to questions asked of FDA regarding the protection of human subjects of research. For ease of reference, the numbers assigned to the questions are consecutive throughout this section. These questions and answers are organized as follows.

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I. IRB Organization

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 protection of the rights and welfare of human subjects of research.

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 studies of FDA regulated products must be established and operated in compliance with 21 CFR part 56.

4. 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 project 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.

5. 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 the information sheet entitled "Significant Differences in HHS and FDA Regulations for the protection of Human Subjects."

6. 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, FDA regulations permit an institution without an IRB to arrange for an "outside" IRB to be responsible for initial and continuing review of studies conducted at the non-IRB institution. Such arrangements should be documented 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."

7. 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 routinely conducts these reviews, the IRB policies should authorize such reviews and the process should be described in the IRB's written procedures. A hospital IRB may review outside studies on an individual basis when the minutes clearly show the members are aware of where the study is to be conducted and when the IRB possesses appropriate knowledge about the study site(s).

8. May IRB members be paid for their services?

The FDA regulations do not preclude a member from being compensated for services rendered. Payment to IRB members should not be related to or dependent upon a favorable decision. Expenses, such as travel costs, may also be reimbursed.

9. 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.

10. 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.

11. 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].

II. IRB Membership

12. 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 may be diminished and could hinder the review procedure. Even greater disruptions may result if this person is chairperson of the IRB.

13. 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"

14. When IRB members cannot attend a convened meeting, may they send someone from their department to vote for them?

No. Alternates who are formally appointed and listed in the membership roster may substitute, but ad hoc substitutes are not permissible as members of an IRB. However, a member who is unable to be present at the convened meeting may participate by video-conference or conference telephone call, when the member has received a copy of the documents that are to be reviewed at the meeting. Such members may vote and be counted as part of the quorum. If allowed by IRB procedures, ad hoc substitutes may attend as consultants and gather information for the absent member, but they may not be counted toward the quorum or participate in either deliberation or voting with the board. The IRB may, of course, ask questions of this representative just as they could of any non-member consultant. Opinions of the absent members that are transmitted by mail, telephone, telefax or e-mail may be considered by the attending IRB members but may not be counted as votes or the quorum for convened meetings.

15. 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.

16. 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. Therefore, frequent absence of all non-affiliated members is not acceptable to FDA. 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.

17. Which IRB members should be considered to be scientists and non-scientists?

21 CFR 56.107(c) requires at least one member of the IRB to have primary concerns in the scientific area and at least one to have primary concerns in the non-scientific area. Most IRBs include physicians and Ph.D. level physical or biological scientists. Such members satisfy the requirement for at least one scientist. When an IRB encounters studies involving science beyond the expertise of the members, the IRB may use a consultant to assist in the review, as provided by 21 CFR 56.107(f).

FDA believes the intent of the requirement for diversity of disciplines was to include members who had little or no scientific or medical training or experience. Therefore, nurses, pharmacists and other biomedical health professionals should not be regarded to have "primary concerns in the non-scientific area." In the past, lawyers, clergy and ethicists have been cited as examples of persons whose primary concerns would be in non-scientific areas.

Some members have training in both scientific and non-scientific disciplines, such as a J. D., R.N. While such members are of great value to an IRB, other members who are unambiguously non-scientific should be appointed to satisfy the non-scientist requirement.

III. IRB Procedures

18. The FDA regulations [21 CFR 56.104(c)] exempt an emergency use of a test article from prospective IRB review, however, "... any 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 be used again, 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.

19. 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 by the IRB in the evaluation and approval of related studies.

20. 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 list is reproduced as Appendix D of this document.

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.

On November 9, FDA published in the *Federal Register* concurrently with OPRR a new Expedited Review List. The entire *Federal Register* publication, including the FDA preamble, was published on pages 60353 - 60356 of the November 9, 1998 *Federal Register* and is available on the World Wide Web at the Dockets Management Page of the FDA home Page at <http://www.fda.gov/ohrms/dockets/98fr/110998b.txt> (or use suffix ".pdf" for Adobe Acrobat version) or alternatively at the Government Printing Office site at http://www.access.gpo.gov/su_docs/fedreg/a981109c.html and scroll down to Food and Drug Administration.

21. 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 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.

22. Are sponsors allowed access to IRB written procedures, minutes and membership rosters?

The FDA regulations do not require public or sponsor access to IRB records. However, FDA does not prohibit the sponsor from requesting IRB records. The IRB and the institution may establish a policy on whether minutes or a pertinent portion of the minutes are provided to sponsors.

Because of variability, each IRB also needs to be aware of State and local laws regarding access to IRB records.

23. 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, much of the 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 adequately evaluated without review of the results of previous animal and human studies, which are summarized in the investigator's brochure.

There is no specific regulatory requirement that the Investigator's Brochure be submitted to the IRB. There are regulatory requirements for submission of information which normally is included in the Investigator's Brochure. It is common that the Investigator's Brochure is submitted to the IRB, and the IRB may establish written procedures which require its submission. Investigator's Brochures may be part of the investigational plan that the IRB reviews when reviewing medical device studies.

24. To what extent is the IRB expected to actively audit and monitor the performance of the investigator with respect to human subject protection issues?

FDA does not expect IRBs to routinely observe consent interviews, observe the conduct of the study or review study records. However, 21 CFR 56.109(f) gives the IRB the authority to observe, or have a third party observe, the consent process and the research. When and if the IRB is concerned about the conduct of the study or the process for obtaining consent, the IRB may consider whether, as part of providing adequate oversight of the study, an active audit is warranted.

25. How can a sponsor know whether an IRB has been inspected by FDA, and the results of the inspection?

The Division of Scientific Investigations, Center for Drug Evaluation and Research, maintains an inventory of the IRBs that have been inspected, including dates of inspection and classification. The Division recently began including the results of inspections assigned by the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health. This information is available through Freedom of Information Act (FOIA) procedures. Once an investigational file has been closed, the correspondence between FDA and the IRB and the narrative inspectional report are also available under FOI.

26. If an IRB disapproves a study submitted to it, and it is subsequently sent to another IRB for review, should the second IRB be told of the disapproval?

Yes. When an IRB disapproves a study, it must provide a written statement of the reasons for its decision to the investigator and the institution [21 CFR 56.109(e)]. If the study is submitted to a second IRB, a copy of this written statement should be included with the study documentation so that it can make an informed decision about the study. 21 CFR 56.109(a) requires an IRB to "... review ... all research activities [emphasis added]" The

FDA regulations do not prohibit submission of a study to another IRB following disapproval. However, all pertinent information about the study should be provided to the second IRB.

27. May an independent IRB review a study to be conducted in an institution with an IRB?

Generally, no. Most institutional IRB have jurisdiction over all studies conducted within that institution. An independent IRB may become the IRB of record for such studies only upon written agreement with the administration of the institution or the in-house IRB.

28. Could an IRB lose its quorum when members with a conflict of interest leave the room for deliberation and voting on a study?

Yes. "The quorum is the count of the number of members present. If the number present falls below a majority, the quorum fails. The regulations only require that a member who is conflicted not participate in the deliberations and voting on a study on which he or she is conflicted. The IRB may decide whether an individual should remain in the room."

29. Does FDA expect the IRB chair to sign the approval letters?

FDA does not specify the procedure that IRBs must use regarding signature of the IRB approval letter. The written operating procedures for the IRB should outline the procedure that is followed.

30. Does FDA prohibit direct communication between sponsors and IRBs?

It is important that a formal line of communication be established between the clinical investigator and the IRB. Clinical investigators should report adverse events directly to the responsible IRB, and should send progress reports directly to that IRB. However, FDA does not prohibit direct communication between the sponsor and the IRB, and recognizes that doing so could result in more efficient resolution of some problems.

FDA does require direct communication between the sponsors and the IRBs for certain studies of medical devices and when the 21 CFR 50.24 informed consent waiver has been invoked. Sponsors and IRBs are required to communicate directly for medical device studies under 21 CFR 812.2, 812.66 and 812.150(b). For informed consent waiver studies, direct communication between sponsors and IRBs is required under 21 CFR 50.24(e), 56.109(e), 56.109(g), 312.54(b), 312.130(d), 812.38(b)(4) and 812.47(b).

IV. IRB Records

31. Are annual IRB reviews required when all studies are reviewed by the IRB each quarter?

The IRB records for each study's initial and continuing review should note the frequency (not to exceed one year) for the next continuing review in either months or other conditions, such as after a particular number of subjects are enrolled.

An IRB may decide, to review all studies on a quarterly basis. If every quarterly report contains sufficient information for an adequate continuing review and is reviewed by the IRB under procedures that meet FDA requirements for continuing review, FDA would not require an additional "annual" review.

32. 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?

Yes. The IRB should receive and review all research activities [21 CFR 56.109(a)]. The documents reviewed should include the complete documents received from the clinical investigator, such as the protocol, the investigator's brochure, a sample consent document and any advertising intended to be seen or heard by prospective study subjects. Some IRBs 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)]. However, when the IRB makes changes, such as in the wording of the informed consent document, only the finally approved copy needs to be retained in the IRB records.

33. What IRB records are required for studies that are approved but never started?

When an IRB approves a study, continuing review should be performed at least annually. All of the records listed in 21 CFR 56.115(a)(1) - (4) are required to be maintained. The clock starts on the date of approval, whether or not subjects have been enrolled. Written progress reports should be received from the clinical investigator for all studies that are in approved status prior to the date of expiration of IRB approval. If subjects were never enrolled, the clinical investigator's progress report would be brief. Such studies may receive continuing IRB review using expedited procedures. If the study is finally canceled without subject enrollment, records should be maintained for at least three years after cancellation [21 CFR 56.115(b)].

V. Informed Consent Process

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

No. The consent document 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 agreement 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.

35. May informed consent be obtained by telephone from a legally authorized representative?

A verbal approval does not satisfy the 21 CFR 56.109(c) requirement for a signed consent document, as outlined in 21 CFR 50.27(a). However, it is acceptable to send the informed consent document to the legally authorized representative (LAR) by facsimile and conduct the consent interview by telephone when the LAR can read the consent as it is discussed. If the LAR agrees, he/she can sign the consent and return the signed document to the clinical investigator by facsimile.

36. 21 CFR 50.27(a) 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 regulation does not require the copy of the form given to the subject to be a copy of the document with the subject's signature, although this is encouraged. 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 to participate in the study, as well as providing a continuing reference for items such as scheduling of procedures and emergency contacts.

37. 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 subjects. The IRB should also review the "process" for conducting the consent interviews, i.e., the circumstances under which consent will be obtained, who will obtain consent, and so forth.

38. 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. FDA generally will not copy a subject's name during the inspection 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 document 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.

39. Who should be present when the informed consent interview is conducted?

FDA does not require a third person to witness the consent interview unless the subject or representative is not given the opportunity to read the consent document before it is signed, see 21 CFR 50.27(b). The person who conducts the consent interview should be knowledgeable about the study and able to answer questions. FDA does not specify who this individual should be. Some sponsors and some IRBs require the clinical investigator to personally conduct the consent interview. However, if someone other than the clinical investigator conducts the interview and obtains consent, this responsibility should be

formally delegated by the clinical investigator and the person so delegated should have received appropriate training to perform this activity.

40. How do you obtain informed consent from someone who speaks and understands English but cannot read?

Illiterate persons who understand English may have the consent read to them and "make their mark," if appropriate under applicable state law. The 21 CFR 50.27(b)(2) requirements for signature of a witness to the consent process and signature of the person conducting consent interview must be followed, if a "short form" is used. Clinical investigators should be cautious when enrolling subjects who may not truly understand what they have agreed to do. The IRB should consider illiterate persons as likely to be vulnerable to coercion and undue influence and should determine that appropriate additional safeguards are in place when enrollment of such persons is anticipated, see 21 CFR 56.111(b).

41. Must a witness observe the entire consent interview or only the signature of the subject?

FDA does not require the signature of a witness when the subject reads and is capable of understanding the consent document, as outlined in 21 CFR 50.27(b)(1). The intended purpose is to have the witness present during the entire consent interview and to attest to the accuracy of the presentation and the apparent understanding of the subject. If the intent of the regulation were only to attest to the validity of the subject's signature, witnessing would also be required when the subject reads the consent.

42. Should the sponsor prepare a model informed consent document?

Although not required by the IND regulations, the sponsor provides a service to the clinical investigator and the IRB when it prepares suggested study-specific wording for the scientific and technical content of the consent document. However, the IRB has the responsibility and authority to determine the adequacy and appropriateness of all of the wording in the consent, see 21 CFR 56.109(a), 111(a)(4) and 111(a)(5). If an IRB insists on wording the sponsor cannot accept, the sponsor may decide not to conduct the study at that site. For medical device studies that are conducted under an IDE, copies of all forms and informational materials to be provided to subjects to obtain informed consent must be submitted to FDA as part of the IDE, see 21 CFR 812.25(g).

43 . Is the sponsor required to review the consent form approved by the IRB to make sure all FDA requirements are met?

For investigational devices, the informed consent is a required part of the IDE submission.

It is, therefore, approved by FDA as part of the IDE application. When an IRB makes substantive changes in the document, FDA reapproval is required and the sponsor is necessarily involved in this process.

FDA regulations for other products do not specifically require the sponsor to review IRB approved consent documents. However, most sponsors do conduct such reviews to assure the wording is acceptable to the sponsor.

44. Are there alternatives to obtaining informed consent from a subject?

The regulations generally require that the investigator obtain informed consent from subjects. Investigators also may obtain informed consent from a legally authorized representative of the subject. FDA recognizes that a durable power of attorney might suffice as identifying a legally authorized representative under some state and local laws. For example, a subject might have designated an individual to provide consent with regard to health care decisions through a durable power of attorney and have specified that the individual also has the power to make decisions on entry into research. FDA defers to state and local laws regarding who is a legally authorized representative. Therefore, the IRB should assure that the consent procedures comply with state and local laws, including assurance that the law applies to obtaining informed consent for subjects participating in research as well as for patients who require health care decisions."

Alternatives 1 and 2 are provided for in the regulations and are appropriate. Alternative 3 allows a designated individual to provide consent for a patient with regard to health care decisions and is appropriate when it specifically includes entry into research. FDA defers to state and local laws regarding substituted consent. Therefore, the IRB must assure itself that the substituted consent procedures comply with state and local law, including assurance the law applies to obtaining informed consent for subjects participating in research as well as for patients who require health care decisions.

45. When should study subjects be informed of changes in the study?

Protocol amendments must receive IRB review and approval before they are implemented, unless an immediate change is necessary to eliminate an apparent hazard to the subjects (21 CFR 56.108(a)(4)). Those subjects who are presently enrolled and actively participating in the study should be informed of the change if it might relate to the subjects' willingness to continue their participation in the study (21 CFR 50.25(b)(5)). FDA does not require reconsenting of subjects that have completed their active participation in the study, or of subjects who are still actively participating when the change will not affect their participation, for example when the change will be implemented only for subsequently enrolled subjects.

VI. Informed Consent Document Content

46. 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)].

47. Does FDA require the informed consent document to 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. [For research supported by DHHS, the additional protections at 45 CFR 46 Subpart D are also required. The Subpart D regulations provide appropriate guidance for all other pediatric studies.]

48. Does FDA require the signature of children on informed 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.

49. Who should be listed on the consent as the contact to answer questions?

21 CFR 50.25(a)(7) requires contacts for questions about the research, the research subject's rights and in case of a research-related injury. It does not specify whom to contact. The same person may be listed for all three. However, FDA and most IRBs believe it is better to name a knowledgeable person other than the clinical investigator as the contact for study subject rights. Having the clinical investigator as the only contact may inhibit subjects from reporting concerns and/or possible abuses.

50. May the "compensation" for participation in a trial offered by a sponsor include a coupon good for a discount on the purchase price of the product once it has been approved for marketing?

No. This presumes, and inappropriately conveys to the subjects, a certainty of favorable outcome of the study and prompt approval for marketing. Also, if the product is approved, the coupon may financially coerce the subject to insist on that product, even though it may not be the most appropriate medically.

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

The signed informed consent document is the written record of the consent interview. Study subjects are given a copy of the consent to be used as a reference document to reinforce their understanding of the study and, if desired, to consult with their physician or family members about the study.

In order to meet the requirements of 21 CFR 50.20, the consent document must be in language understandable to the subject. When the prospective subject is fluent in English, and the consent interview is conducted in English, the consent document should be in English. However, when the study subject population includes non-English speaking people so that the clinical investigator or the IRB anticipates that the consent interviews are likely to be conducted in a language other than English, the IRB should assure that a translated consent form is prepared and that the translation is accurate.

A consultant may be utilized to assure that the translation is correct. A copy of the translated consent document must be given to each appropriate subject. While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the consent document may not be substituted for a written translation.

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

52. Is it acceptable for the consent document to say specimens are "donated"?

What about a separate donation statement? It would be acceptable for the consent to say that specimens are to be used for research purposes. However, the word "donation" implies abandonment of rights to the "property". 21 CFR 50.20 prohibits requiring subjects to waive or appear to waive any rights as a condition for participation in the study. Whether or not the wording is contained in "the actual consent form" is immaterial. All study-related documents must be submitted to the IRB for review. Any separate "donation" agreement is regarded to be part of the informed consent documentation, and must be in compliance with 21 CFR 50.

53. Do informed consent forms have to justify fees charged to study subjects?

FDA does not require the consent to contain justification of charges.

VII. Clinical Investigations

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

Yes. 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).

55. 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(b)(1), 361.1, 601.2, and 812.2]. Also, see the information sheet entitled "'Off-label' and Investigational Use of Marketed Drugs and Biologics" for more information.

VIII. General Questions

56. 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 Drug Information Branch, Center for Drug Evaluation and Research (CDER), at (301) 827-4573.

For a biological blood product, contact the Office of Blood Research and Review, Center for Biologics Evaluation and Research (CBER), at 301-827-3518. For a biological vaccine product, contact the Office of Vaccines Research and Review at 301-827-0648. For a biological Therapeutic product, contact the Office of Therapeutics Research and Review, CBER, at 301-594-2860.

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.

57. 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.

58. Does a treatment IND/IDE [21 CFR 312.34/812.36] require prior IRB approval?

Test articles given to human subjects under a treatment IND/IDE 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."

59. How have the FDA policies on enrollment 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.

60. 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: (a) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them; (b) 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** (c) 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," "Frequently Asked Questions about IRB Review of Medical Devices" and "Significant Risk and Nonsignificant Risk Medical Device Studies."

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

Yes. 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.

62. What are the IRB's general obligations towards intraocular lens (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.

63. Considering the large number of 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.

64. Must a manufacturer comply with 21 CFR 50 and 56 when conducting trials within its own facility using employees as subjects?

Yes. This situation represents a prime example of a vulnerable subject population.

65. Do Radioactive Drug Research Committees (RDRCs) have authority to approve initial clinical studies in lieu of an IND?

No. An IND is required when the purpose of the study is to determine safety and efficacy of the drug or for immediate therapeutic, diagnostic or similar purposes. RDRCs are provided for in 21 CFR 361.1 *Radioactive Drugs for Certain Research Uses*. Radioactive drugs (as defined in 21 CFR 310.3(n)) may be administered to human research subjects without obtaining an IND when the purpose of the research project is to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labelled drug or regarding human physiology, pathophysiology, or biochemistry. Certain basic research studies, e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of 21 CFR 361.1. Such basic research studies must be conducted under the conditions set forth in 21 CFR 361.1(b).

All RDRC approved studies must also be approved by an IRB prior to initiation of the studies.

66. Does FDA approve RDRCs?

Yes. An RDRC must obtain and maintain approval by the Food and Drug Administration, as outlined in 21 CFR 361.1(c). RDRCs must register with the Division of Medical Imaging and Radiopharmaceutical Drug Products, (HFD-160), Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, Maryland 20857. The FDA contact for compliance issues is the Human Subject Protection Team (HFD-343), CDER, FDA, 7520 Standish Place, Rockville, MD 20855.

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U.S. Food and Drug Administration

INFORMATION SHEETS

Guidance for Institutional Review Boards and Clinical Investigators 1998 Update

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]. 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 center 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"](#)

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U.S. Food and Drug Administration

INFORMATION SHEETS

Guidance for Institutional Review Boards and Clinical Investigators 1998 Update

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 or non-institutional 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) for each study site. 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 with a site visit by a representative of the IRB, by appointing an IRB member from that community, or by having a consultant from the community advise the IRB, either prior to or during the deliberations. If travel is not feasible, participation in the IRB meeting can be by video-conference or conference telephone call, or by using other technologies that allow for real-time conversational interaction between the remote member and the members at the convened location. All IRB members should receive an advance copy of the documents that are to be reviewed at the meeting. 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.

IRB Jurisdiction

When an institution has a local IRB, the written procedures of that IRB or of the institution should define the scope of studies subject to review by that IRB. A non-local IRB may not become the IRB of record for studies within that defined scope unless the local IRB or the administration of the institution agree. Any agreement to allow review by a non-local IRB should be in writing.

[Also see FDA Information Sheet: "Cooperative Research."](#)

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U.S. Food and Drug Administration**INFORMATION SHEETS****Guidance for Institutional Review Boards and Clinical Investigators
1998 Update**

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(f)];
- 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)];
- ensuring that changes in approved research are promptly reported to, and approved by, the IRB [21 CFR 56.108(a)(3-4)]; and
- 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 since the previous IRB review. 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 progress of 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. 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. However, 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, the IRB may permit the study to continue for the brief time required to complete the review process.

When study approval is terminated by the IRB, 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, 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 Adverse Reactions and Unexpected Events

a. Written Procedures

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. The level and promptness of review may depend upon factors such as the seriousness of the event, whether the event is described in the study protocol and consent and whether the event occurred at a location for which the IRB is the IRB of record. The written procedures may include a brief form to be completed by the principal investigator when an adverse event occurs, asking for his/her opinion as to whether the event was related to the study and other information to aid the IRB in an appropriate and efficient review of the event.

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.

b. Process

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.

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U.S. Food and Drug Administration

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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 generally 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(e)]. This correspondence should be made available to the sponsor by the clinical investigator. In the Agency's view, this required documentation provides the sponsor with reasonable assurance that an IRB complies with 21 CFR part 56 and that it will be responsible for initial and continuing review of the study. 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 requires 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

"A sponsor's preliminary determination that a medical device study presents an NSR is subject to IRB approval." 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.

Acceptance of Foreign Clinical Studies

The Food and Drug Administration (FDA) may accept clinical studies conducted outside the United States in support of safety and efficacy claims for drugs, biological products and medical devices.

All drug, biologic and device studies conducted under an Investigational New Drug (IND) or Investigational Device Exemption (IDE) are governed by the FDA informed consent and IRB requirements. [See 21 CFR part 312 IND regulations and 21 CFR part 812 IDE regulations.]

Under 21 CFR 312.120(c)(1), FDA will accept a foreign clinical study involving a drug or biological product not conducted under an IND only if the study conforms to whichever of

the following provides greater protection of the human subjects:

- the ethical principles contained in the 1989 version of the Declaration of Helsinki, or
- the laws and regulations of the country in which the research was conducted.

Under 21 CFR 814.15(a) and (b), FDA will accept a foreign clinical study involving a medical device not conducted under an IDE only if the study conforms to whichever of the following provides greater protection of the human subjects:

- the ethical principles contained in the 1983 version of the Declaration of Helsinki, or
- the laws and regulations of the country in which the research was conducted.

Also see these FDA Information Sheets:

["Non-Local IRB Review"](#)

["Waiver of IRB Requirements for Drug and Biologic Studies"](#)

"Informed Consent and the Clinical Investigator"

Declaration of Helsinki--the [1983](#) and [1989](#) versions

Charging for Investigational Products

This information sheet discusses FDA policy on allowing charges for the test articles in clinical investigations.

Decisions concerning charging subjects for investigational products are guided by professional ethics, institutional policies, and FDA regulations. 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)]. IRBs should ensure that the informed consent documents outline any additional costs that will be billed to study subjects or their insurance company as a result of participation in the study. IRBs should also ensure that any such charges are appropriate and equitable.

Because the regulations governing drugs and biologics vary from those governing medical devices, the Agency's position on charging for the test articles will be discussed separately. FDA does not prohibit charging the subjects 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

The Investigational New Drug (IND) regulations [21 CFR 312.7(d)] permit a sponsor to charge for an investigational drug or biologic that has not been approved for marketing, only under the conditions outlined below. 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.

(i) 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 [21 CFR 312.7(d)(1)].

(ii) 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, as outlined in 21 CFR 312.34 and 312.35, 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 [21 CFR 312.7(d)(2)].

There is no specific regulatory requirement that the Investigator's Brochure be submitted to the IRB. There are regulatory requirements for submission of information which normally is included in the Investigator's Brochure. It is common that the Investigator's Brochure is

submitted to the IRB, and the IRB may establish written procedures which require its submission. Investigator's Brochures may be part of the investigational plan that the IRB reviews when reviewing medical device studies.

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 and material that investigators propose to use to recruit subjects.

A. Media Advertising:

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study, is not in and of itself, an objectionable practice. Direct advertising includes, but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects. **Not included** are: (1) communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), (2) news stories and (3) publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.

IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements should be reviewed and approved by the IRB as part of the package for initial review. However, when the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to the ongoing study. When such advertisements are easily compared to the approved consent document, the IRB chair, or other designated IRB member, may review and approve by expedited means, as provided by 21 CFR 56.110(b)(2). When the IRB reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

FDA expects IRBs to review the advertising to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence. [21 CFR 50.20, 50.25, 56.111(a)(3), 56.111(b) and 812.20 (b)(11).]

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 wording. The review of the final taped message prepared from IRB-approved text may be accomplished through expedited procedures. The IRB may wish to caution the clinical investigators to obtain IRB approval of message text prior to taping, in order to avoid re-taping because of inappropriate wording.

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" leads study subjects to believe they will be receiving newly improved 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. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

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 all 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.

B. Receptionist Scripts.

The first contact prospective study subjects make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects. In some cases personal and sensitive information is gathered about the individual. The IRB should have assurance that the information will be appropriately handled. A simple statement such as "confidentiality will be maintained" does not adequately inform the IRB of the procedures that will be used.

Examples of issues that are appropriate for IRB review: What happens to personal information if the caller ends the interview or simply hangs up? Are the data gathered by a marketing company? If so, are names, etc. sold to others? Are names of non-eligibles maintained in case they would qualify for another study? Are paper copies of records shredded or are readable copies put out as trash? The acceptability of the procedures would depend on the sensitivity of the data gathered, including; personal, medical and financial.

Also see these FDA Information Sheets:

["A Guide to Informed Consent Documents"](#)

["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 health benefits to subjects are 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 credit for 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 as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Also see these FDA Information Sheets:

["A Guide to Informed Consent Documents"](#)

["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 clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out). When wash-out is done in anticipation of or in preparation for the research, it is part of the 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 clinical screening procedures that is performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility 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.

Clinical screening procedures for research eligibility are considered part of the subject selection and recruitment process and, therefore, require IRB oversight. If the screening qualifies as a minimal risk procedure [21 CFR 56.102(i)], the IRB may choose to use expedited review procedures [21 CFR 56.110]. 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 then be followed.

Certain clinical tests, such as for HIV infection, may have State requirements regarding (1) the information that must be provided to the participant, (2) which organizations have access to the test results and (3) whether a positive result has to be reported to the health department. Prospective subjects should be informed of any such requirements and how an unfavorable test result could affect employment or insurance before the test is conducted. The IRB may wish to confirm that such tests are required by the protocol of the study.

Also see this FDA Information Sheet:

["Recruiting Study Subjects"](#)

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Consent Document Content

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 basic elements of 21 CFR 50.25(a), and each of the six elements of 21 CFR 50.25(b) that is appropriate to the study. IRBs have the final authority for ensuring the adequacy of the information in the informed consent document.

IRB standard format

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.

Sponsor-prepared sample consent documents

Sample or draft consent documents may be developed by a sponsor or cooperative study group. However, the IRB of record is the final authority on the content of the consent documents that is presented to the prospective study subjects.

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.

Revision of Consent Documents during the study

Study protocols are often changed during the course of the study. When these changes require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. While not required by FDA regulations, some IRBs stamp the final copy of the consent document with the approval date. The investigator then photocopies the consent document for use. [Note: the wording of the regulations is provided in *italics*, followed by explanatory comments.]

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.

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 concepts that the typical subject can read and comprehend.

Although not prohibited by the FDA regulations, use of the wording, "I understand..." in informed consent documents 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 (e.g., "I understand the statements in this informed consent document.") 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 unproven claims of effectiveness or certainty of benefit, either 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)] as well as the requirement to minimize the possibility of coercion or undue influence [21 CFR 50.20].

FDA approval of studies

Investigational drug and biologic studies are not officially approved by FDA. 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.

Therefore, 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. If FDA does not place the study on hold within the thirty day period, the study may begin (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.

Non-English Speaking Subjects

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).

Illiterate English-Speaking Subjects

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, when consistent with

applicable state law.

A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the consent interview is recommended.

Assent of children

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. Although not required by FDA regulations, the HHS regulations for conduct of studies in children may be used as guidance [45 CFR 46, Subpart D].

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, placebo control, additional tests) should be explained to the subjects. The procedures subjects will encounter should be outlined in the consent document, or an explanation of the procedures, such as a treatment chart, 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 about participating 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 including, when appropriate, the alternative of supportive care with no additional disease-directed therapy. 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. The consent should also indicate whether subjects will be billed for the cost of such medical treatments. When costs will be billed, statements such as "will be billed to you or your insurer in the ordinary manner," "the sponsor has set some funds aside for medical costs related to.... Here's how to apply for reimbursement if you think you might be eligible" or "no funds have been set aside..." are preferred. Statements such as: "will be the responsibility of you or your insurance company" or "compensation is not available," could appear to relieve the sponsor or investigator of liability for negligence, see 21 CFR 50.20.

Compensation v. Waiver of Subject's Rights

The consent document must explain whether there is compensation available in case of injury but must not waive or appear to waive the rights of the subject or release or appear

to release those conducting the study from liability for negligence. When no system has been set up to provide funds, the preferred wording is: "no funds have been set aside for" "[the cost] will be billed to you or your insurance," or similar wording that explains the provisions or the process. Wording such as: "will be your responsibility or that of your third-party payor" has been erroneously interpreted by some subjects to mean the insurance company is required to pay.

(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. If the subjects who withdraw will be asked to permit follow-up of their condition by the researchers, the process and option should be outlined in the consent document.

(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 the potential risks that the study poses are adequately explained to subjects who are asked to enter a study. 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 additional 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 the subject's continued participation are likely to occur during the subject's participation in the study, 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 IRB determines that the numbers of subjects in a study is material to the subjects' decision to participate, the informed consent document should state the approximate number of subjects involved in the study.

The Consent Process

Informed consent is more than just a signature on a form, it is a process of information exchange that may include, in addition to reading and signing the informed consent document, subject recruitment materials, verbal instructions, question/answer sessions and measures of subject understanding. Institutional Review Boards (IRBs), clinical investigators, and research sponsors all share responsibility for ensuring that the informed consent process is adequate. Thus, rather than an endpoint, the consent document should be the basis for a meaningful exchange between the investigator and the subject.

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 conduct the consent interview. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent to another individual knowledgeable about the research.

In addition to signing the consent, the subject/representative should enter the date of signature on the consent document, to permit verification that consent was actually obtained before the subject began participation in the study. If consent is obtained the same day that the subject's involvement in the study begins, the subject's medical records/

case report form should document that consent was obtained prior to participation in the research. A copy of the consent document must be provided to the subject and the original signed consent document should be retained in the study records. Note that the FDA regulations do not require the subject's copy to be a signed copy, although a photocopy with signature(s) is preferred.

The IRB should be aware of who will conduct the consent interview. 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.

21 CFR 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 and dated by the subject or the subject's legally authorized representative at the time of consent. 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.

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.

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 subjects. A witness is required to attest to the adequacy of the consent process and to the subject's voluntary consent. Therefore, the witness must be present during the entire consent interview, not just for signing the documents. The subject or the subject's legally authorized representative must sign and date 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. While the regulations do not prohibit the use of multiple consent documents, FDA suggests that they be used with caution. 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. For certain types of studies, the Agency encourages the process of renewing the consent of subjects.

Also see these FDA information sheets:

["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"](#)

["Evaluation of Gender Differences in Clinical Investigations"](#)

["Significant Differences in HHS and FDA Regulations for the Protection of Human Subject"](#)

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U.S. Food and Drug Administration

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Emergency Use of an Investigation 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

Product	Office/Divison to Contact
<i>The grayed-out information in this chart is no longer accurate. Get current information.</i>	
drug products	<div style="background-color: #cccccc; height: 15px; width: 100%;"></div> (HFD-210) <div style="background-color: #cccccc; height: 15px; width: 100%;"></div>
biological blood products	Office of Blood Research and Review (HFM-300) 301-827-3518
biological vaccine products	Office of Vaccines Research <div style="background-color: #cccccc; width: 100px; height: 15px;"></div> (HFM-400) <div style="background-color: #cccccc; height: 15px; width: 100%;"></div>
On nights and weekends	<div style="background-color: #cccccc; height: 15px; width: 100%;"></div> <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> (HFC-160) 301-443-1240

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.

Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below.

Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

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 acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

This policy is undergoing review and is subject to change.

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)].

Exception from Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived, is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are usually not eligible for the emergency approvals described above. The information sheet "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble," is a compilation of the wording of 21 CFR 50.24 and pertinent portions of the preamble from the October 2, 1996 Federal Register.

Also see these FDA Information Sheets:

["Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble"](#)

["Emergency Use of Unapproved Medical Devices"](#)

["Treatment Use of Investigational Drugs"](#)

Expanded Access 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 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/HIV related diseases under a separate "expanded access" 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 AIDS/HIV. 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 filing an appropriate application as soon as practicable. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exception are met [21 CFR 50.23].

Also see this FDA Information Sheet:

["Emergency Use of an Investigational Drug or Biologic"](#)

Waiver of IRB Requirements for Drug and Biologics 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:
Drug Information Branch (HFD-211)

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827- 4573

For a BIOLOGICAL BLOOD product, contact:
Office of Blood Research and Review (HFM-300)
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852
301-827-3518

For a BIOLOGICAL VACCINE product, contact:
Office of Vaccines Research and Review (HFM-400)
Food and Drug Administration
8800 Rockville Pike
Bethesda, Maryland 20892-0001
301-827-0648

For a BIOLOGICAL THERAPEUTIC product, contact:
Office of Therapeutics Research and Review (HFM-500)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1420
301-594-2860

Also see these FDA Information Sheets:

["Emergency Use of an Investigational Drug or Biologic"](#)

["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 314.126] 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 anti-anxiety 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:

Drug Information Branch (HFD-211)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827- 4573

For a BIOLOGICAL BLOOD product, contact:

Office of Blood Research and Review (HFM-300)
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852
301-827-3518

For a BIOLOGICAL VACCINE product, contact:

Office of Vaccines Research and Review (HFM-400)
Food and Drug Administration
8800 Rockville Pike
Bethesda, Maryland 20892-0001
301-827-0648

For a BIOLOGICAL THERAPEUTIC product, contact:

Office of Therapeutics Research and Review (HFM-500)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1420
301-594-2860

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.

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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]. An IDE study may not necessarily commence 30 days after an IDE submission to FDA. 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 these FDA Information Sheets:

["Significant Risk and Nonsignificant Risk Medical Device Studies"](#)

["Sponsor-Investigator-IRB Interrelationship"](#)

Frequently Asked Questions About IRB Review of Medical Devices

1. What is meant by Class I, II and III devices?

The class distinction is made primarily on the level of risk to users/patients and, therefore, the level of FDA oversight needed to ensure that the device is safe and effective as labeled. Generally, but not always, this corresponds to logical risk evaluations.

Class	Controls	Products
Class I	General controls	crutches, band aids
Class II	Special controls	wheelchairs, tampons

Class III	PreMarket Approval	heart valves (known to present hazards requiring clinical demonstration of safety and effectiveness) - OR - not enough known about safety or effectiveness to assign to Class I or II
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2. What is the difference between marketing approval under a 510(k) and under a PMA?

A 510(k) application demonstrates that a new device is substantially equivalent to another device that is legally on the market without a PMA. If FDA agrees that the new device is substantially equivalent, it can be marketed. Clinical data are not required in most 510(k) applications; however if clinical data are necessary to demonstrate substantial equivalence, the clinical studies need to be conducted in compliance with the requirements of the IDE regulations, IRB review and informed consent (21 CFR parts 812, 56 and 50, respectively).

3. Why should an IRB decide whether a device is non-significant risk (NSR)?

The sponsors (usually the manufacturer of the device) makes the initial decision whether a device imparts significant risk (SR) to study subjects or others. If so, the sponsor obtains an Investigational Device Exemption (IDE) from FDA. If the sponsor believes the device does not impart significant risk, IRB approval of a study as an NSR device can be sought. The NSR category was created to avoid delay and expense where the anticipated risk to human subjects did not justify the involvement of FDA. If the IRB agrees that the study is NSR, no submission to or review by FDA is necessary before starting studies in humans. If the IRB considers the study to be SR, the sponsor must obtain an IDE from FDA before proceeding with clinical studies.

4. What does FDA know about an NSR study?

"There is no requirement to report to FDA when an NSR study starts." The requirements for IRB review, informed consent, adverse event reporting and labeling still apply. In addition, the sponsor should understand that proceeding with an NSR study is at their risk (meaning that the FDA can later disagree) and they may voluntarily seek advice or inform FDA about the decision to proceed without filing an IDE with FDA.

5. How does an IRB decide whether a device is SR or NSR?

The IRB uses its best abilities, the information in the regulations and the guidelines, and the risk evaluation provided by the applicant. It can, as always, seek outside assistance. The IRB should have written policies and procedures regarding device review. The information sheet "Significant Risk and Non-Significant Risk Medical Device Studies"

provides additional guidance.

6. Does an IRB that reviews medical device studies need written procedures for determining whether the device is SR or NSR?

When the IRB determines that an investigation presented for approval as involving an NSR device actually involves an SR device, 21 CFR 812.66 requires the IRB to so notify the investigator and, where appropriate, the sponsor. 21 CFR 56.108(a)(1) requires the IRB to follow written procedures for conducting its initial review of research and for reporting its findings and actions to the investigator. The procedures followed in determining whether a study is SR or NSR should be included among those written procedures.

7. Does FDA require IRB review of the off-label use of a marketed device?

YES, if the off-label use is part of a research project involving human subjects. NO, if the off-label use is intended to be solely the practice of medicine, i.e., for a physician treating a patient and no research is being done.

8. What is the meaning of exemption in 21 CFR 812.2(c)(2)?

The exemption applies only to investigations in which 510(k)'d products are being used in accordance with the labeling cleared by FDA. Investigation of an off-label use of a 510(k) product takes it outside this exemption. A device subject to 510(k) remains "investigational" until the 510(k) is cleared by FDA and the investigational use is subject to the requirements of the IDE regulation, informed consent and IRB review (21 CFR 812, 50 and 56, respectively).

9. Must an IRB review a clinical investigation being done after submission of a 510 (k)?

YES, if it's research the 21 CFR 50 and 56 regulations apply, and an IRB should review it. A 510(k) allows commercial distribution; it doesn't address research use. A 510(k) application can take time to process during which it remains an investigational product. It cannot be distributed except for investigational use until FDA clears the 510(k) application.

Also see these FDA Information Sheets:

["Medical Devices"](#)

["Significant Risk and Nonsignificant Risk Medical Device Studies"](#)

["Emergency Use of Unapproved Medical Devices."](#)

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 intended as 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 sponsor should provide the IRB with 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 sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must 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 should notify FDA that an SR determination has been made. The study can be conducted as an 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 an 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 the 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

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 General Hospital Catheters (long-term percutaneous, implanted, subcutaneous and intravascular)

Conventional Implantable Vascular Access Devices (Ports)

Conventional Laparoscopes, Culdoscopes, and Hysteroscopes

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

Denture Repair Kits and Realignment

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

Manual Image Guided Surgery

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 - except for conventional 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 Valvuplasty 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 Protheses
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 Protheses
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 Protheses
Repeat Access Devices for surgical procedures

Sutures

General Hospital

Implantable Vascular Access Devices (Ports) - if new routes of administration or new design

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)

Computer Guided Robotic Surgery

Radiology

Boron Neutron Capture Therapy

Hyperthermia Systems and Applicators

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. Medical devices that have not received marketing clearance under section 510(k) of the FD&C Act are also considered unapproved devices which require an IDE.

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 FDA Office of Emergency Operations (HFA-615) 301-443-1240.

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.

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)].

Exception from Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived, is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are usually not eligible for the emergency approvals described above. The information sheet "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble," is a compilation of the wording of 21 CFR 50.24 and pertinent portions of the preamble from the October 2, 1996 Federal Register.

Also see these FDA Information Sheets:

["Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble"](#)
["Emergency Use of an Investigational Drug or Biologic"](#)

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U.S. Food and Drug Administration

INFORMATION SHEETS

Guidance for Institutional Review Boards and Clinical Investigators 1998 Update

FDA Operations

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[FDA Clinical Investigator Inspections](#)

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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-35)
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 (Inspectional 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-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857.

Also see this FDA Information Sheet
["Clinical Investigator Regulatory Sanctions"](#)

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 devices, medical foods or food additives. [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).]

Regulations do not state that hearings will be held at FDA headquarters. Investigators may suggest another location. Hearings can be denied if investigators fail to submit any information that raises any question of fact.

The Disqualification Process

Informal Conference or Written Explanation

FDA may disqualify clinical investigators from receiving investigational drugs, biologics and devices 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 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.

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 test articles.

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. If the investigator does not respond within the time period specified in the letter, 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 notices of any published articles or written information to be presented or relied upon 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. The investigator or the Center may each file a motion for summary decision.

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, biologics or devices. The notification will include a statement explaining the basis for this determination.
- (2) Notify the sponsors of studies conducted under each IND, IDE 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 or IDE 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 or IDE 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 or IDE 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

A danger to the public health includes 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.

The Notice of Opportunity for a Hearing letter is available under the Freedom of Information provisions but is not placed on public display. 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, biologics and devices or who have agreed to some restriction of use of investigational drugs, biologics and devices (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, biologics and devices 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, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health 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 FDA regulated test articles or who have agreed to some restriction of use of FDA regulated test articles. 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-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857.

The list is also available on the internet at: www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

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**Guidance for Institutional Review Boards and Clinical Investigators
1998 Update**

Appendix A

**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 314 - New Drug Applications
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 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 amended)
Public Health Service Act of 1944 (as amended)
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
FDA Modernization Act of 1997

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