

# **Federal Register**

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Tuesday  
August 14, 1979

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## **Part II**

### **Department of Health, Education, and Welfare**

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Food and Drug Administration, Office of  
the Secretary

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Protection of Human Research Subjects

**DEPARTMENT OF HEALTH,  
EDUCATION, AND WELFARE**

**Office of the Secretary**

**[45 CFR Part 46]**

**Proposed Regulations Amending  
Basic HEW Policy for Protection of  
Human Research Subjects**

**AGENCY:** Department of Health,  
Education, and Welfare.

**ACTION:** Proposed rule.

**SUMMARY:** The Department of Health, Education, and Welfare (HEW or Department) is proposing regulations amending HEW policy for the protection of human research subjects and responding to the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Commission) concerning institutional review boards (IRBs or Boards). These proposed rules adopt, for the most part, the recommendations of the Commission and, if adopted in their present form, would have the following primary effects: (1) continue to provide protections for human subjects of research conducted or supported by the Department of Health, Education, and Welfare; (2) require IRB review and approval of research involving human subjects, even if it is not supported by Department funds, if it is conducted at or supported by an institution receiving HEW funds for research not exempt from these regulations—research not supported by Department funds are subject to the same exemption clauses as Department funded research; (3) require review of human subject research irrespective of risk—unless the research is specifically exempted from coverage; (4) exempt from coverage certain kinds of social, economic and educational research; (5) either exempt or require only expedited review of certain kinds of research involving solely the use of survey instruments, solely the observation of public behavior, solely the study of documents, records and specimens, or solely a combination of any of these activities [public comment is especially invited concerning whether to exempt or to require only expedited review for these categories of research]; (6) require only expedited review for certain categories of proposed research involving no more than minimal risk and for minor changes in research already approved by the IRB; (7) provide specific procedures for full IRB review and for expedited IRB review; (8) designate basic elements of

informed consent which are a necessary prerequisite to research subject participation and additional elements which, when appropriate, are a necessary prerequisite to subject participation; (9) indicate circumstances under which the IRB may approve withholding or altering certain information otherwise required to be presented to research subjects; (10) require that IRB membership include at least one nonscientist; and (11) establish regulations which to the extent possible, are compatible and consistent with the soon to be published, FDA proposed standards for IRB's.

**Note.**— These are "proposed" regulations and public comment on them is encouraged.

**DATES:** Written comments on the proposed rules should be received on or before November 12, 1979, if they are to be given full consideration.

**ADDRESS:** Please send comments or requests for additional information to:

F. William Dommel, Jr., J.D., Assistant Director for Regulations, Office for Protection from Research Risks; National Institutes of Health, 5333 Westbard Avenue, Room 3A18, Bethesda, Maryland 20205, Telephone: (301) 496-7163,

where all comments received will be available for inspection weekdays (Federal holidays excepted) between the hours of 9 a.m. and 4:30 p.m.

**FOR FURTHER INFORMATION CONTACT:** F. William Dommel, Jr. (301) 496-7163.

**SUPPLEMENTARY INFORMATION:** Basic regulations governing the protection of human subjects involved in research, supported by HEW through grants and contracts were published in the **Federal Register** on May 30, 1974 (30 FR 18914). Subsequently, regulations were published to accord additional protections for "special groups" which may have diminished capacity to consent or which may be at high risk (i.e., fetuses, pregnant women, and prisoners). These "special group" regulations which, have previously been published in final form, will be amended to conform (where necessary) with the basic regulations proposed below, when these basic regulations are published in final form. In addition, regulations have been proposed to provide additional safeguards for others who may have diminished capacity. These were published in the **Federal Register** as follows: Research Involving Children (43 FR 31786, July 21, 1978) and Research Involving Those Institutionalized as Mentally Disabled (43 FR 53950, November 17, 1978). Final regulations on those two categories are being withheld

pending further comment on them as well as the proposed regulations below.

Therefore, the public comment period for each of these proposed regulations (including their relationship to the basic regulations published in proposed form below) has been extended to November 12, 1979. The decision to postpone final regulations on these special categories of participants was reached on the basis of procedural considerations. By finalizing first the regulations applicable to the review and monitoring of all research involving human subjects and covered by these regulations, the Department may then issue only those additional regulations necessary for the protection of specific categories of subjects who may have diminished capacity to consent. By following this order of regulation development, the Department hopes to avoid the possibility of duplicative and inconsistent requirements among the several sections of these regulations.

On August 8, 1978, the Food and Drug Administration published proposed standards for Institutional Review Boards for Clinical Investigations (43 FR 35186). Shortly thereafter, the Commission submitted its report and recommendations on IRBs and informed consent, and that document was published in the **Federal Register** on November 30, 1978 (43 FR 56174). In its report, the Commission recommended revisions of the current HEW regulations for IRBs. Because the FDA stated in the August 8, 1978 proposal that its regulations should be compatible with, if not identical to, those of the Department, FDA is withdrawing its IRB proposal of August 8, 1978 and is publishing a revised proposal which has been developed in conjunction with HEW. The Department and FDA both agree in principle with the recommendation of the Commission that IRBs should operate under one set of federal regulations. Within the constraints of their independent statutory obligations and missions, the Department and FDA have developed IRB proposals which have virtually the same structure and functions, so that IRBs will have essentially uniform requirements in areas such as scope of responsibility, quorum requirements, and records retention.

It should be emphasized that, although the regulations proposed below will be essentially compatible and consistent with the regulations to be proposed by FDA, the two sets of regulations cannot be identical. The statutory authorities under which FDA regulates clinical research are different from the authorities relied upon by the

Department to regulate research which it either funds or conducts. In addition, because the Department's regulations encompass behavioral research, the scope of coverage and types of review required are somewhat different.

The regulations proposed below attempt to achieve a common, flexible framework within which IRBs can operate whether they are reviewing HEW supported research or FDA regulated research. Because FDA is a regulatory agency, the compliance aspects of its regulations must be explicitly stated. In its proposal, FDA will provide for inspection and disqualification of IRBs. However, the Department, which employs the institutional assurance mechanism for dealing with institutions, and which may cut off funding of projects for noncompliance, has made no such provision.

The Department will continue to consult with FDA during the development of final regulations so that consistency of IRB structure and function can be maintained, as much as possible.

Background: The National Research Act (Pub. L. 93-348) was signed into law on July 12, 1974, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the topics of study identified in the mandate to the Commission was "Institutional Review Boards." The Commission was required to recommend to the Secretary of Health, Education, and Welfare ". . . mechanisms for evaluating and monitoring the performance of Institutional Review Boards in accordance with section 474 of the Public Health Service Act and appropriate enforcement mechanisms for carrying out their decisions." And was further required to make recommendations regarding the protection of subjects involved in research not subject to regulation by HEW.

In discharging its duties under this mandate, the Commission studied the performance of IRBs which are required to review all research involving human subjects that is conducted at institutions receiving funds for such research from HEW under the Public Health Service Act. The Commission found that the review of proposed research by IRBs is the primary mechanism for assuring that the rights of human subjects are protected. Thus, the Commission's previous recommendations regarding particular categories of research subjects are intended ultimately to be carried out by the IRBs through the

establishment of conditions and requirements that IRBs should determine to have been satisfied before approving research.

The commission, therefore, undertook a substantial effort to develop information about the performance of IRBs, the research they review, and the strengths and weaknesses of this mechanism. This effort included the support of an extensive survey of IRB members, investigators and research subjects at a sample of 61 institutions including medical schools, hospitals, universities, prisons, institutions for the mentally ill and retarded, and research organizations. Also, the background, development, and administration of the present HEW regulations governing IRBs were examined. Three public hearings were held at which Federal officials, representatives of IRBs, investigators, and other concerned persons presented their views on IRBs. The National Minority Conference on Human Experimentation, convoked by the Commission to assure that viewpoints of minorities would be heard, made recommendations to the Commission that pertained to IRBs. The Commission also reviewed several papers prepared under contract on such topics as informed consent, evaluation of risks and benefits, issues that arise in particular kinds of research (such as social experimentation or deception research), and the legal aspects of IRB operation. A substantial amount of correspondence on IRBs was received and reviewed by the Commission.

In addition, a survey was made of the standards and procedures for the protection of human subjects in research conducted or sponsored by Federal departments and agencies. Finally, the Commission conducted public deliberations to develop its recommendations on IRBs.

Action on recommendations of the Commission: Pursuant to section 205 of the National Research Act (Pub. L. 93-348), the recommendations of the Commission regarding Institutional Review Boards were published in the **Federal Register** (43 FR 56174) on November 30, 1978. Comments were received from 104 individuals, institutions, organizations and groups. After reviewing the recommendations and the comments, the Secretary has prepared the notice of proposed rulemaking set forth below, which in essence accepts the recommendations. The proposed rules depart from the recommendations of the Commission to the Department in a few respects.

## Recommendations of the Commission and HEW Responses

### Recommendation (1)

(A) Federal law should be enacted or amended to authorize the Secretary of Health, Education, and Welfare to promulgate regulations governing ethical review of all research involving human subjects that is subject to Federal regulation.

(B) Federal law should be enacted or amended to provide that each institution which sponsors or conducts involving human subjects that is supported by any Federal department or agency or otherwise subject to Federal regulation, and each Federal department or agency which itself conducts research involving human subjects, shall give assurances satisfactory to the Secretary of Health, Education, and Welfare that all research involving human subjects sponsored or conducted by such institution, or conducted by such department or agency, will be reviewed by and conducted in accordance with the determinations of a review board established and operated in accordance with the regulations promulgated by the Secretary under the authority recommended in paragraph (A) of this recommendation.

(C) Federal law should be enacted or amended to provide that all research involving human subjects sponsored or conducted by an institution that receives funds from any Federal department or agency to provide health care or conduct health-related research shall be subject to Federal regulation regarding the review and conduct of such research, as provided under paragraphs (A) and (B) of this recommendation.

(D) Federal law should be enacted or amended to authorize and appropriate funds to support the operation of Institutional Review Boards by direct cost funding.

### HEW Response

The legislative mandate to the Commission included a charge to make recommendations to the Congress regarding the protection of subjects involved in research not subject to HEW regulation. Recommendation (1) responds to that charge. The Department contemplates no HEW action on this recommendation which is directed to the Congress. However, most of the twenty-two Federal agencies conducting or supporting research with human subjects have adopted the HEW regulations in whole or in part. The Department encourages this voluntary

approach and will continue to serve these agencies in an advisory capacity.

#### Recommendation (2)

(A) Federal law should be enacted or amended to authorize the Secretary of Health, Education, and Welfare to establish a single office to carry out the following duties:

(i) Accreditation of Institutional Review Boards based upon the submission of assurances containing descriptions of their membership, authority, staff, meeting facilities, review and monitoring procedures and provisions for recordkeeping; (ii) Compliance activities, including site visits and audits of Institutional Review Board records, to examine the performance of the Boards and their fulfillment of institutional assurances and regulatory requirements; and (iii) Educational activities to assist members of Institutional Review Boards in recognizing and considering the ethical issues that are presented by research involving human subjects.

(B) Federal law should be enacted or amended to authorize and appropriate funds to support the duties described in paragraph (A) of this recommendation.

#### HEW Response

Recommendation (2), just as Recommendation (1), is directed to the Congress. However, current HEW policy and regulations, as well as the regulations proposed below, implement for the main part this recommendation.

Recommendations (2)(A)(i) and (2)(A)(ii) are implemented by §§ 46.105 and 46.106 which establish the minimum requirements for institutional assurances regarding IRBs. Currently, FDA compliance activities and the aforementioned assurances, required under current HEW regulations and negotiated by the Office for Protection from Research Risks (OPRR), National Institutes of Health (NIH) and the FDA compliance activities meet and will continue to meet the requirements of these recommendations.

Educational activities such as those proposed in Recommendation (2)(A)(iii), although not described in the regulations, are currently being conducted by FDA and are being planned by OPRR, NIH.

#### Recommendation (3)

*The Secretary of Health, Education, and Welfare should require by regulation that an Institutional Review Board:*

(A) Consist of at least five men and women of diverse backgrounds and sufficient maturity, experience and

*competence to assure that the Board will be able to discharge its responsibilities and that its determinations will be accorded respect by investigators and the community served by the institution or in which it is located;*

(B) Include at least one member who is not otherwise affiliated with the institution;

(C) Have the authority to review and approve, require modifications in, or disapprove all research involving human subjects conducted at the institution;

(D) Have the authority to conduct continuing review of research involving human subjects and to suspend approval of research that is not being conducted in accordance with the determinations of the Board or in which there is unexpected serious harm to subjects;

(E) Maintain appropriate records, including copies of proposals reviewed, approved consent forms, minutes of Board meetings, progress reports submitted by investigators, reports of injuries to subjects, and records of continuing review activities;

(F) Be provided with meeting space and sufficient staff to support its review and recordkeeping duties;

(G) Be authorized and directed to report to institutional authorities and the Secretary any serious or continuing noncompliance by investigators with the requirements and determinations of the Board;

(H) Be provided with protection for members in connection with any liability arising out of their performance of duties on the Board.

#### HEW Response

Recommendation (3)(A) would be implemented by § 46.107(a), (b), and (c) of the proposed regulations set forth below. Several of the Commission's comments on the recommendation were included on the proposed regulations for purposes of clarification. One comment, however, suggested that ". . . at least one-third but no more than two-thirds of the IRB members should be scientists." The Department recognizes the need for diversity of professions among IRB members, and provision is made for this diversity at § 46.107(a) and (b) of the proposed regulations. It was decided, however, that to require in the regulation that "No board may consist entirely of members of one profession, and at least one member must be a nonscientist" provides a flexible means for institutions to establish diverse membership.

Recommendation (3)(B) would be implemented in its entirety by § 46.107(d) of the proposed regulations.

Recommendation (3)(C) would be implemented in part by §§ 46.101 and 46.108(a) of the proposed regulations. This recommendation would assign to IRBs the review, approval, disapproval, and modification authority (to secure approval) over all research ". . . conducted at the institution." The proposed regulations would afford this authority to the IRBs for research sponsored by, as well as conducted at the institution. The issue of what categories of research and which institutions must comply with the proposed regulations is described below in ADDITIONAL HEW COMMENTS or provided for at § 46.101 of the proposed regulations.

Recommendation (3)(D) would be implemented in its entirety by § 46.108(b) of the proposed regulations.

Recommendation (3)(E) would be implemented in its entirety by §§ 46.105(f) and 46.106(g) of the proposed regulations.

Recommendation (3)(F) would be implemented in its entirety by §§ 46.105(g) and 46.106(i) of the proposed regulations.

Recommendation (3)(G) would be implemented in its entirety by § 46.108(c) of the proposed regulations.

Recommendation (3)(H) would not be implemented by the regulations proposed below. The Commission recommended that protection be provided for IRB members in connection with any liability arising out of their performance of duties on the Board. The Department is hesitant to make this an absolute requirement because there is not certainty, at this time, that reasonable mechanisms are available to provide this protection. Furthermore the Department is not aware of any negligence action which has named an IRB member as a defendant and therefore believes that liability protections might prove to be an unnecessary, yet costly, requirement.

#### Recommendation (4)

*The Secretary of Health, Education, and Welfare should require by regulation that all research involving human subjects that is subject to Federal regulation shall be reviewed by an Institutional Review Board and that the approval of such research shall be based upon affirmative determinations by the Board that:*

(A) The research methods are appropriate to the objectives of the research and the field of study;

(B) Selection of subjects is equitable;

(C) Risks to subjects are minimized by using the safest procedures consistent with sound research design and, whenever appropriate, by using procedures being performed for diagnostic or treatment purposes;

(D) Risks to subjects are reasonable in relation to anticipated benefits to subjects and importance of the knowledge to be gained;

(E) Informed consent will be sought under circumstances that provide sufficient opportunity for subjects to consider whether or not to participate and that minimize the possibility of coercion or undue influence;

(F) Informed consent will be based upon communicating to subjects, in language they can understand, information that the subjects may reasonably be expected to desire in considering whether or not to participate, generally including:

(i) That an Institutional Review Board has approved the solicitation of subjects to participate in the research, that such participation is voluntary, that refusal to participate will involve no penalties or loss of benefits to which subjects are otherwise entitled, that participation can be terminated at any time, and that the conditions of such termination are stated;

(ii) The aims and specific purposes of the research, whether it includes procedures designed to provide direct benefit to subjects, and available alternative ways to pursue any such benefit;

(iii) What will happen to subjects in the research, and what they will be expected to do;

(iv) Any reasonably foreseeable risks to subjects, and whether treatment or compensation is available if harm occurs;

(v) Who is conducting the study, who is funding it, and who should be contacted if harm occurs or there are complaints; and

(vi) Any additional costs to subjects or third parties that may result from participation;

(G) Informed consent will be appropriately documented, unless the Board determines that written consent is not necessary or appropriate because (I) the existence of signed consent forms would place subjects at risk, or (II) the research presents no more than minimal risk and involves no procedures for which written consent is normally required;

(H) Notwithstanding the requirements of paragraphs (E), (F) and (G) above, informed consent is unnecessary (I) where the subjects' interests are

in studies of documents, records or pathological specimens and the importance of the research justifies such invasion of the subjects' privacy, or (II) in studies of public behavior where the research presents no more than minimal risk, is unlikely to cause embarrassment, and has scientific merit;

(I) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and

(J) Applicable regulatory provisions for the protection of fetuses, pregnant women, prisoners, children and those institutionalized as mentally infirm will be fulfilled.

#### HEW Response

Recommendations (4)(A–D) would be implemented in their entirety by § 46.110(1–4) of the proposed regulations.

Recommendations (4)(E) and (4)(F)(I–III) would be implemented in their entirety by § 46.112(a)(1).

Recommendation (4)(F)(IV) would be implemented in part by 46.112(a)(1)(c) concerning description of foreseeable risks. The second part of this recommendation suggests notification of whether treatment or compensation is available if harm occurs. At § 46.112(a)(1)(I), the proposed regulation would require this notification if the research involves more than minimal risk and would further require an explanation of the extent of available coverage (if any). The Department feels that where the risk is no greater than minimal, an explanation of injury benefits would be inappropriate.

Recommendations (4)(F)(V–VI) would be implemented in part by 46.112(a)(1)(J) concerning who should be contacted if harm occurs or there are complaints (referred to in the regulations as questions or problems instead of complaints). The other parts of the recommendations suggest that the subject be informed of who is conducting the study and of any additional costs to subjects or third parties that may result from participation. These later notifications, while at times appropriate, are not seen by the Department as being essential to every informed consent procedure. Therefore, these two notifications as well as notice of the possible involvement of currently unforeseeable risks, notice of foreseeable circumstances under which the subjects participation may be terminated by the investigator, and notice of the approximate number of subjects involved are included under an optional set of informed consent elements

(§ 46.112(a)(2)). The IRB, when appropriate, shall require that some or all of these elements of information be provided to the subject.

Recommendation (4)(G) regarding the waiver of the required documentation of consent would be implemented by § 46.113(b) where the Department has added additional requirements for the waiver.

Recommendation (4)(H) would waive the informed consent requirement for certain kinds of research presenting no more than minimal risk. The proposed regulations do not provide for this total waiver of consent requirements because the categories of research to which it would apply are under consideration for exemption from these regulations (§ 46.101(c) [option A]). However, the Department would support waiving consent for these categories if they are not exempted (§ 46.101(c) [option B]).

Recommendation (4)(I) would be implemented in its entirety by § 46.119 of the proposed regulations.

Recommendation (4)(J) is implemented for fetuses and pregnant women by 45 CFR 46 Subpart B and for prisoners by 45 CFR 46 Subpart C. The recommendation would be implemented for children by 45 CFR 46 Subpart D (proposed) and for those institutionalized as mentally disabled by 45 CFR 46 Subpart E (proposed).

#### Recommendation (5)

*The Secretary of Health, Education, and Welfare should require by regulation that an Institutional Review Board shall review proposed research at convened meetings at which a majority of the members of the Board are present and that approval of such research shall be reached by a majority of those members who are present at the meeting, provided, however, that the Secretary may specifically approve expedited review procedures adopted by an Institutional Review Board for carefully defined categories of research that present no more than minimal risk. The Secretary should require, further, that an Institutional Review Board inform investigators of the basis of decisions to disapprove or require the modification of proposed research and give investigators an opportunity to respond in person or in writing.*

#### HEW Response

Recommendation (5) would be implemented in its entirety by §§ 46.105e, 46.106(b), and 46.111 of the proposed regulations.

**Additional HEW Comments***Alternative Exemptions*

The Department is considering and requesting comments on two alternative lists of exemptions or some combination thereof. The two lists reflect differing opinions concerning: (1) whether to exempt research involving solely observation, (2) what types of survey or related research should be exempted, (3) under what conditions research involving solely the study of documents, records or specimens should be exempted (assuming the investigator is not collecting identifiers).

The list of exemptions in alternative A (especially items 4, 5 and 6) reflect the belief held by some that almost all of this research is innocuous. Those who advocated this alternative felt that there is no need to include such research under the regulations because there is no evidence of adverse consequences and little evidence of risk apart from possible breaches of confidentiality. Furthermore they contended that institutions which currently have no IRB would have to create one to review minimal-risk research. It was argued that to require an institution to review a large volume of minimal-risk research in order to find the rare proposal that might be potentially harmful, could create an unwarranted burden on the institution.

Alternative B reflects the view of those who feel that not all survey research and records research should be exempted. Furthermore they believe that observational research should be entirely subject to the regulations because at least some of this research can present serious risks for subjects. Examples of these research are: research involving collection of information about mental disorders or child abuse, observation of illegal conduct, or collection of data on alcohol abuse from medical records or specimens. Inadvertent or compulsory disclosure of information collected in such research can have serious consequences for subjects' future employability, family relationships or financial credit; also, some surveys can cause psychological distress for subjects.

The argument for IRB review of such research is based not only on the need to protect from harm, but on the need for an independent, social mechanism to ensure that research is ethically acceptable and that the rights and welfare of subjects will be protected.

Alternative B, along with inclusion of certain procedures in the expedited review list will permit significant

reduction in the workload by IRBs, though not as much of a reduction as alternative A.

*Filing Justification for Exemption*

The Department is also considering whether to require a principal investigator who proposes to carry out research involving human subjects which he judges to be exempt from the regulations should be required to document the reasons underlying the judgement that his research project is exempt. The investigator who claims exemption would be required to file a justification with an appropriate IRB or with the Secretary. It is felt that such a requirement would reduce the possibility of investigators claiming exemptions for non-exempt research. Comments on this procedure are requested.

Notice is given that it is proposed to make any amendments that are adopted effective upon publication in the **Federal Register**.

Dated July 26, 1979.

**Julius B. Richmond,**  
*Assistant Secretary for Health.*

Approved July 27, 1979.

**Joseph A. Califano, Jr.,**  
*Secretary.*

It is therefore proposed to amend Part 46 of 45 CFR, by repealing current Subparts A and D, and replacing them with the following new Subpart A.

**Subpart A—Basic HEW Policy for Protection of Human Research Subjects**

Sec.

- 46.101 To what do these regulations apply?
- 46.102 Definitions.
- 46.103 Submission of assurances.
- 46.104 Types of assurances.
- 46.105 Minimum requirements for general assurances.
- 46.106 Minimum requirements for special assurances.
- 46.107 Institutional Review Board membership.
- 46.108 Institutional Review Board functions
- 46.109 Evaluation and disposition of assurances.
- 46.110 Review of proposed research by the Institutional Review Board.
- 46.111 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 46.112 Informed consent.
- 46.113 Documentation of informed consent.
- 46.114 Applications and proposals lacking definite plans for involvement of human subjects.
- 46.115 Research undertaken without the intention of involving human subjects.
- 46.116 Evaluation and disposition of applications and proposals.
- 46.117 Cooperative research projects.

46.118 Investigational new drug 30-day delay requirement.

46.119 Confidentiality of records.

46.120 Use of Federal funds.

46.121 Early termination of research support; evaluation of subsequent applications and proposals.

46.122 Research not conducted or supported by the Department.

46.123 Conditions.

**Authority:** 5 U.S.C. 301.

**Subpart A—Basic HEW Policy for Protection of Human Research Subjects****§46.101 To what do these regulations apply?**

(a) Except as provided in paragraph (c), this subpart applies to all research involving human subjects conducted or supported by the Department of Health, Education, and Welfare.

(b) Except as provided in paragraph (c) below, only §§ 46.104(c) and 46.122 of these regulations apply to research involving human subjects which is not funded by the Department, but is conducted at or supported by any institution receiving funds from the Department for the conduct of research involving human subjects.

(c) These regulations do not apply to:

[The Department will include a list of exempted categories of research in the final regulations. Two alternative lists are provided below for public comment. (The first three items and the last item in each list are identical.) If the list in Alternative B is adopted, additions will also be made to the list of procedures which can receive expedited review (see § 46.111).]

**Alternative A**

(1) Research designed to study on a large scale: (A) the effects of proposed social or economic change, or (B) methods or systems for the delivery of or payment for social or health services.

(2) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (A) research on regular and special education instructional strategies, or (B) research on the effectiveness of or the comparison among instructional techniques, curriculum, or classroom management.

(3) Research involving solely the use of standard educational diagnostic, aptitude, or achievement tests, if information taken from these sources is recorded in such a manner that subjects cannot be reasonably identified, directly or through identifiers linked to the subjects.

(4) Research involving solely the use of survey instruments if: (A) results are recorded in such a manner that subjects cannot be reasonably identified, directly or through identifiers linked to the subjects, or (B) the research (although not exempted under clause (A)) does not deal with sensitive topics, such as sexual behavior, drug or alcohol use, illegal conduct, or family planning.

(5) Research involving solely the observation (including observation by participants) of public behavior, if observations are recorded in such a manner that subjects cannot be reasonably identified, directly or through identifiers linked to the subjects.

(6) Research involving solely the study of documents, records, or pathological or diagnostic specimens, if information taken from these sources is recorded in such a manner that subjects cannot be reasonably identified, directly or through identifiers linked to the subjects.

(7) Research involving solely a combination of any of the activities described above.

#### Alternative B

(1) Research designed to study on a large scale: (A) the effects of proposed social or economic change, or (B) methods or systems for the delivery of or payment for social or health services.

(2) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (A) research on regular and special education instructional strategies, or (B) research on the effectiveness of or the comparison among instructional techniques, curriculum, or classroom management.

(3) Research involving solely the use of standard educational diagnostic, aptitude, or achievement tests, if information taken from these sources is recorded in such a manner that subjects cannot be reasonably identified, directly or through identifiers linked to the subjects.

(4) Survey activities involving solely product or marketing research, journalistic research, historical research, studies of organizations, public opinion polls, or management evaluations, in which the potential for invasion of privacy is absent or minimal.

(5) Research involving the study of documents, records, data sets or human materials, when the sources or materials do not contain identifiers or cannot reasonably be linked to individuals.

(6) Research involving solely a combination of any of the activities described above.

(d) The Secretary has final authority to determine whether an activity is exempt from these regulations under paragraph (b), and may override an institution's decision, for example, that the activity is exempt.

(e) The Secretary may require that specific research or nonresearch activities or classes of research or nonresearch activities conducted or supported by the Department, but not otherwise covered by these regulations, comply with these regulations.

(f) The Secretary may also exempt specific activities or classes of activities, otherwise covered by these regulations, from some or all of these regulations. Notices of these actions will be published in the **Federal Register** as they occur.

(g) Compliance with these regulations will in no way render inapplicable pertinent State or local laws or regulations or other Federal laws or regulations, including those of the Food and Drug Administration bearing upon activities covered by these regulations.

(h) Each subpart of these regulations contains a separate section describing to what the subpart applies. Research which is covered by more than one subpart must comply with all applicable subparts.

#### § 46.102 Definitions.

(a) "Secretary" means the Secretary of Health, Education, and Welfare and any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been delegated.

(b) "Department" means the Department of Health, Education, and Welfare.

(c) "Institution" means any public or private entity or agency (including Federal, State, and other agencies).

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

(e) "Research" means a formal investigation designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute "research" for purposes of this part, whether or not they are supported or conducted under a program which is considered research for other purposes. For example, some "demonstration" and "service"

programs may include research activities.

(f) "Human subject" means an individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the person, or (2) identifiable information.

(g) "Minimal risk" is the probability and magnitude of harm that is normally encountered in the daily lives of healthy individuals, or in the routine medical, dental or psychological examination of healthy individuals.

#### § 46.103 Submission of assurances.

(a) Each institution engaged in research covered by these regulations shall provide written assurance satisfactory to the Secretary that it will comply with the requirements set forth in the regulations, including the requirements that: (1) the research will be reviewed by an Institutional Review Board established and operated in accordance with these regulations, and (2) the research will be conducted in accordance with the Board's determinations.

(b) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by these regulations, and shall be filed in such form and manner as the Secretary may prescribe.

#### § 46.104 Types of assurances.

(a) *General assurances.* A general assurance is a comprehensive plan for the review and implementation procedures applicable to all research covered by these regulations at a particular institution, regardless of the number, location, or types of its components or field activities. Institutions having a significant number of concurrent research projects involving human subjects will be required to file general assurances.

(b) *Special assurances.* A special assurance describes the review and implementation procedures applicable to, and reports the findings of the Institutional Review Board on, a single research project. Institutions not having on file with the Department an approved general assurance will be required to file special assurances.

(c) *Assurances applicable to research not funded by the Department.* Each institution which applies to the Department for a grant or contract for any research project or program involving human subjects, unless such project or program is an exempted category listed at § 46.101(c), must

provide assurance in a document submitted with its application or proposal that it will comply with § 46.122 of these regulations.

(d) *Department-conducted research.* Research by Department employees must be conducted in conformity with these regulations, except each Principal Operating Component head may adopt such nonsubstantive, procedural modifications as may be appropriate, from an administrative standpoint.

(e) *Awards to individuals.* No individual may receive Department support for research covered by these regulations unless he or she is affiliated with or sponsored by an institution which assumes responsibility for the research under an assurance satisfying the requirements of this part.

**§ 46.105 Minimum requirements for general assurances.**

In order to satisfy the requirements of these regulations, a general assurance shall provide specifically for the following:

(a) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of subjects. This may include appropriate existing codes, declarations, or statements of basic ethical principles, or statements formulated by the institution itself. However, these principles do not supersede Department policy or applicable law.

(b) One or more Institutional Review Boards, each satisfying the requirements of § 46.107 regarding membership and § 46.108 regarding functions.

(c) A list of the Board members identified by name; earned degrees (if any); position or occupation; specialty field (if any); representative capacity; and by other pertinent indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to Board deliberations. Any employment or other relationship between each member and the institution shall be identified (e.g., full-time employee, part-time employee, member of governing panel or board, stockholder, paid consultant, unpaid consultant). Changes in Board membership must be reported to the Department in such form and at such times as the Secretary may require.

(d) Written procedures which the Board will follow (1) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution, (2) for determining which projects require review more often than annually and

which projects need verification from sources other than the researchers that no material changes have occurred since initial Board review, (3) to insure prompt reporting to the Board of proposed changes in an activity and of unanticipated problems involving risks to subjects or others, and (4) to insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope labelled drugs, or medical devices, are promptly reported to the Department. These procedures may be promulgated by the institution or by the Board, if this authority is delegated to it by the institution.

(e) Board review of proposed research at convened meetings at which a majority of the members of the Board are present, including at least one member whose primary concerns are in nonscientific areas, except when an approved expedited review procedure is utilized (see § 46.111). In order for the research to be approved, it must receive the approval of a majority of those members present at the meeting. The Board shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure Board approval of the activity. If the Board decided to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(f) Maintenance of appropriate records, including information on Board members required by paragraph (c), copies of proposals reviewed and approved sample consent forms, minutes of Board meetings, progress reports submitted by investigators, reports of injuries to subjects, and records of continuing review activities. These records must be accessible for inspection by Department representatives and retained for at least five years after completion of the research, or such longer period as may be specified by program requirements. Minutes must be in sufficient detail to show attendance at Board meetings, actions taken by the Board, the number of members voting for and against these actions, and the basis for the actions (including a written summary of the discussion of substantive issues and their resolution).

(g) Provision for meeting space and sufficient staff to support the Board's review and recordkeeping duties.

**§ 46.106 Minimum requirements for special assurances.**

In order to satisfy the requirements of these regulations, a special assurance shall:

(a) Identify the specific research project covered by the assurance.

(b) Include a statement, executed by an appropriate institutional official, indicating that the institution has established a Board satisfying the requirements of §§ 46.107 and 46.108 and that the Board will follow the procedures set forth in §§ 46.105(d) and 46.105(e).

(c) Describe the makeup of the Board, including the information required by § 46.105(c).

(d) Describe the risks to subjects that the Board recognizes as inherent in the activity, and justify its finding that these risks are reasonable in relation to the anticipated benefits to subjects and the importance of the knowledge to be gained.

(e) Describe the informed consent procedures to be used and attach samples of the documentation to be required under § 46.113.

(f) Describe procedures which the Board will follow to insure prompt reporting to the Board of proposed changes in the activity and of any unanticipated problems, involving risks to subjects or others, and to insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope labelled drugs, or medical devices are promptly reported to the Department.

(g) Maintain appropriate records, including information on Board members required by paragraph (c), copies of proposals reviewed and approved sample consent forms, minutes of Board meetings, progress reports submitted by investigators, reports of injuries to subjects, and records of continuing review activities. These records must be accessible for inspection by Department representatives and retained for at least five years after completion of the research, or such longer period as may be specified by program requirements. Minutes must be in sufficient detail to show attendance at Board meetings, actions taken by the Board, the number of members voting for and against these actions, and the basis for the actions (including a written summary of the discussion of substantive issues and their resolution).

(h) Provide for meeting space and necessary staff (if any) to support the Board's review and reporting duties.



**§ 46.107 Institutional Review Board membership.**

(a) Each Institutional Review Board must have at least five members, with varying backgrounds to promote complete and adequate review of activities commonly conducted by the institution. The Board must be sufficiently qualified through the maturity, experience, and expertise of its members, and the sufficient diversity of the members' racial and cultural backgrounds, to promote respect for its advice and counsel for safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The Board must therefore include persons knowledgeable in these areas. If a Board regularly reviews research that has an impact on a vulnerable category of subjects, the Board should have one or more individuals who are primarily concerned with the welfare of these subjects.

(b) No Board may consist entirely of members of one profession, and at least one member must be an individual whose primary concerns are in nonscientific areas (e.g., lawyers, ethicists, members of the clergy).

(c) The membership of the Board may not consist entirely of men or entirely of women.

(a) Each Board shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. The records of the Board must identify the employment or other relationship between each member and the institution (e.g., full-time employee, part-time employee, a member of governing panel or board, stockholder, paid consultant, or unpaid consultant).

(e) No member of a Board may participate in the Board's initial or continuing review of any project in which the member has a conflicting interest, or any project involving an investigator who participated in the member's selection for the Board, except to provide information requested by the Board. The Board has responsibility for determining whether a member has a conflicting interest. The Secretary may waive the requirements of this paragraph upon request. Any request should contain information describing the reasons why it is essential for the

member to participate in the particular review in question.

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

**§ 46.108 Institutional Review Board functions.**

In order to fulfill the requirements of these regulations each Institutional Review Board shall:

(a) Review and have authority to approve, require modifications in (to secure approval), or disapprove all research described in § 46.101(a) which is conducted at or sponsored by the institution.<sup>1</sup>

(b) Conduct continuing review (as provided in § 46.105(d)) of research covered by these regulations and have authority to suspend, and if appropriate, terminate approval of research that is not being conducted in accordance with the determination of the Board or in which there is unexpected serious harm to subjects. Any such suspension or termination of approval must be reported promptly to the investigator, appropriate institutional officials, and the Secretary, including a statement of the reasons for the Board's action. As part of its continuing review responsibility, the Board must have authority to observe the consent process or the research itself on a sample or routine basis, or have a third party (not otherwise associated with the research or the investigator) do so. Continuing review shall be undertaken at intervals appropriate to the degree of risk, but not less than once per year.

(c) Be responsible for reporting to the appropriate institutional officials and the Secretary any serious or continuing noncompliance by investigators with the requirements and determinations of the Boards.

(d) Carry out such other duties as may be assigned by the institution or the Secretary.

**§ 46.109 Evaluation and disposition of assurances.**

(a) The Secretary will evaluate all assurances submitted in accordance with § 46.105 and § 46.106 through such officers and employees of the Department and such experts or consultants engaged for this purpose as the Secretary determines to be appropriate. The Secretary's evaluation will take into consideration the

<sup>1</sup> Where applicable, the Board shall also review other research, described at § 46.101(b), which is conducted at or sponsored by the institution.

adequacy of the proposed Institutional Review Board in the light of the anticipated scope of the institution's activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(b) On the basis of this evaluation, the Secretary may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The Secretary may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval. The Secretary may, pending completion of negotiations for a general assurance, require an institution otherwise eligible for such assurance, to submit special assurances.

**§ 46.110 Review of proposed research by the Institutional Review Board.**

(a) Except as provided in this section or § 46.111, the Department will conduct or support research covered by these regulations only if the institution has an assurance approved under § 46.109, and only if the institution has certified to the Secretary that the research has been reviewed and approved by the Institutional Review Board provided for in the assurance. In order to give its approval, the Board must determine that all of the following requirements are satisfied:

(1) The research methods are appropriate to the objectives the research and the field of study.

(2) Selection of subjects is equitable, taking into account the purposes of the research.

(3) Risks to subjects are minimized by using the safest procedures consistent with sound research design and, whenever appropriate, by using procedures already being performed for diagnostic or treatment purposes.

(4) Risks to subjects are reasonable in relation to anticipated benefits to subjects and importance of the knowledge to be gained. In making this determination, the Board should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits the subjects would be exposed to or receive even if not participating in the research). Also, the Board should not consider possible effects of applying knowledge gained in the research as among those research risks which fall within the purview of its responsibility.

(5) Informed consent will be sought from each prospective subject or his or

her legally authorized representative, in accordance with, and to the extent required by, § 46.112.

(6) Informed consent will be appropriately documented, in accordance with, and to the extent required by, § 46.113.

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

(8) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(9) Applicable regulations for the protection of fetuses, pregnant women, children, prisoners, and those institutionalized as mentally disabled are satisfied.

(b) Within 60 days after the date of submission of an application or proposal, an institution with a general assurance must certify that the application or proposal has been reviewed and approved by the Board. Other institutions must certify that the application or proposal has been approved by the Board within 30 days after receipt of a request for such a certification from the Department. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

(c) Department funds may not be used to support research covered by these regulations until certification of the Board's review and approval (under this section or § 46.111) is received by the Department from the institution; except that only Board review (but not approval) will be required for research projects which the Secretary is specifically directed by statute to carry out.

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

(a) The Secretary will publish in the **Federal Register** a list<sup>1</sup> of categories of

<sup>1</sup> The Department proposes to include the following procedures in the list to be promulgated under this section:

"Research in which the only involvement of human subjects will be in one or more of the following activities (carried out through standard methods):

(1) Collection (in a nondisfiguring manner) of hair, nail clippings, and deciduous teeth.

(2) Collection of excreta and external secretions including sweat, saliva, placenta expelled at delivery, umbilical cord blood after the cord is clamped at delivery, and amniotic fluid at the time of artificial rupture of the membrane prior to or during labor.

(3) Recording of data from adults through the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of

research, involving no more than minimal risk, that may be reviewed by the Institutional Review Board through an expedited review procedure. The Secretary will amend this list, as appropriate, through republication in the **Federal Register**.

(b) A Board at an institution with an approved general assurance may review some or all of the research appearing on the list through an expedited review procedure. The Board may also use the expedited review procedure to review minor changes in previously approved research. However, the institution must describe the Board's expedited review procedure in its general assurance.

(c) Under an expedited review procedure, the review may be carried out by the Board chairperson or by one or more experienced reviewers designated by the chairperson from among members of the Board. The reviewer has authority to approve the research if it meets the requirements set forth in § 46.110, to request the investigator to modify the research, or to refer the proposal to the Board for full review. If the reviewer has any significant doubt about whether the research should be approved, it should be referred to the Board for full review.

energy into the subject or an invasion of the subject's privacy. Such procedures include weighing, electrocardiogram, electroencephalogram, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography.

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in a six-week period and no more often than two times per week, from subjects 18 years of age or older who are not anemic, pregnant, or in a significantly weakened condition.

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

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

(7) Moderate exercise by healthy volunteers.

(8) Program evaluation activities that entail no deviation for subjects from the normal requirements of their involvement in the program being evaluated or benefits related to their participation in such program."

**Note.**— [The Department would add the following procedures to the above list if Alternative B under § 46.101(b) is adopted:

(9) Survey activities in which responses are recorded in such a manner that individuals cannot reasonably be identified or in which the records will not contain sensitive information about the individuals.

(10) Research activities involving the observation of human subjects carrying out their normal day-to-day activities, where observations are recorded in such a manner that individuals cannot reasonably be identified.

(11) Research involving the study of documents, records, data sets, or human materials where the sources contain identifiers, but the researcher will take information from them in such a way as to prevent future identification of any individual.]

(d) The Secretary may restrict, suspend, or terminate an institution's or Board's right to use an expedited review procedure when necessary to protect the rights of subjects.

**§ 46.112 Informed consent.**

(a) Except as provided elsewhere in this section, no subject may be involved in research covered by these regulations without the legally effective informed consent of the subject or the subject's legally authorized representative. This consent shall be sought under circumstances that provide the subject (or the subject's legally authorized 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 subject's legally authorized representative must be in a language understandable to the subject or the legally authorized representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the subject's legally authorized representative is made to waive, or to appear to waive, the subject's legal rights, including any release of the institution or its agents from liability for negligence.

(1) *Basic elements of informed consent.* In seeking informed consent, the following information shall be provided:

(A) A statement that the activity involves research, and that the Institutional Review Board has approved the solicitation of subjects to participate in the research;

(B) An explanation of the scope, aims, and purposes of the research, and the procedures to be followed (including identification of any treatments or procedures which are experimental), and the expected duration of the subject's participation;

(C) A description of any reasonably foreseeable risks or discomforts to the subject (including likely results if an experimental treatment should prove ineffective);

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

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

(F) A statement that new information developed during the course of the research which may relate to the subject's willingness to continue

participation will be provided to the subject;

(G) A statement describing the extent to which confidentiality of records identifying the subject will be maintained.

(H) An offer to answer any questions the subject (or the subject's representative) may have about the research the subject's rights, or related matters;

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

(J) Who should be contacted if harm occurs or there are questions or problems; and

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

(2) *Additional elements.* When appropriate, the Institutional Review Board shall require that some or all of the following elements of information also be provided:

(A) A statement that the particular treatment or procedure being tested may involve risks to the subject (or fetus, if the subject is pregnant or becomes pregnant) which are currently unforeseeable. This statement will often be appropriate in connection with tests of experimental drugs, or where the subjects are children, pregnant women, or women of childbearing age.

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

(C) Any additional costs to the subject or others that may result from their participation in the research.

(D) Who is conducting the study, the approximate number of subjects involved, the institution responsible for the study, and who is funding it.

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

(b) The Board may approved a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in paragraph (a), provided the Board finds (and documents) the following:

(1) The withholding or altering will not materially affect the ability of the

subject to assess the harm or discomfort of the research to the subject or others;

(2) Sufficient information will be disclosed to give the subject a fair opportunity to decide whether or not to participate;

(3) The research could not reasonably be carried out without the withholding or alteration;

(4) Information is not withheld or altered for the purpose of eliciting participation; and

(5) Whenever feasible the subject will be debriefed after his or her participation.

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

#### **§ 46.113 Documentation of informed consent.**

(a) Except as provided in paragraph (b), informed consent shall be documented in writing (and a copy provided to the subject or the subject's legally authorized representative) through either of the following methods:

(1) A written consent document embodying the elements of informed consent. This may be read to the subject or to his or her legally authorized representative, but in any event the subject or his or her legally authorized representative must be given adequate opportunity to read it. This document is to be signed by the subject or his or her legally authorized representative, and a copy supplied to the subject or representative. The Board shall retain approved sample copies of the consent form.

(2) A "short form" written consent document indicating that the elements of informed consent have been presented orally to the subject or his or her legally authorized representative. Written summaries of what is to be said to the subject (or representative) are to be approved by the Board. The short form is to be signed by the subject or his or her legally authorized representative and by a witness to the oral presentation and to the subject's signature, or that of the representative. A copy of the approved summary is to be signed by the persons officially obtaining the consent and by the witness. Copies of the form and the summary shall be provided to the subject or representative. The Board shall retain approved sample copies of the consent form and the summaries.

(b) The Board may waive the requirement for the researcher to obtain documentation of consent for some or

all subjects if it finds (and documents) either:

(1) That the only record linking the subject and the research would be the consent document, the only significant risk would be potential harm resulting from a breach of confidentiality, each subject will be asked whether he or she wants there to be documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In many cases covered by this paragraph it may be appropriate for the Board to require the investigator to provide subjects with a written statement regarding the research, but not to request their signature, or to require that oral consent be witnessed.

(c) In those cases when new information is provided to the subject during the course of the research, the information shall be reviewed and approved by the Board and a copy retained in its records.

#### **§ 46.114 Applications and proposals lacking definite plans for involvement of human subjects.**

Certain types of applications for grants or contracts are submitted to the Department with the knowledge that subjects may be involved within the support period, but definite plans would not normally be set forth in the application or proposal. These include such activities as institutional type grants (including bloc grants) where selection of specific projects is the institution's responsibility; training grants where the activities involving subjects remain to be selected and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an Institutional Review Board before an award may be made. However, except for research described in § 46.101(c), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the Institutional Review Board, as provided in these regulations, and certification submitted to the Department.

#### **§ 46.115 Research undertaken without the intention of involving human subjects.**

In the event research (conducted or supported by the Department) is undertaken without the intention of involving human subjects, but it is later

proposed to use human subjects in the research, the research must first be reviewed and approved by the Institutional Review Board, as provided in these regulations, a certification submitted to the Department, and final approval given to the proposed change by the Department.

**§ 46.116 Evaluation and disposition of applications and proposals.**

(a) The Secretary will evaluate all applications and proposals involving human subjects submitted to the Department through such officers and employees of the Department and such experts and consultants as the Secretary determines to be appropriate. This evaluation will take into consideration the apparent risks to the subjects, the adequacy of protection against these risks, the potential benefits of the proposed research to the subjects and to others, and the importance of the knowledge to be gained.

(b) On the basis of this evaluation, the Secretary may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

**§ 46.117 Cooperative research projects.**

(a) Cooperative research projects are those projects, normally supported through grants, contracts, or similar arrangements, which involve institutions in addition to the grantee or prime contractor (such as a contractor with the grantee or a subcontractor with the prime contractor). In such instances, the grantee or prime contractor remains responsible to the Department for safeguarding the rights and welfare of subjects. However, except as provided in paragraph (b), when cooperating institutions in fact conduct some or all of the research involving some or all of these subjects, each cooperating institution must comply with these regulations as though it received support for its participation in the project directly from the Department.

(b) With prior approval by the Secretary, institutions involved in cooperative research projects may comply with these regulations through joint review or other arrangements aimed at avoidance of duplication of effort.

**§ 46.118 Investigational new drug 30-day delay requirement.**

Where an institution is required to prepare or to submit a certification under these regulations and the application or proposal involves an investigational new drug within the meaning of the Food, Drug, and

Cosmetic Act, the drug must be identified in the certification together with a statement that the 30-day delay required by 21 CFR 312.1(a)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement: Provided, however, that in those cases in which the 30-day delay interval has neither expired nor been waived, a statement shall be forwarded to the Department upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received.

**§ 46.119 Confidentiality of records.**

Except as otherwise provided by Federal, State, or local law, information in the records or possession of an institution acquired in connection with an activity covered by these regulations (including all subparts of these regulations), which information refers to or can be identified with a particular subject, may not be disclosed except:

(a) With the consent of the subject or his legally authorized representative; or

(b) As may be necessary for the Secretary to carry out his responsibilities.

**§ 46.120 Use of Federal funds.**

Federal funds administered by the Department may not be expended for research involving human subjects unless the requirements of these regulations (including all subparts of these regulations) have been satisfied.

**§ 46.121 Early termination of research support; evaluation of subsequent applications and proposals**

(a) If, in the judgment of the Secretary, an institution has failed materially to comply with the terms of these regulations (including any subpart of these regulations), with respect to any particular research project, the Secretary may require that Department support for the project be terminated or suspended in the manner prescribed in applicable program requirements.

(b) In making decisions about funding applications or proposals covered by these regulations (including any subpart of these regulations), the Secretary may take into account, in addition to all other eligibility requirements and program criteria, such factors as: (1) Whether the applicant has been subject to a termination or suspension under paragraph (a) of this section; (2) whether

the applicant or the person who would direct the scientific and technical aspects of an activity has in the judgment of the Secretary failed materially to discharge his, her, or its responsibility for the protection of the rights and welfare of subjects in his, her, or its care (whether or not Department funds were involved); and (3) whether, where past deficiencies have existed in discharging this responsibility, adequate steps have in the judgment of the Secretary been taken to eliminate these deficiencies.

**§ 46.122 Research not conducted or supported by the Department.**

Except for the categories of research exempted under § 46.101(c), prior and continuing review and approval by an Institutional Review Board is required for the conduct of all research involving human subjects not funded by the Department, if the research is conducted at or supported by any institution receiving funds from the Department for the conduct of research involving human subjects.

**§ 46.123 Conditions.**

The Secretary may with respect to any research project or any class of research projects impose additional conditions prior to or at the time of funding when in the Secretary's judgment conditions are necessary for the protection of human subjects.

[FR Doc. 79-24788 Filed 8-13-79; 8:45 am]

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**Food and Drug Administration**

[21 CFR Parts 16, 56, 71, 171, 180, 310, 312, 314, 320, 330, 361, 430, 431, 601, 630, 1003, and 1010]

[Docket No. 77N-0350]

**Standards for Institutional Review Boards for Clinical Investigations; Withdrawal of Proposal**

**AGENCY:** Food and Drug Administration.

**ACTION:** Withdrawal of Proposal.

**SUMMARY:** The Food and Drug Administration (FDA) is withdrawing a proposal to establish standards for institutional review boards (IRB's) which review clinical investigations regulated by FDA. The National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (National Commission) published its IRB report after FDA published its IRB proposal. FDA is withdrawing its IRB proposal and issuing a new proposal that reflects a

consideration of the National Commission's IRB report.

**EFFECTIVE DATE:** August 14, 1979.

**FOR FURTHER INFORMATION CONTACT:** John C. Petricciani, Bureau of Biologics (HFB-4), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-496-9320.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of August 8, 1978 (43 FR 35186), FDA issued a proposal to establish standards for IRBs that review clinical investigations regulated by the agency. The proposal would have clarified IRB standards and extended the IRB requirement to articles other than new human drug products regulated by FDA.

Because the National Commission published its IRB report in the **Federal Register** on November 30, 1978 (43 FR 56174), FDA has decided to withdraw its IRB proposal of August 8, 1978, and issue a new proposal to take into account the National Commission's recommendations and the Department of Health, Education and Welfare's draft IRB proposal based on the National Commission's report.

Therefore, the proposal published in the **Federal Register** of August 8, 1978, on this matter is hereby withdrawn. Elsewhere in this issue of the **Federal Register**, the agency is reproposing an IRB regulation as well as a proposed revision of regulations governing informed consent.

This withdrawal is issued under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 602, 701(a), 52 Stat. 1041-1042 as amended, 1050-1051 as amended by 76 Stat. 791, 1054 as amended, 1055 (21 U.S.C. 321, 352, 362, 371(a))), and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1).

Dated: August 6, 1979.

**Sherwin Gardner,**

*Acting Commissioner of Food and Drugs.*

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**[21 CFR Parts 16, 56, 71, 171, 180, 310, 312, 314, 320, 330, 361, 430, 431, 601, 630, 1003, and 1010]**

**[Docket No. 77N-0350]**

**Protection of Human Subjects;  
Standards for Institutional Review  
Boards for Clinical Investigations**

**AGENCY:** Food and Drug Administration

**ACTION:** Withdrawal of Proposal;  
Reproposed Rulemaking.

**SUMMARY:** The Food and Drug Administration (FDA) is reproposing regulations governing the activities of institutional review boards (IRB's) that review clinical investigations involving human subjects and new human drug products. This proposal would clarify and extend those regulations to include IRB's that review clinical investigations involving human subjects and articles other than new human drug products regulated by FDA. FDA has decided to repropose its IRB regulations to take into account the Report and Recommendations in Institutional Review Boards (DHEW Pub. No. (OS)78008) issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) and to make the proposed regulation more compatible with the new revised regulations planned by the Department of Health, Education, and Welfare (HEW). The proposed regulations are intended to provide a common framework of operation for IRB's that review both HEW-funded research and research conducted under FDA regulatory requirements.

**DATES:** Comments by November 12, 1979. Public hearings on September 18, October 2, and October 16, 1979. The proposed effective date of the final rule is 60 days after the date of its publication in the **Federal Register**.

**ADDRESS:** Written comments, to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857. Public hearings in Bethesda, MD; San Francisco, CA; and Houston, TX.

**FOR FURTHER INFORMATION CONTACT:** John C. Petricciani, Bureau of Biologics (HFB-4), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-496-9320.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of August 8, 1978, FDA published proposed standards for institutional review boards for clinical investigations (43 FR 35186). Interested persons were given until December 6, 1978, to submit written comments on the proposal. By notice in the **Federal Register** of December 15, 1978 (43 FR 58574, the comment period was extended to June 6, 1979. During the comment period, the National Commission submitted its report and recommendations on IRB's and informed consent, and that document was published in the **Federal Register** of November 30, 1978 (43 FR 56174). In its report, the National Commission recommended revisions of the current

HEW IRB regulations (45 CFR Part 46). Because the agency stated in the August 8, 1978 proposal that FDA's regulations should be compatible with, if not identical to, those of the Department, FDA is withdrawing its IRB proposal of August 8, 1978 and in this document is publishing a revised proposal developed in conjunction with HEW in response to the recommendations made by the National Commission. The agency is also publishing elsewhere in this issue of the **Federal Register** its proposed regulation concerning informed consent. HEW and FDA both agree in principle with the recommendation of the National Commission that IRB's should operate under one set of Federal regulations. Within the constraints of their independent statutory obligations and missions, HEW and FDA have developed IRB proposals that specify, for IRB's, virtually the same structural and functional requirements, so that IRB's will have essentially uniform requirements in areas such as scope of responsibility, quorum requirements, and record retention.

The agency emphasizes that although this proposal will be essentially compatible and consistent with the regulations to be proposed by HEW, the two sets of regulations cannot be identical. The statutory authorities under which FDA regulates clinical research are different from the authorities relied upon by HEW to regulate research that it either funds or conducts. In addition, because HEW's regulations will encompass behavioral research (which FDA does not regulate), the scope of coverage and types of review required will be somewhat different.

This proposal is concerned with those IRB's that review clinical investigations regulated by FDA under sections 505(i), 507(d), and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as those clinical investigations that support applications for research or marketing permits for products regulated by FDA. This revised proposal represents the agency's attempt to achieve a common, flexible framework within which IRB's can operate, whether they are reviewing HEW-supported research or FDA-regulated research.

Because FDA is a regulatory agency, the compliance aspects of this proposal must be explicitly stated. In the initial proposal, the agency proposed sections that provide for inspection and disqualification of IRB's, and these sections have been retained without change. HEW, which employs the institutional assurance mechanism for dealing with institutions, and which may

cut off funding of projects for noncompliance, will not propose similar provisions. FDA will continue to consult with HEW during the development of final regulations so that, as much as possible, consistency of IRB structure and function can be maintained.

#### Opportunity for Public Hearing

The Food and Drug Administration stated in the August 8, 1978 proposal setting forth the standards for IRB's that three open hearings would be held to give the public an opportunity to make oral comments on both the IRB and the informed consent proposals. These hearings will be held under the administrative practices and procedures regulations, § 15.1(a) (21 CFR 15.1(a)), in (1) Bethesda, Maryland, September 18, 1979; (2) San Francisco, California, October 2, 1979 and (3) Houston, Texas, October 16, 1979.

The purpose of the hearings is (1) to provide an open forum to present views concerning the merit of the proposed regulations and their general applicability and practicability and (2) to foster greater consideration of the proposal among the scientific community, the regulated industry, and the public. Although the hearings will encompass all aspects of the proposed regulations, several specific areas of consideration on which the agency seeks advice are:

1. Administrative expense for IRB's;
2. IRB member compensation;
3. Paragraph (a) of § 56.26

*Relationship between members and investigator or investigation;*

4. § 56.81 *Quorum requirements;*
5. § 56.83 *Expedited review procedures for minor changes in the protocol of an approved clinical investigation;* and

6. Subpart K—Disqualification of an Institutional Review Board.

In preparing a final regulation, the agency will consider the administrative record of these hearings along with all other written comments received during the comment period specified in this proposal.

The hearings will take place at 9 a.m. as follows:

#### Bethesda Hearing (September 18, 1979)

Conference Room 4, Building 31, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20205

#### San Francisco Hearing (October 2, 1979)

Federal Building, Room 2007, 450 Golden Gate Avenue, San Francisco, CA 94102.

#### Houston Hearing (October 16, 1979)

University of Texas at Houston, Main Building Auditorium, 1100 East Holcombe Boulevard, Houston, TX 77030.

The presiding officer will be Dr. Mark Novitch, Associate Commissioner for Health Affairs.

A written notice of participation under the requirements of § 15.21 (21 CFR 15.21) must be filed with the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, not later than September 4 for the Bethesda hearing, September 18 for the San Francisco hearing, and October 2 for the Houston hearing. The notice of participation should contain Hearing Clerk Docket No. 77N-0350, the name, address, and telephone number of the person desiring to make a statement, along with any business affiliation, a summary of the scope of the presentation with references to the appropriate subpart of the proposed regulations, and the approximate amount of time requested for the presentation. A schedule for the hearing will be filed with the Hearing Clerk and mailed to each person who files a notice of participation within the specified filing time. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations and to request time for a joint presentation.

If the response to this notice of hearing is such that insufficient time is available to accommodate the full amount of time requested in the notices of participation received, the agency will allocate the available time among the persons making the oral presentation to be used as they wish. Formal written statements on the issues may be presented to the presiding officer on the day of the hearing for inclusion in the administrative record.

If the response to this notice of hearing is such that all persons cannot be accommodated even though the agency has allocated the available time as indicated above, the hearings will be extended for an additional day, as appropriate, for each hearing site.

The hearings will be open to the public. Any interested person may be heard on matters relevant to the issues under consideration.

#### Comments Received on the August 8, 1978 Proposal

In formulating the final regulation, the agency will consider comments received in response to the August 8, 1978 proposal along with the comments responding to this reproposal. Thus, the agency urges that comments be directed

especially to the provisions of the proposed regulation that are changed by this reproposal. To the extent that this proposal is not changed from the earlier proposal, the agency incorporates the preamble discussion that was published on August 8, 1978. The changes that have been made and the reasons for those changes are discussed below.

#### Definitions

The definitions remain largely unchanged. Some of the definitions will differ from those proposed by the Department and reflect the fact that FDA's major concern is biomedical and not behavioral research. The definitions proposed also are consistent with the definitions proposed as part of the other regulations that make up FDA's bioresearch monitoring program. The definition of "institutional review board" has been slightly modified to emphasize that the major function of an IRB is to review and approve clinical, investigations, and is not to oversee the actual conduct of such investigations. However, IRB's do have a duty to engage in periodic review of ongoing studies, as specified in §§ 56.5(a) and 56.87(a) (21 CFR 56.5(a) and 56.87(a)).

Also, a definition of "minimal risk," which conforms to that proposed by HEW, has been added as new § 56.3(h) (21 CFR 56.3(h)).

#### Circumstances in Which an Institutional Review Board Is Required

Proposed § 56.5 *Circumstances in which an institutional review board is required* has been renumbered from its designation as § 56.2 in the August 8, 1978 proposal, and the provision covering waiver of the requirement has been set out separately as § 56.6. A paragraph has been added to § 56.5 to clarify that compliance with the proposed FDA IRB regulations does not relieve IRB's from compliance with other applicable Federal, State, or local laws or regulations.

#### Cooperative Clinical Investigations

New § 56.9 (21 CFR 56.9) has been added to explicitly reduce duplicative review of multi-institutional studies.

#### Diversity of Membership of an IRB

Proposed § 56.21 (21 CFR 56.21) has been modified to be consistent with the requirements to be proposed by HEW. The requirement that an IRB possess the competence to comprehend the scientific nature of the investigation has been deleted. Although it is necessary that a board have sufficient expertise to weigh the risks inherent in a clinical investigation, actual evaluation of the

scientific merits of a proposal is not intended as a major function of an IRB.

#### **Relationship Between Members and Institution**

Proposed § 56.25 (21 CFR 56.25) has been slightly modified to be consistent with HEW requirements. Paragraph (a) now states explicitly that members of the immediate family of persons affiliated with the institution may not serve as the only unaffiliated member of a board.

#### **Relationship Between Members and Investigator or Investigation**

Paragraph (a) of § 56.26 (21 CFR 56.26) has been modified to allow sponsors to participate in the selection of members of a board when that board will review a sponsor's study. The agency foresees situations in which an institution might act as the sponsor of a study conducted within that institution and might be required to have those studies reviewed by an IRB, the members of which were selected by the institution. To prohibit these institutional sponsors from participating in the selection of their own IRB, except by requesting a waiver, would be unnecessarily burdensome. The agency invites comments on this section.

#### **Written Procedures for Review of Clinical Investigations by an IRB**

The requirement that an IRB monitor a clinical investigation has been deleted from proposed § 56.80 (21 CFR 56.80) because the monitoring function is inconsistent with the generally accepted scope of IRB responsibilities and the recommendations of the national Commission.

#### **Quorum Requirements**

This section (§ 56.82 in the August 8, 1978 proposal) has been renumbered § 56.81 (21 CFR 56.81) and has been rewritten for consistency with HEW requirements. Because research regulated by FDA always involves some degree of medical risk, however, the minimum FDA IRB quorum requirement includes at least one licensed physician to help assure the protection of the human subjects in clinical investigations.

#### **Procedures for Initial Review of a Clinical Investigation**

This section (§ 56.85 in the August 8, 1978 proposal) has been renumbered § 56.82 (21 CFR 56.82). Paragraph (e) has been modified to require that if an IRB disapproves a proposal, it must give the clinical investigator an opportunity to respond in person or in writing.

#### **Expedited Review Procedures for Minor Changes in the Protocol of an Approved Clinical Investigation**

The agency is proposing new § 56.83 (21 CFR 56.83) in response to recommendation (5) of the National Commission, which said that expedited review procedures may be adopted by IRB's for carefully defined categories of research and for minor changes in an already approved study. The agency invites comments on what constitutes a minor change in a study. No provision has been made for applying the expedited review procedure to other than minor changes in an already approved protocol because FDA has been unable to identify any studies subject to these proposed regulations that would be limited to any of the low-risk procedures identified by the National Commission. However, the agency welcomes comment on whether there are specific examples of regulated research that are limited to and that fall into any of the following classes of low-risk procedures specifically mentioned by the National Commission so that the agency can include them in the final order. The categories cited by the National Commission as appropriate for expedited review are:

Research in which the only involvement of human subjects will be in one or more of the following activities:

(1) Collection (in a nondisfiguring manner) of hair, nail clippings, and deciduous teeth.

(2) Collection of excreta and external secretions including sweat, saliva, placenta expelled at delivery, umbilical cord blood after the cord is clamped at delivery, and amniotic fluid at the time of artificial rupture of the membranes prior to or during labor.

(3) Recording of data from adults through the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. Such procedures include weighing, electrocardiogram, electroencephalogram, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography.

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in a 6-week period and no more often than two times per week, from subjects 16 years of age or older who are not anemic, pregnant, or in a significantly weakened condition.

(5) Collection of both supra- and subgingival plaque, provided the

procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

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

(7) Moderate exercise by healthy volunteers.

(8) Program evaluation activities that entail no deviation for subjects from the normal requirements of their involvement in the program being evaluated or benefits related to their participation in such program.

#### **Criteria for Approval of a Clinical Investigation**

New § 56.86 (21 CFR 56.86) describes for IRB's the basic elements required for an acceptable protocol for a clinical investigation. These elements coincide, where applicable within the limits of statutory authority, with the National Commission's recommendations and the HEW IRB proposal.

#### **Procedures for Continuing Review and Suspension or Termination of the Approval of a Clinical Investigation**

Proposed § 56.87 (21 CFR 56.87) has been changed to conform to language used by HEW and to provide IRB's with authority to suspend or terminate approval of a study rather than to suspend or terminate the study itself. Accordingly, § 56.87(b) makes it clear that if an IRB suspends or terminates the approval of a clinical investigation, the IRB must report the action immediately to FDA. The agency contemplates that when an IRB takes such serious action, the sponsor, FDA, or, in the case of funded studies, HEW, would promptly evaluate the situation and take necessary steps to suspend or terminate the clinical investigation if that were warranted on the basis of the IRB's report. Paragraph (c) responds to recommendation 3D of the National Commission as discussed in their comments on that recommendation, and conforms to proposed HEW requirements. It authorizes the IRB or its representative to observe the consent process or the clinical investigation. Paragraph (d) requires the IRB to report to institutional officials and to FDA any serious or continuing problems with clinical investigators. Paragraph (e) requires the IRB to review, at the time of periodic review of each clinical investigation, the adequacy of informed consent for subjects already entered into the study as well as for those who will be entered after the date of the periodic review. Adequacy of the

informed consent must be considered in terms of the new requirements of informed consent (see proposed Part 50, published elsewhere in this issue of the **Federal Register**).

#### Criteria for Disapproval, Suspension, or Termination of Approval of a Clinical Investigation

Proposed § 56.90 (21 CFR 56.90) has been slightly modified. The substance of proposed paragraph (b)(5) (i) through (iii) has been moved to § 56.86 (a) through (d). Paragraph (b)(5)(iv) has been deleted due to redundancy with § 56.87(a).

#### Suspension or Termination of Approval of a Clinical Investigation

The language of proposed § 56.92 (21 CFR 56.92) has been revised to conform to changes made in §§ 56.87 and 56.90, which specify that an IRB may suspend or terminate the approval of a clinical investigation, rather than the study itself.

#### Records of an IRB

Proposed § 56.185 (21 CFR 56.185) has been revised to be consistent with the recordkeeping requirements being proposed by HEW.

#### Retention of Records

Proposed § 56.195 (21 CFR 56.195) has been revised and simplified to conform to both the recommendations of the National Commission and proposed HEW requirements. IRB records are now required to be kept for a standard period of 5 years after completion of a study.

#### Disqualification of IRB's

Subpart K has been retained as originally proposed. The agency invites additional comments on this provision.

#### Conforming Amendments

The conforming amendments are repropounded without change.

The Food and Drug Administration has determined that this document does not contain an agency action covered by § 25.1(b) (21 CFR 25.1(b)), and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 601, 701(a), 706, and 801, 52 Stat. 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 76 Stat. 794-795 as amended, 90 Stat. 540-560, 562-574 (21 U.S.C. 346, 346a,

348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 361, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n)) and under authority delegated to the Commissioner of Food and Drugs, (21 CFR 5.1), the proposal published in the **Federal Register** of August 8, 1978 is withdrawn and it is repropounded that Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

#### SUBCHAPTER A—GENERAL

#### PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. In § 16.1. by adding new paragraph (b)(27) to read as follows:

§ 16.1 Scope.

\* \* \* \* \*

(b) \* \* \*  
(27) Section 56.204(b), relating to disqualifying an institutional review board.

2. By adding new Part 56 to read as follows:

#### PART 56—INSTITUTIONAL REVIEW BOARDS

##### Subpart A—General Provisions

Sec.

56.1 Scope.

56.3 Definitions.

56.5 Circumstances in which an institutional review board is required.

56.6 Waiver of requirement.

56.8 Review by institution.

56.15 Inspection of an institutional review board.

##### Subpart B—Organization and Personnel

56.21 Diversity of membership of an institutional review board.

56.9 Cooperative clinical investigations.

56.25 Relationship between members and institution.

56.26 Relationship between members and investigator or investigation.

56.34 Consultants.

##### Subparts C and D [Reserved]

##### Subpart E—Board Operations

56.80 Written procedures for review of clinical investigations by an institutional review board.

56.81 Quorum requirements.

56.82 Procedures for initial review of a clinical investigation.

56.83 Expedited review procedures for minor changes in the protocol of an approved clinical investigation.

56.86 Criteria for approval of a clinical investigation.

56.87 Procedures for continuing review and suspension or termination of the approval of a clinical investigation.

56.90 Criteria for disapproval, suspension, or termination of the approval of a clinical investigation.

56.92 Suspension or termination of the approval of a clinical investigation.

#### Subparts F through I [Reserved]

#### Subpart J—Records and Reports

56.185 Records of an institutional review board.

56.195 Retention of records.

#### Subpart K—Disqualification of an Institutional Review Board

56.200 Purpose.

56.202 Grounds for disqualification.

56.204 Notice of and opportunity for a hearing on proposed disqualification.

56.206 Final order on disqualification.

56.210 Actions on disqualification.

56.213 Public disclosure of information regarding disqualification.

56.215 Actions alternative or additional to disqualification.

56.219 Reinstatement of a disqualified institutional review board.

**Authority:** Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 601, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 76 Stat. 794-795 as amended, 90 Stat. 540-560, 562-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 361, 371(a), 376, and 381), secs. 215, 351, 354-360F, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n).

#### Subpart A—General Provisions

##### § 56.1 Scope.

This part contains the general standards for the composition, operation, and responsibility of an institutional review board that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, cosmetics, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific standards for the composition, operation, and responsibility of an institutional review board that reviews clinical investigations involving particular test articles and products may be found in other parts, e.g., Parts 312 and 812, of this chapter. Compliance with these parts is intended to protect the rights and safety of human subjects involved in such investigations and to help assure the quality and integrity of the data filed pursuant to sections 406, 408, 409, 502,



503, 505, 506, 507, 510, 513-516, 518-520, 601, 706, and 801 of the act and sections 351 and 354-360F of the Public Health Service Act.

### § 56.3 Definitions.

As used in this part:

- (a) "Act" means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392)).
- (b) "Application for research or marketing permit" includes:
- (1) A color additive petition, described in Part 71 of this chapter.
  - (2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.35 and 570.35 of this chapter.
  - (3) A food additive petition, described in Part 171 of this chapter.
  - (4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1 of this chapter.
  - (5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.
  - (6) A "Notice of Claimed Investigational Exemption for a New Drug," described in Part 312 of this chapter.
  - (7) A new drug application, described in Part 314 of this chapter.
  - (8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in Part 320 of this chapter.
  - (9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in Part 330 of this chapter.
  - (10) Data and information regarding a prescription drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, to be described in this chapter.
  - (11) Data and information regarding an antibiotic drug submitted as part of

the procedures for issuing, amending, or repealing regulations for such drugs, described in Part 430 of this chapter.

(12) An application for a biological product license, described in Part 601 of this chapter.

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

(14) An "Application for an Investigational Device Exemption", described in Part 812 of this chapter.

(15) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in section 513 of the act.

(16) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in section 514 of the act.

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

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

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

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

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

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

(c) "Clinical investigation" means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug

Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research on marketing permit. The term does not include experiments that are subject to the provisions of Part 58 of this chapter, regarding nonclinical laboratory studies.

(d) "Institution" means a person (other than an individual) who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes, for example, a hospital, retirement home, prison, academic establishment, and pharmaceutical or device manufacturer. The word "facility" as used in section 520(g) of the act is deemed to be synonymous with the term "institution" for purposes of this part.

(e) "Institutional review board" means any board, committee, or other group formally designated by an institution for the purposes of reviewing clinical investigations or other types of biomedical research involving humans as subjects, approving the initiation and conducting periodic review of such investigations or research. The term has the same meaning as the phrase "institutional review committee" as used in section 520(g) of the act.

(f) "Institutionalized subject" means:

(1) A subject who is voluntarily confined for a period of more than 24 continuous hours on the premises of, and in the care of, an institution (e.g., hospital inpatient or a retirement home resident), whether or not that institution is a sponsor of the clinical investigation; and

(2) A subject who is involuntarily confined for any period of time in a penal institution (e.g., jail, workhouse, house of detention, or prison), or another institution (e.g., a hospital) by virtue of a sentence, order, decree, or judgment under a criminal or civil statute, or awaiting arraignment, commitment, trial, or sentencing under such a statute, or by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal facility.

(g) "Investigator" means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject).

(h) "Minimal risk" means that risk of harm that is no greater in probability and no greater in magnitude than that

risk of harm that is normally encountered in the medical examination of healthy individuals.

(i) "Person" includes any individual, partnership, corporation, association, scientific or academic establishment, Government agency or organizational unit of a Government agency, and any other legal entity.

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

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

(l) "Subject" means a human who is or becomes a participant in a clinical investigation either as a recipient of the test article or as a control. A subject may be either a person in normal health or a patient to whom the test article might offer a therapeutic benefit or provide diagnostic information or a better understanding of a disease or metabolic process.

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

#### **§ 56.5 Circumstances in which an institutional review board is required.**

(a) Except as provided in § 56.6, the Food and Drug Administration will not accept any application for a research permit for a clinical investigation (as required in Parts 312, 812, and 813 of this chapter) unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an institutional review board meeting the requirements of this part.

(b) Except as provided in § 56.6, the Food and Drug Administration will not consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation unless that investigation had been approved by, and was subject to initial and continuing review by, an institutional review board meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent State or local laws or regulations, or other Federal laws or regulations, bearing upon activities covered by these regulations.

#### **§ 56.6 Waiver of requirement**

(a) The Food and Drug Administration will waive the requirement for institutional review board review where an investigation commenced prior to and was completed within 1 year following (insert effective date of this section) and was not otherwise subject to requirements for institutional review under Food and Drug Administration regulations prior to that date.

(b) Except as provided in this section, the Food and Drug Administration will waive the requirement on request of an applicant, if the Commissioner determines that the requirement is not necessary either for protecting the subjects involved or for assuring the validity or reliability of the scientific data, e.g., in a phase 3 investigational drug study (see § 312.1(a)(2), form FD-1571, item 10, of this chapter) on outpatient subjects. Any applicant for a research or marketing permit may include a request for waiver, with supporting information, in the application. In the case of an application for a research permit granted on an emergency basis, such request for waiver may be made over the telephone and be granted orally by the Food and Drug Administration at the same time the emergency application is approved on an oral basis; the approval may be conditioned upon subsequent review by an institutional review board. Written confirmation of any oral request for and grant of a waiver shall be included in the official application submitted subsequent to the emergency authorization of such application. Except in an emergency, the requirement

will not be waived in any of the following situations:

(i) When the clinical investigation involves institutionalized human subjects.

(ii) When the clinical investigation is conducted on the premises of an institution that has an institutional review board meeting the requirements of this part:

(iii) When the Food and Drug Administration determines that the risks to the subjects justify such review.

#### **§ 56.8 Review by institution.**

Approval by an institutional review board of a clinical investigation may be subject to further appropriate review and approval or disapproval by officials of the institution. Disapproval of such an investigation by an institutional review board, however, may not be overruled by such officials.

#### **§ 56.9 Cooperative clinical investigations.**

Institutions involved in multi-institutional clinical investigations may comply with these regulations through joint interinstitutional review or through any other mechanism that complies with the requirements for institutional review but avoids duplication of effort.

#### **§ 56.15 Inspection of an institutional review board.**

(a) An institutional review board shall permit authorized employees of the Food and Drug Administration, at reasonable times and in a reasonable manner, for purposes of verification of case reports and other information prepared as part of the data and information to be submitted by the sponsor to the Food and Drug Administration and for purposes of assessment of compliance with the requirements set forth in this and other parts, e.g., Parts 312 and 812 of this chapter—

(1) To inspect records required to be made or kept by the institutional review board as part of, or relevant to, its activities relating to clinical investigations;

(2) To copy such records which do not identify the names of human subjects or from which the identifying information has been deleted; and

(3) To copy such records that identify the human subjects, without deletion of the identifying information, but only upon notice that the Food and Drug Administration has reason to believe that the consent of human subjects was not obtained, that the reports submitted by the investigator to the sponsor (or to the institutional review board) do not represent actual cases or actual results

obtained, or that such reports or other required records are otherwise false or misleading.

(b) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institutional review board that reviewed the investigation refuses to allow an inspection under this section. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable statute or regulation to submit the results of the investigation to the Food and Drug Administration.

#### **Subpart B—Organization and Personnel**

##### **§ 56.21 Diversity of membership of an institutional review board.**

(a) Each institutional review board shall be composed of not fewer than five individuals with varying backgrounds to promote complete and adequate review of any clinical investigation. The board shall be sufficiently qualified through the maturity, experience, and expertise of its members and the sufficient diversity of the members' racial and cultural backgrounds to promote respect for its advice and counsel for safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the board shall be able to ascertain the acceptability of clinical investigations in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The board shall therefore include persons familiar with these areas. If a board regularly reviews research that involves a vulnerable category of subjects (e.g., prisoners, children), the board should have one or more individuals who are primarily concerned with the welfare of those subjects.

(b) A board shall not consist entirely of members of one profession, nor entirely of men, nor entirely of women.

(c) Each board shall include at least one licensed physician, one scientist, and at least one individual whose primary concerns are in a nonscientific area (e.g., a lawyer, ethicist, or member of the clergy).

(d) The records of a board shall identify each member by name, earned degrees (if any), position or occupation, specialty field (if any), representative

capacity, and by other pertinent indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to board deliberations.

##### **§ 56.25 Relationship between members and institution.**

(a) Each board shall include at least one member whose only affiliation with the institution is his or her board membership. A member of the immediate family of a person who is affiliated with the institution may not be appointed to serve as the board's unaffiliated member.

(b) The records of a board shall identify the employment or other relationship between each member and the institution, including the membership on the board (e.g., full-time employee, part-time employee, a member of governing panel or board, paid consultant, or unpaid consultant).

##### **§ 56.26 Relationship between members and investigator or investigation.**

(a) A member of a board shall not participate in the board's initial or continuing review of any clinical investigation in which the member has a conflicting interest, or of any investigation involving an investigator who participated in the member's selection for the board, except to provide information requested by the board. The board is responsible for determining whether a member has a conflicting interest. An investigator shall not participate in the selection of members for a board that will review his or her investigation. The Food and Drug Administration may waive the requirements of this section upon a request contained in the relevant application for a research or marketing permit; the request shall contain information describing the reasons why it is necessary for the investigator or sponsor to participate in the selection of board members.

(b) The records of a board shall identify the employment or other relationship between each member and the investigator or sponsor of any clinical investigation reviewed by the board (e.g., full-time employee, part-time employee, member of the governing board or panel, paid consultant, or unpaid consultant). If any such relationship exists, the records shall describe the extent to which the member participated in the initial or continuing review of the investigation.

##### **§ 56.34 Consultants.**

An institutional review board may, at its discretion, invite persons with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the board. Such persons may not vote with the board.

#### **Subparts C and D [Reserved]**

#### **Subpart E—Board Operations**

##### **§ 56.80 Written procedures for review of clinical investigations by an institutional review board.**

An institutional review board shall follow written procedures for conducting its initial and continuing review of clinical investigations and for reporting its findings and actions to the investigator, the institution and where appropriate, the sponsor. Such procedures may be promulgated by the institution or by the board.

##### **§ 56.81 Quorum requirements.**

Except when an expedited review procedure under § 56.83 is followed, an institutional review board shall conduct all significant business (e.g., approval or disapproval of a clinical investigation, or approval of a consent form) by a majority of its members present at a meeting. The majority shall include at least one licensed physician, one scientist, and one person who is neither a medical practitioner nor a scientist,

##### **§ 56.82 Procedures for initial review of a clinical investigation.**

(a) An institutional review board shall not approve a proposed clinical investigation until it has received in writing and reviews the investigational plan or protocol, reports of pertinent prior animal and human studies conducted with the test article, and the materials to be used in obtaining consent of subjects.

(b) Upon receipt of a proposed investigation, the board shall inform in writing the investigator or sponsor, as appropriate, of the date of such receipt and that the investigation may not begin until the board notifies the investigator or sponsor, as appropriate, that it has approved the investigation and until the sponsor has complied with any other preinvestigation requirements of the Food and Drug Administration.

(c) If the board has any question regarding the proposed investigation or desires any further information, it may request the investigator or sponsor to provide the necessary information or materials as written amendments to the submission. The board may advise the investigator or sponsor, as appropriate,

on modifications, conditions, or other amendments to the investigational plan or protocol and/or the material to be used to obtain consent of subjects, which might improve the acceptability of the proposed investigation to the board. Any modifications, conditions, or other amendments to the investigational plan or protocol shall be made in writing as amendments to the submission.

(d) The board should review and approve or disapprove a proposed investigation as soon as possible after receipt of the submission and any amendments in response to requests or advice from the board.

(e) The board shall notify in writing the investigator or the sponsor, as appropriate, and the institution, of its decision to approve or disapprove the proposed investigation. If the board decides to disapprove an investigation, it shall include in its written notification a statement of the reasons for its decision, and give the investigator an opportunity to respond in person or in writing.

**§ 56.83 Expedited review procedures for minor changes in the protocol of an approved clinical investigation.**

Review of any minor change in the protocol of an approved clinical investigation may be carried out by the board chairperson or by one or more experienced reviewers (who are members of the board) designated by the chairperson. The reviewer may approve the change if it meets the requirements set forth in § 56.86, may request the investigator to modify the change, or may refer the proposed change to the board for full review. If the reviewer has any significant doubt about whether the change in the protocol should be approved, the reviewer should refer the proposed change to the board for full review.

**§ 56.86 Criteria for approval of a clinical investigation.**

An institutional review board may approve a clinical investigation only where it determines that all of the following requirements are satisfied:

- (a) The research methods are appropriate to the objectives of the clinical investigation.
- (b) Selection of subjects is equitable, taking into account the purposes of the clinical investigation.
- (c) Risks to subjects are minimized by using the safest procedures consistent with sound research design.
- (d) Risks to subjects are reasonable in relation to anticipated benefits to subjects and importance of the knowledge to be gained. In making this

determination, the board should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits the subjects would be exposed to or receive even if not participating in the research). The board should not consider possible long-range effects of applying knowledge gained in the research as among those research risks that fall within the purview of its responsibility.

(e) Informed consent will be sought from each prospective subject or his or her legally authorized representative, as required by Part 50 of this chapter.

(f) Informed consent will be appropriately documented, as required by § 50.27 of this chapter.

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

(h) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(i) Applicable regulations for the protection of children, prisoners, and those institutionalized as mentally disabled are satisfied.

**§ 56.87 Procedures for continuing review and suspension or termination of the approval of a clinical investigation.**

(a) An institutional review board shall continue to review, periodically, a clinical investigation that it has approved until the investigation is concluded or is discontinued. Such continuing review shall be undertaken at intervals appropriate to the degree of risk, but not less often than once per year, to assure that the investigation is being conducted in compliance with the requirements and understandings of the board and with the requirements of the act and implementing regulations (e.g., Parts 312 and 812 of this chapter).

(b) A board may suspend and, if appropriate, terminate the approval of a clinical investigation that either is not being conducted in compliance with the requirements of § 56.86, or in which there is unexpected serious harm to the subjects. Any such suspension or termination of approval shall be reported immediately in writing to the investigator, appropriate institutional officials, and the Food and Drug Administration, and the report of such action shall include a statement of the reasons for the suspension or termination.

(c) Where appropriate, a board may observe, or may appoint a person not otherwise associated with the research or the investigator to observe, the consent process or the clinical investigation,

(d) A board shall report to the appropriate institutional officials and the Food and Drug Administration any serious or continuing noncompliance by an investigator with a requirement or determination of the board.

(e) At the time of the periodic review of studies in progress on the effective date of the informed consent order, the institutional review board shall determine whether or not: (1) revised informed consent should be obtained from human subjects already entered into the study; and (2) revised informed consent should be obtained from human subjects who will enter the study after the continuing review. In making those determinations, the institutional review board should consider the nature of the study, the degree of risk to human subjects in the study, and the adequacy of the informed consent initially approved. The decision of the institutional review board regarding the need for revised informed consent for studies in progress on the effective date of the informed consent order shall be recorded in the minutes of the meetings at which the studies undergo continuing review. Where such periodic review results in a finding that the consent obtained initially was inadequate (e.g., it contained exculpatory language, failed to reveal the experimental nature of the investigation, or did not reveal risks to the subjects), a second informed consent shall be obtained from all subjects continuing in the investigation.

**§ 56.90 Criteria for disapproval, suspension, or termination of the approval of a clinical investigation.**

(a) An institutional review board may disapprove, suspend, or terminate the approval of a clinical investigation for any of the reasons within the scope of the review authority conferred upon the board by the institution that created it. It shall state its reasons in writing. A board may reconsider its action, with or without submission of additional information, and the decision of a board of any one institution regarding a proposed clinical investigation shall not preclude a different decision by the board of another institution that might consider the same investigation.

(b) A board shall disapprove, and may suspend or terminate the approval of, a clinical investigation if it finds that:

(1) The information submitted to the board contains an untrue statement of fact material to the board or omits material information required by the board to review and evaluate the clinical investigation.

(2) The report of prior investigations with the test article is adequate to

support a conclusion that it is reasonably safe to initiate or continue the clinical investigation.

(3) The investigator does not possess the scientific training and experience appropriate to qualify the investigator as a suitable expert to investigate the safety and, where relevant, effectiveness of the test article.

(4) The available clinical laboratory facilities and medical support are inadequate to assure that the clinical investigation will be conducted properly and in conformity with the protocol.

(5) The clinical investigation exposes or will expose subjects to undue risks.

(6) The clinical investigation does not conform to, or is not being conducted in accordance with, the submission to the board and the requirements of the Act and implementing regulations (e.g., parts 312 and 812 of this chapter).

#### **§ 56.92 Suspension or termination of the approval of a clinical investigation.**

If an institutional review board decides to suspend or terminate the approval of a clinical investigation, it shall make recommendations to the institution, the Food and Drug Administration, and where appropriate, the Department of Health, Education, and Welfare regarding any subject who has previously been allowed to participate in the investigation and who either would (if the investigation were not suspended or terminated) continue to receive the test article or have it used involving him or her, or who would not continue to receive it or have it used involving him or her but who remains under the supervision of the investigator. In determining what recommendations to make, the board shall take into account, among other factors, the risks to the subject from the withdrawal of the test article or from its continued administration by another physician, the need for further medical supervision, the availability of qualified medical personnel, and the rights of the subject, including the right to participate in the decision, as to future care.

#### **Subparts F Through I [Reserved]**

#### **Subpart J—Records and Reports**

##### **§ 56.185 Records of an institutional review board.**

An institutional review board shall prepare and maintain adequate documentation of its activities, including the following:

(a) A statement of the principles that will govern the institution in the discharge of its responsibilities for protecting the rights and welfare of

subjects. This statement may include appropriate existing codes, declarations, or statements of basic ethical principles, or principles formulated by the institution itself. However, the statement of principles does not supersede Food and Drug Administration policy or applicable law.

(b) Copies of all protocols of clinical investigations reviewed, scientific evaluations, if any, that accompany the protocol, approved sample consent forms, progress reports submitted by investigators, and reports of injuries to subjects.

(c) Information on board members required under Subpart B of this part.

(d) Attendance at and minutes of board meetings, including a written summary of the discussion of any substantive issues and their resolution. Minutes shall be in sufficient detail to show the basis of actions taken by the board.

(e) Board recommendations and actions, with a record of the number of members voting in favor of and the number voting against the decision.

(f) Records of continuing review activities.

##### **§ 56.195 Retention of records.**

An institutional review board shall retain the records required by this part regarding a particular clinical investigation for at least 5 years after completion of the clinical investigation. The board shall make the records accessible for inspection by authorized employees of the Food and Drug Administration, as required by § 56.15.

#### **Subpart K—Disqualification of an Institutional Review Board**

##### **§ 56.200 Purpose.**

The purpose of disqualification of an institutional review board that fails to comply with the standards set forth in this part (or other regulations regarding such boards in this chapter) may be one or both of the following:

(a) To preclude it from reviewing clinical investigations subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the Act until such time as it becomes likely that it will abide by such regulations or that such violations will not recur. Such preclusion will assure that all such clinical investigations are under the review of a board that complies with appropriate Federal standards. The determination to disqualify an institutional review board does not necessarily constitute a finding or recommendation that the board or any

of its members should be subject to other sanctions by the institution that created it or by sponsors of clinical investigations under its review.

(b) To preclude the consideration of any clinical investigations in support of applications for a research or marketing permit from the Food and Drug Administration, which investigations have been conducted under the review of the board, until such time as the investigations are subject to review by an institutional review board that complies with the applicable standards, or it can be adequately demonstrated that such violations did not occur during, or affect the validity or acceptability of, a particular investigation or investigations. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable statute or regulation to submit the results of the investigation to the Food and Drug Administration.

##### **§ 56.202 Grounds for disqualification.**

The Commissioner may disqualify an institutional review board upon finding all of the following:

(a) The institutional review board failed to comply with any of the regulations set forth in this part or other regulations regarding such boards in this chapter;

(b) The noncompliance adversely affected the validity of the clinical investigation or the rights or the safety of the subjects; and

(c) Other lesser regulatory actions (e.g., warnings or rejection of data from individual investigations) have not been or will probably not be adequate to assure that the board will comply with such regulations in the future.

##### **§ 56.204 Notice of and opportunity for a hearing on proposed disqualification.**

(a) Whenever the Commissioner has information indicating that grounds exist under § 56.202 which in the Commissioner's opinion may justify disqualification of an institutional review board, the Commissioner may issue to the board a written notice proposing that the board be disqualified.

(b) A hearing on the disqualification of an institutional review board will be conducted in accordance with the requirements for a regulatory hearing set forth in Part 16 of this chapter.

##### **§ 56.206 Final order on disqualification.**

(a) If the Commissioner, after the regulatory hearing or after the time for

requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, makes the findings required in § 56.202, the Commissioner shall issue a final order disqualifying the institutional review board. Such order shall include a statement of the basis for that determination and shall prescribe any actions (set forth in § 56.210(b)) to be taken with regard to ongoing clinical investigations being conducted under the review of the board. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the board of the action, as well as the institution that established the board, the sponsor of each clinical investigation subject to requirements for prior submission to the Food and Drug Administration which was under the review of the board, and the investigators of such investigations who were under the review of the board.

(b) If the Commissioner, after a regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, determines not to make the findings required in § 56.202, the Commissioner shall issue a final order terminating the disqualification proceeding. Such order shall include a statement of the basis for that determination. Upon issuing a final order, the Commissioner shall notify the board and provide a copy of the order.

**§ 56.210 Actions on disqualification.**

(a) No clinical investigation subject to a requirement for prior submission to the Food and Drug Administration and to a requirement for institutional review board review under § 56.5 will be authorized by the Commissioner if such investigation is to be conducted under the review of a disqualified board.

(b) The Commissioner, after considering the nature of each ongoing clinical investigation subject to a requirement for prior submission to the Food and Drug Administration which is being conducted under the review of the board, the number of subjects involved, the risks to them from suspension of the investigation, and the need for involvement of an acceptable institutional review board, may direct, in the final order disqualifying a board under § 56.206(a), that, among other things, one or more of the following actions be taken with regard to each such investigation:

(1) The investigation may be terminated or suspended in its entirety until the board is reinstated under

§ 56.219 or another board accepts responsibility for review of the investigation.

(2) No new subject shall be allowed to participate, or be requested to participate, in the investigation until the board is reinstated under § 56.219 or, another board accepts responsibility for review of the investigation.

(3) Any subject who has previously been allowed to participate in the investigation and who remains under the supervision of an investigator, but who is no longer receiving the test article or having it used involving him or her (i.e., one having followup monitoring by the investigation or one acting as a control) should continue to be monitored by the investigator but shall not again receive the test article, or have it used involving him or her, until the board is reinstated under § 56.219 or another board accepts responsibility for review of the investigation.

(4) Any subject who has been allowed to participate in the investigation and who, but for suspension of the investigation, would continue to receive the test article or have it used involving him or her, shall not receive it or have it used until either.

(i) Another board accepts responsibility for review of the investigation, or

(ii) The clinical investigator determines in writing that it is contrary to the health of the subject to defer further use of the test article until another board can assume responsibility for review of the investigation. In such a case, the Commissioner may impose any further conditions that the Commissioner deems appropriate to protect the rights and safety of the subject.

(c) Once an institutional review board has been disqualified, each application for a research or marketing permit, whether approved or not, containing or relying upon any clinical investigation conducted under the review of the board may be examined to determine whether the investigation was or would be essential to a regulatory decision regarding the application. If it is determined that the investigation was or would be essential, the Commissioner shall also determine whether the investigation is acceptable, notwithstanding the disqualification of the board. Any investigation reviewed by a board before or after its disqualification may be presumed to be unacceptable, and the person relying on the investigation may be required to establish that the investigation was not affected by the circumstances which led to disqualification of the board, e.g., by

submitting validating information. If the investigation is determined to be unacceptable, such investigation shall be eliminated from consideration in support of the application, and such elimination may serve as new information justifying the termination or withdrawal of approval of the application.

(d) No clinical investigation begun under the review of an institutional review board after the date of its disqualification may be considered in support of any application for a research or marketing permit, unless the board has been reinstated under § 56.219. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable statute or regulation to submit the results of the investigation to the Food and Drug Administration.

**§ 56.213 Public disclosure of information regarding disqualification.**

(a) Upon issuance of a final order disqualifying an institutional review board, the Commissioner may notify all or any interested persons. Such notice may be given in the discretion of the Commissioner whenever the Commissioner believes that such disclosure would further the public interest or would promote compliance with the regulations set forth in this part. Such notice, if given, will include a copy of the final order issued under § 56.206(a) and will state that the disqualification constitutes a determination by the Commissioner that the board is not eligible to review clinical investigations subject to requirements for prior submission to the Food and Drug Administration and that the results of any clinical investigations conducted under the review of the board may not be considered by the Food and Drug Administration in support of any application for a research or marketing permit. The notice will further state that it is given because of the professional relations between the board and the person notified and that the Food and Drug Administration is not advising or recommending that any action be taken by the person notified.

(b) A determination that an institutional review board has been disqualified and the administrative record regarding such determination are disclosable to the public under Part 20 of this chapter.

(c) Whenever the Commissioner has reason to believe that an institutional review board may be subject to

disqualification, the Commissioner shall so notify other agencies in the Department of Health, Education, and Welfare that support research involving human subjects at the time of or after proposing disqualification of the board under § 56.204(a).

**§ 56.215 Actions alternative or additional to disqualification.**

Disqualification of an institutional review board under this subpart is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Commissioner may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The Commissioner may also refer pertinent matters to another Federal, State, or local government agency for such action as that agency determines to be appropriate.

**§ 56.219 Reinstatement of a disqualified institutional review board.**

(a) An institutional review board that has been disqualified may be reinstated as eligible to review clinical investigations subject to requirements for prior submission to the Food and Drug Administration, or as acceptable to be the reviewer of clinical investigations to be submitted to the Food and Drug Administration, if the Commissioner determines, upon an evaluation of a written submission from the board, that the board has adequately assured that it will operate in compliance with the standards set forth in this part and other applicable regulations in this chapter, e.g., Parts 312 or 812.

(b) A disqualified board that wishes to be so reinstated shall present in writing to the Commissioner reasons why it believes it should be reinstated and a detailed description of the corrective actions it has taken or intends to take to assure that the acts or omissions that led to disqualification will not recur. The Commissioner may condition reinstatement upon the board's being found in compliance with the applicable regulations upon an inspection.

(c) If a board is reinstated, the Commissioner shall so notify the board and all persons who were notified under § 56.213 of the disqualification of the board. A determination that a board has been reinstated is disclosable to the public under Part 20 of this chapter.

**PART 71—COLOR ADDITIVE PETITIONS**

3. By amending Part 71:

a. In § 71.1 by adding new paragraph (i) to read as follows:

**§ 71.1 Petitions.**

(i) If clinical investigations involving human subjects are involved, petitions filed with the Commissioner under section 706(b) of the act shall include a statement regarding each such clinical investigation contained in the petition that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

b. In § 71.6 by adding a new sentence at the end of paragraph (b) to read as follows:

**§ 71.6 Extension of time for studying petitions; substantive amendments; withdrawal of petitions without prejudice.**

(b) \* \* \* If clinical investigations involving human subjects are involved, additional information or data submitted in support of filed petitions shall include a statement regarding each such clinical investigation from which the information or data are derived, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

**SUBCHAPTER 9—FOOD FOR HUMAN CONSUMPTION**

**PART 171—FOOD ADDITIVE PETITIONS**

4. By amending Part 171:

a. In § 171.1 by adding new paragraph (m) to read as follows:

**§ 171.1 Petitions.**

(m) If clinical investigations involving human subjects are involved, petitions filed with the Commissioner under section 409(b) of the act shall include a statement regarding each such clinical investigation relied upon in the petition that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

b. In § 171.6 by adding a new sentence at the end of the paragraph to read as follows:

**§ 171.6 Amendment of petition.**

\* \* \* If clinical investigations involving human subjects are involved, additional information and data submitted in support of filed petitions shall include a statement regarding each such clinical investigation from which the information or data are derived that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6) of this chapter.

**PART 180—FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS OR IN CONTACT WITH FOOD PENDING ADDITIONAL STUDY**

Part 180 is amended in § 180.1 by adding a new paragraph (c)(6) to read as follows:

**§ 180.1 General.**

(c) \* \* \*

(6) If clinical investigations involving human subjects are involved, such investigations filed with the Commissioner shall include, with respect to each investigation, either a statement that the investigation has been or will be conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter; or a statement that the investigation is not subject to such requirements in accordance with § 56.6 of this chapter.

**SUBCHAPTER D—DRUGS FOR HUMAN USE**

**PART 310—NEW DRUGS**

**§ 310.3 [Amended]**

5. By amending Part 310 in § 310.3 *Definitions and interpretations*, by deleting and reserving paragraph (j).

**PART 312—NEW DRUGS FOR INVESTIGATIONAL USE**

6. By amending Part 312 in § 312.1 by redesignating paragraphs (d)(11) and (d)(12) as (d)(12) and (d)(13) and adding a new paragraph (d)(11) to read as follows:

**§ 312.1 Conditions for exemption of new drugs for investigational use.**

(d) \* \* \*  
(11) The clinical investigations are not being conducted in compliance with the requirements regarding institutional

review set forth in this part or Part 56 of this chapter, or

**PART 314—NEW DRUG APPLICATIONS**

7. Part 314 is amended:  
a. In § 314.1 by adding a new item 17 to Form FD-356H in paragraph (c)(2) and by redesignating paragraphs (f)(7) and (f)(8) as (f)(8) and (f)(9) and adding a new paragraph (f)(7) to read as follows:

**§ 314.1 Applications.**

- (c) \* \* \*
(2) \* \* \*

Form FD-356H—Rev. 1974:

17. Conduct of clinical investigations. A statement regarding each clinical investigation involving human subjects contained in the application that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

(f) \* \* \*
(7) A statement regarding each clinical investigation involving human subjects contained in the application that it either was conducted in compliance with the requirements the institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

b. In § 314.8 by adding a new paragraph (n) to read as follows:

**§ 314.8 Supplemental applications.**

(n) A supplemental application that contains clinical investigations involving human subjects shall include a statement by the applicant regarding each such investigation that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

c. In § 314.9 by adding new paragraph (e) to read as follows:

**§ 314.9 Insufficient information in application.**

(e) The information contained in an application shall be considered insufficient to determine whether a drug is safe and effective for use unless the

application includes a statement regarding each clinical investigation involving human subjects contained in the application that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

d. In § 314.12 by adding new paragraph (e) to read as follows:

**§ 314.12 Untrue statements in application.**

(e) Any clinical investigation involving human subjects contained in the application subject to the requirements for institutional review set forth in Part 56 of this chapter was not conducted in compliance with such requirements.

e. In § 314.110 by adding new paragraph (a)(11) to read as follows:

**§ 314.110 Reasons for refusing to file applications.**

(11) The applicant fails to include in the application a statement regarding each clinical investigation involving human subjects contained in the application that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.26 of this chapter.

f. In § 314.111 by adding paragraph (a)(11) to read as follows:

**§ 314.111 Refusal to approve the application.**

(11) Any clinical investigation involving human subjects contained in the application subject to the requirements for institutional review set forth in Part 56 of this chapter was not conducted in compliance with such requirements.

g. In § 314.115 by adding new paragraph (c)(7) to read as follows:

**§ 314.115 Withdrawal of approval of an application.**

(7) That any clinical investigation involving human subjects contained in the application subject to the requirements for institutional review set forth in Part 56 of this chapter was not conducted in compliance with such requirements.

**PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS**

8. Part 320 is amended:  
a. In § 320.31 by adding a new paragraph (f) to read as follows:

**§ 320.31 Applicability of requirements regarding a "Notice of Claimed Investigational Exemption for a New Drug."**

(f) An in vivo bioavailability study in humans shall be conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, regardless of whether the study is conducted under a "Notice of Claimed Investigational Exemption for a New Drug."

b. In § 320.57 by adding a new paragraph (e) to read as follows:

**§ 320.57 Requirements of the conduct of in vivo bioequivalence testing in humans.**

(e) If a bioequivalence requirement provides for in vivo testing in humans, any person conducting such testing shall comply with the requirements of § 320.31.

**PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED**

9. Part 330 is amended in § 330.10 by adding new paragraph (e) to read as follows:

**§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.**

(e) Institutional review. Information and data submitted under this section after (insert effective date of this paragraph) shall include a statement regarding each clinical investigation involving human subjects, from which the information and data are derived, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

**PART 361—PRESCRIPTION DRUGS FOR HUMAN USE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED: DRUGS USED IN RESEARCH**

10. Part 361 is amended in § 361.1 by revising paragraph (d)(9) to read as follows:



**§361.1 Radioactive drugs for certain research uses.**

\* \* \* \* \*

(d) \* \* \*  
 (9) *Approval by an institutional review board.* The investigator shall obtain the review and approval of an institutional review board that conforms to the requirements for Part 56 of this chapter.

\* \* \* \* \*

**PART 430—ANTIBIOTIC DRUGS; GENERAL**

11. Part 430 is amended in § 430.20 by adding new paragraph (g) to read as follows:

**§ 430.20 Procedures for the issuance, amendment, or repeal of regulations.**

\* \* \* \* \*

(g) No regulation providing for the certification of an antibiotic drug for human use shall be issued or amended unless each clinical investigation in involving human subjects on which the issuance or amendment or the regulation is based was conducted in compliance with the requirements for institutional review set for the in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

**PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS**

12. Part 431 is amended in § 431.17 by adding a new paragraph (1) to read as follows:

**§ 431.17 New antibiotic and antibiotic-containing products.**

\* \* \* \* \*

(1) A statement regarding each clinical investigation involving human subjects contained in the request that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

**SUBCHAPTER F—BIOLOGICS**

**PART 601—LICENSING**

13. Part 601 is amended:

a. In § 601.2 by revising paragraph (a) to read as follows:

**§ 601.2 Applications for establishment and product licenses; procedures for filing.**

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data

derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the, practices used in the study and those required in the regulations; a statement regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data have been received from the manufacturer by the Bureau of Biologics. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section.

b. In § 601.25 by revising paragraph (h)(1) and adding a new paragraph (1) to read as follows:

**§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.**

\* \* \* \* \*

(h) *Additional studies.* (1) Within 30 days following publication of the final order, each licensee for a biological product designated as requiring further study to justify continued marketing on an interim basis, pursuant to paragraph (f)(3) of this section, shall satisfy the Commissioner of Food and Drugs in writing that studies adequate and appropriate to resolve the questions raised about the product have been undertaken, or the Federal Government may undertake these studies. Any study involving a clinical investigation that

involves human subjects shall be conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, unless it is not subject to such requirements in accordance with § 56.6 of this chapter. The Commissioner may extend this 30-day period if necessary, either to review and act on proposed protocols or upon indication from the licensee that the studies will commence at a specified reasonable time. If no such commitment is made, or adequate and appropriate studies are not undertaken, the product licenses shall be revoked.

(j) [Reserved]

(k) [Reserved]

(l) *Institutional review.* Information and data submitted under this section after (insert effective date of this paragraph) shall include statements regarding each clinical investigation involving human subjects that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.6 of this chapter.

\* \* \* \* \*

b. By revising § 601.30 to read as follows:

**§ 601.30 Licenses required; products for controlled investigation only.**

Any biological or trivalent organic arsenical manufactured in any foreign country and intended for sale, barter or exchange shall be refused entry by collectors of customs unless manufactured in an establishment holding an unsuspended and unrevoked establishment license and license for the product. Unlicensed products that are not imported for sale, barter or exchange and that are intended solely for purposes of controlled investigation are admissible only if the investigation is conducted in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act and the requirements set forth in Parts 56, 58, and 312 of this chapter.

**PART 630—ADDITIONAL STANDARDS FOR VIRAL VACCINES**

14. Part 630 is amended;

By revising the first sentence of § 630.11 to read as follows:

**§ 630.11 Clinical trials to qualify for license.**

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with Part 56 of this chapter, unless exempted under § 56.6. \* \* \*

b. By revising the first sentence of § 630.31 to read as follows:

**§ 630.31 Clinical trials to qualify for license.**

To qualify for license, the antigenicity of the vaccine shall be determined by clinical trials of adequate statistical design conducted in compliance with Part 56 of this chapter, unless exempted under § 56.6 of this chapter, by subcutaneous administration of the product. \* \* \*

c. By revising § 630.51 to read as follows:

**§ 630.51 Clinical trials to qualify for license.**

To qualify for license, the antigenicity of Mumps Virus Vaccine, Live, shall be determined by clinical trials conducted in compliance with Part 56 of this chapter, unless exempted under § 56.6 of this chapter, that follow the procedures prescribed in § 630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of mumps-susceptible individuals, each having received the parenteral administration of a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies (§ 630.50(b)) when used under comparable conditions.

d. By revising § 630.61 to read as follows:

**§ 630.61 Clinical trials to qualify for license.**

To qualify for license, the antigenicity of Rubella Virus Vaccine, Live, shall be determined by clinical trials conducted in compliance with Part 56 of this chapter, unless exempted under § 56.6 of this chapter, that follow the procedures prescribed in § 630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of rubella susceptible individuals, each having received the parenteral administration of a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies when used under comparable conditions.

e. By revising the first sentence of § 630.81 to read as follows:

**§ 630.81 Clinical trials to qualify for license.**

In addition to demonstrating that the measles component meets the requirements of § 630.31, the measles and smallpox antigenicity of the final product shall be determined by clinical

trials of adequate statistical design conducted in compliance with Part 56 of this chapter, unless exempted under § 56.6 of this chapter, and with three consecutive lots of final vaccine manufactured by the same methods and administered as recommended by the manufacturer. \* \* \*

**PART 1003—NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY**

15. In § 1003.31 by revising paragraph (b) to read as follows:

**§ 1003.31 Granting the exemption.**

(b) Such views and evidence shall be confined to matters relevant to whether the defect in the product or its failure to comply with an applicable Federal standard is such as to create a significant risk of injury, including genetic injury, to any person and shall be presented in writing unless the Secretary determines that an oral presentation is desirable. Where such evidence includes clinical investigations involving human subjects, the data submitted shall include, with respect to each clinical investigation, either a statement that each investigation was conducted in compliance with the requirements set forth in Part 56 of this chapter, or a statement that the investigation is not subject to such requirements in accordance with § 56.6 of this chapter. \* \* \* \* \*

**SUBCHAPTER I—RADIOLOGICAL HEALTH**

**PART 1010—PERFORMANCE STANDARDS FOR ELECTRONIC PRODUCTS: GENERAL**

16. Part 1010 is amended

a. By amending § 1010.4 by adding paragraph (b)(1)(xi) to read as follows:

**§ 1010.4 Variances.**

\* \* \* \* \*

(b) \* \* \*

(1) \* \* \*

(xi) If the electronic product is used in a clinical investigation involving human subjects and subject to the requirements for institutional review set forth in Part 56 of this chapter, the investigation shall be conducted in compliance with such requirements. \* \* \* \* \*

b. In § 1010.5 by revising paragraph (c)(12) to read as follows:

**§ 1010.5 Exemptions for products intended for United States Government use.**

\* \* \* \* \*

(c) \* \* \*

(12) Such other information required by regulation or by the Director, Bureau of Radiological Health, to evaluate and act on the application. Where such information includes nonclinical laboratory studies, the information shall include, with respect to each nonclinical study, either a statement that each study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations. Where such information includes clinical investigations involving human subjects, the information shall include, with respect to each clinical investigation, either a statement that each investigation was conducted in compliance with the requirements set forth in Part 56 of this chapter, or a statement that the investigation is not subject to such requirements in accordance with § 56.6 of this chapter. \* \* \* \* \*

Interested persons may, on or before November 12, 1979, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: August 6, 1979.

**Sherwin Gardner,**  
*Acting Commissioner of Food and Drugs,*

[FR Doc. 79-24786 Filed 8-13-79; 8:45 am]

**BILLING CODE 4110-03-M**

[21 CFR Parts 50, 71, 171, 180, 310, 312, 314, 320, 330, 361, 430, 431, 601, 630, 813, 1003, 1010]

[Docket No. 78N-0400]

### Protection of Human Subjects; Informed Consent

**AGENCY:** Food and Drug Administration.  
**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing a regulation to provide protection for human subjects of clinical investigations that are subject to requirements for prior submission to FDA or conducted in support of applications for permission to conduct further research or to market regulated products. This proposal is intended to clarify existing agency regulations governing informed consent and to provide greater protection of the rights of human subjects involved in research activities that fall within the jurisdiction of FDA. In addition, the agency is announcing three informal public hearings concerning both this proposal and the reproposal of standards for Institutional Review Boards (IRB's), which is also being published in this issue of the **Federal Register**.

**DATES:** Written comments on this proposal by November 12, 1979 public hearings on September 18, October 2, and October 16, 1979 the proposed effective date of the final rule is 90 days after the date of its publication in the **Federal Register**.

**ADDRESS:** Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857. Public hearings in Bethesda, MD; San Francisco, CA; and Houston, TX.

**FOR FURTHER INFORMATION CONTACT:** John C. Petricciani, Bureau of Biologics (HFB-4), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-496-9320.

**SUPPLEMENTARY INFORMATION:** The agency believes that a complete revision of FDA requirements relating to informed consent is needed because (1) current regulations have not been comprehensively reviewed in 12 years; (2) actions by the Department of Health, Education, and Welfare (HEW) and the Congress suggest the need for, and desirability of, strengthening and clarifying informed consent requirements as they apply to research that involves human subjects and is intended for submission to FDA (3) when possible, informed consent requirements adopted by FDA should be

identical to, or compatible with, HEW regulations; (4) the General Accounting Office (GAO) has recommended changes in current FDA regulations; (5) Congress, in enacting the Medical Device Amendments of 1976 (Pub. L. 94-295, 90 Stat. 539-583), required that informed consent be obtained before an investigational device is used on a human subject; (6) the new FDA Bioresearch Monitoring Program, designed to ensure compliance with FDA requirements to protect human research subjects and reinforce the validity and reliability of clinical data submitted to FDA, can be more efficiently and effectively conducted with uniform, agency-wide requirements for informed consent; and (7) the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) has issued its report and recommendations regarding Institutional Review Boards and informed consent, published in the **Federal Register** of November 30, 1978 (43 FR 56174). Because the agency finds that informed consent is a concept that has grown more complex as it has evolved, and because the standards for informed consent reflected by the Medical Device Amendments of 1976 are more stringent than the standards reflected by the Drug Amendments of 1962 (Pub. L. 87-781, 76 Stat. 780-796), there is included in this preamble an extensive discussion of the background and history of informed consent as it applies to experimentation with human subjects.

### Opportunity for Public Hearing

As announced in the proposal on Institutional Review Boards, published elsewhere in this issue of the **Federal Register**, FDA will hold three open hearings to give the public an opportunity to make oral comments on both the informed consent and the IRB proposals. Interested parties are referred to the IRB proposal on page 47698 of this issue for full information.

### Background

#### *The Federal Food, Drug, and Cosmetic Act of 1938*

In 1938, Congress for the first time required that a manufacturer demonstrate the safety of a new drug before introducing the drug into interstate commerce. This requirement was not intended, however, to apply to shipments to clinical investigators who were testing drugs to determine toxicity or other safety problems. Therefore section 505(i) of the Federal Food, Drug,

and Cosmetic Act of 1938 (Pub. L. 717, 52 Stat 1052 (21 U.S.C. 355(i)) directed that:

The Secretary shall promulgate regulations for exempting from the operation of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety of drugs.

In implementing this section, FDA did not require notice to, or review by, the agency of the proposed research, nor did FDA impose extensive conditions on the person claiming the exemption. The agency required that the drug be labeled "for investigational use only," that the manufacturer keep records on how much drug was supplied and to which investigators it was sent, and that the investigators file with the manufacturer (but not with FDA) a statement that the drug was intended for investigational use by the investigator or under the investigator's supervision. Under section 505(i) of the act, the FDA's only review of the conduct of research occurred when the manufacturer submitted a New Drug Application (NDA). Between 1938 and 1962, FDA regulations were silent on the matter of informed consent.

#### *Nuremberg Code of Ethics in Medical Practice*

Following World War II, disclosure of brutal experiments conducted in Nazi concentration camps forced a re-evaluation of the moral, ethical, and legal principles applied to research involving human subjects. The war crimes trial of physicians at Nuremberg produced a set of ten basic principles, which has since been termed the "Nuremberg Code of Ethics in Medical Research." First on the list was informed consent, which was described in terms of the information to be provided and the ability of the subject to consent:

The voluntary consent of the human subject is absolutely essential.

This means that the person should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted all inconveniences and hazards reasonably

to be expected and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

The Code did not discuss either the situations in which consent might not be necessary or the requirements for documenting consent.

#### *The Drug Amendments of 1962*

In late July 1962, during the deliberations leading to the Drug Amendments of 1962 (Pub. L. 87-781, 76 Stat. 780-796), reports of the thalidomide drug disaster appeared in print. One of the many unfortunate aspects of that tragedy was that many of the pregnant women in the United States to whom thalidomide was given were not informed that the drug was experimental, that they were research subjects, or that the safety of the drug had not been established. As a result of the thalidomide reports, a revised and strengthened bill, substitute S. 1552, was reported out of the Senate Committee on the Judiciary.

During Senate floor debates on August 23, 1962, Senator Jacob Javits of New York offered an amendment (No. 8-22-62-A) that marked the first appearance of recommended legislation regarding information to be provided to human subjects of clinical investigations. Although the amendment did not require that consent be obtained, it did provide that no investigational drug could be administered unless the person to whom the drug was to be given had been advised as to the safety status of the drug. In his remarks, Senator Javits cited, as one reason for Federal legislation on patient consent, a survey of State laws conducted by the American Law Division of the Library of Congress. In this survey, no State statutes were found that covered the experimental use of a drug or required a physician to inform a patient of such use. The Javits amendment was supported by Senators Carroll, Eastland, and McClellan, all of whom endorsed the principle of consent. The amendment itself was not adopted, however, at least in part due to concern that an absolute requirement that information be given in every case might be detrimental to certain patients. Instead, the Senate voted that regulations issued by the Secretary have "due regard for the professional ethics of the medical

profession and the interests of patients." (See 108 Cong. Record 16329-30, 16333-39, 16341-43, 87th Cong., 2d Sess., Aug. 23, 1962.)

In the House of Representatives, the Interstate and Foreign Commerce Committee reported out H.R. 11581 on September 22, 1962. This bill directed the Secretary to condition investigational drug exemptions upon the requirement that investigators inform every subject of the experimental nature of a drug and obtain the consent of the subject or the subject's representative. The legislation also required investigators to certify to their research sponsors that consent would be obtained from their patients and subjects. These provisions were similar to the Javits amendment in that no specific proposals were made regarding the information to be given to a subject, the ability of the subject to consent, or circumstances in which consent might not be obtainable. During the debates on the House floor, the issue of whether consent should be mandatory in all cases was discussed in detail, but the House bill was adopted unchanged. (See 108 Cong. Record 19889-90, 19896, 19903-04, 87th Cong., 2d Sess., Sept. 27, 1962.)

On October 3, 1962, the House-Senate Committee reported out a revised version of S. 1552, in which section 103(b) proposed new language on consent of research subjects. (H. Rept. No. 2526, 87th Cong., 2d Sess., Oct. 3, 1962, pp. 4-5.)

This language was ultimately enacted on October 10, 1962, in section 505(i) of the act (21 U.S.C. 355(i)). In discussing this revised version, Senator Estes Kefauver of Tennessee and Senator Javits offered the following statements (108 Cong. Record 22038, 22042-43, 87th Cong., 2d Sess., Oct. 3, 1962):

**Mr. Kefauver.** \* \* \* With regard to patient consent the Senate bill required that investigators shall have due regard to the "interest of patients," while the House bill specifically required that regulations on experimental-use drugs must condition the use of such drugs on the patient's consent to such use. The conferees adopted substituted language which requires the Secretary of HEW to include in his regulations an experimental drug provision for obtaining patient consent, "except where obtaining such consent would not be feasible, or in the professional judgment of the investigator would be contrary to the best interest of the patient."

The Senator from Nebraska offered the compromise language, and after some rearrangement, it was adopted. It was satisfactory and solved one of the

very difficult problems we had in the conference. \* \* \*

**Mr. Javits.** \* \* \* As I understand the conference report, it requires that the Secretary of Health, Education, and Welfare shall include in his regulations a provision to the effect that experimental drugs may be used only after the patient's consent is obtained. I point out, in that connection, the importance of the use of the word "shall" at that point in this measure. The use of the word "shall" definitely imposes this responsibility on the medical profession, with the result that the doctor will have, in addition to his responsibility under his Hippocratic oath and under the canon of ethics, the clear responsibility of finding, if he decides not to obtain the consent of the patient, that to obtain his consent would not be "feasible" or in the professional judgment of the investigator would be "contrary to the best interests" of the patient. \* \* \*

**Mr. Kefauver.** \* \* \* The resultant language requires the patient's consent except in instances—as the Senator from New York has said—in which it is deemed not feasible or, in the doctor's best judgment, is contrary to the best interests of such human beings. The decision must be according to the best judgment of the doctors involved. There will be no interference with the doctor-patient relationship. But the responsibility for not obtaining the patient's consent will clearly rest with the physicians.

**Mr. Javits.** I was seeking to establish the point that it will be the professional responsibility of the doctor in both cases—both as to the determination of feasibility and as to the determination of the effect on the patient. The inclusion of that provision imposes a greater sanction than merely the use of the word "feasible."

As professional men, the Senator from Tennessee and the Senator from Colorado and I understand that one will not assume that responsibility except on the basis of the greatest exercise of conscience. That is what the conferees have provided for.

Senator Carroll also supported the revised language (id., 22041-42).

As enacted on October 10, 1962, the Drug Amendments of 1962 added the following, among other, language to section 505(i) of the act:

Such regulations [exempting drugs intended solely for investigational use by experts from the requirement for approval of a new drug application before interstate shipment] shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional

judgment, contrary to the best interests of such human beings. (76 Stat. 783.)

The legislative history provides little guidance as to what information must be given to subjects to obtain consent, or how the legal and actual ability of a subject to consent freely and knowingly should be determined.

*Implementation of the Drug Amendments of 1962 (1962-1976).*

On August 10, 1962, before enactment of the Drug Amendments, the FDA proposed in the **Federal Register** (27 FR 7990) an extensive revision and expansion of its regulations under section 505(i) of the act as enacted in 1938. These proposals did not refer to informed consent; nevertheless, when made final on January 8, 1963 (28 FR 179), the regulations included a requirement now codified in § 312.1(a)(12) and (13) (21 CFR 312.1(a)(12) and (13), formerly § 130.3(a)(12) and (13) before recodification published in the **Federal Register** of March 29, 1974 (39 FR 11680)) that each clinical investigator certify to the sponsor of the drug research that informed consent would be obtained in accordance with the newly revised section 505(i) of the act, except where not required by that statute. (See Form FD-1572, item 6g, and Form FD-1573, item 4g.)

The FDA did not attempt to define specifically the content or form of informed consent, or the circumstances under which the law did not require consent of the research subject, until 1966. In the **Federal Register** of August 30, 1966 (31 FR 11415), the Commissioner issued § 130.37 (21 CFR 130.37) that required consent in all nontherapeutic drug studies and in all but exceptional cases of therapeutic application of an experimental drug. The exceptions were allowed (a) when communication with the patient or the patient's legal representative was not possible and it was imperative to administer the drug without delay, and (b) when communication of the necessary information would seriously affect the disease state of the patient and the physician had made a professional judgment that the patient's best interests would suffer if consent were sought. The regulation also spelled out the types of information that were to be conveyed to the subject: (a) the nature, duration, and purpose of the administration of the investigational drug; (b) the method and means by which the drug was to be administered; (c) all inconveniences and hazards reasonably to be expected, including the fact (when applicable) that the person might be used as a control;

(d) the existence of alternative forms of therapy, if any; and (e) the effects upon the subject's health or person that might possibly come from the administration of the investigational drug. Finally, the 1966 order established an absolute rule that consent was always to be obtained in writing.

In 1967, the FDA reconsidered the new regulation in light of the Declaration of Helsinki, adopted by the World Health Organization in 1984, and the "Ethical Guidelines for Clinical Investigation," adopted by the House of Delegates of the American Medical Association (AMA) in 1966. The 1964 Declaration of Helsinki, now set forth in full in § 312.20(b)(1)(iv) (21 CFR 312.20(b)(1)(iv)), established the following principles regarding informed consent:

**II. Clinical Research Combined With Professional Care**

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.

\* \* \* \* \*

**III. Nontherapeutic Clinical Research**

\* \* \* \* \*

2. The nature, the purpose, and the risks of clinical research must be explained to the subject by the doctor.

3a. Clinical research on the human being cannot be undertaken without his free consent after he has been fully informed if he is legally incompetent, the consent of the legal guardian should be procured.

3b. The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.

\* \* \* \* \*

The 1966 AMA "Ethical Guidelines for Clinical Investigation" discuss informed consent in this way:

(3) In clinical investigation primarily for treatment—

\* \* \* \* \*

B. Voluntary consent must be obtained from the patient, or from his legally authorized representative if the patient lacks the capacity to consent, following—

(a) Disclosure that the physician intends to use an investigational drug or experimental procedure.

(b) A reasonable explanation of the nature of the drug or procedure to be used, risks to be expected, and possible therapeutic benefits;

(c) An offer to answer any inquiries concerning the drug or procedure; and

(d) A disclosure of alternative drugs or procedures that may be available.

i. In exceptional circumstances and to the extent that disclosure of information concerning the nature of the drug or experimental procedure or risks would be expected to materially affect the health of the patient and would be detrimental to his best interests, such information may be withheld from the patient. In such circumstances such information shall be disclosed to a responsible relative or friend of the patient where possible.

ii. Ordinarily, consent should be in writing, except where the physician deems it necessary to rely upon consent in other than written form because of the physical or emotional state of the patient.

iii. Where emergency treatment is necessary and the patient is incapable of giving consent and no one is available who has authority to act on his behalf, consent is assumed.

(4) In clinical investigation primarily for the accumulation of scientific knowledge—

\* \* \* \* \*

B. Consent, in writing, should be obtained from the subject or from his legally authorized representative if the subject lacks the capacity to consent, following—

(a) A disclosure of the fact that an investigational drug or procedure is to be used

(b) A reasonable explanation of the nature of the procedure to be used and risks to be expected and

(c) An offer to answer any inquiries concerning the drug or procedure.

\* \* \* \* \*

D. No person may be used as a subject against his will.

\* \* \* \* \*

As a consequence of this reconsideration, FDA published proposed changes to what is now § 310.102 (21 CFR 310.102, formerly § 130.37 before the March 29, 1974 recodification) on March 11, 1967 (32 FR 3994), which were adopted on June 20, 1967 (32 FR 8753). Two significant changes were made. First the amended regulations allowed oral rather than written consent in large-scale clinical studies in the later stages of the research and development of a drug (the so-called "phase 3" trials), if the investigator determined that oral consent was preferable or necessary given the physical and mental state of the patient and if the investigator documented the consent. Second, the amended regulations clarified the information that must be given to the

subject before requesting consent. They established (i) the proviso that, in presenting the information, the investigator should take into consideration the subject's well-being and ability to understand, and (ii) the requirement that "the hazards involved," instead of the former "all inconveniences and hazards reasonably to be expected," be disclosed. Except for the recodification, these regulations have not changed since 1967.

*Regulations Governing Research Funded or Supported by the Department of Health, Education, and Welfare*

In the **Federal Register** of October 9, 1973 (38 FR 27882), the Secretary of Health, Education, and Welfare proposed to modify existing policies governing protection of human subjects in research funded or supported by grants or contracts of HEW. These proposals were commented upon by over 200 parties. In the **Federal Register** of May 30, 1974 (39 FR 18914), the Secretary adopted final regulations on this matter (codified in 45 CFR Part 46) and, in the preamble to the order, discussed the comments in detail. Technical amendments were issued in the **Federal Register** of March 13, 1975 (40 FR 11854) to conform the regulations to certain portions of the National Research Act (Pub. L. 93-348, 88 Stat. 342).

The initial HEW regulations differ from the FDA regulations in several significant respects. First, in setting forth the elements of information that must be given to the subject, the HEW regulations include two items not explicitly described in the FDA regulations: an offer to answer any inquiries that the subject might have concerning the procedure; and an instruction that the person is free to withdraw his or her consent and to discontinue participation in the project or activity at any time without prejudice to the subject. (Compare 21 CFR 310.102(h) with 45 CFR 46.103(c).) Second, in every study an independent IRB is required to review the materials used to obtain informed consent (45 CFR 46.110). Although the FDA reproposal on IRB's contains a similar requirement (§ 56.82(a)), FDA's current requirements (§ 312.1(a)(2) (Form FD-1571, item 10c)) apply only when the study is performed on institutionalized subjects or when an institution takes responsibility for the study. Third, HEW requires consent to be in writing in every case, except in those cases in which the IRB establishes (1) that the risk to the subject is minimal, (2) that use of written consent would "invalidate objectives of

considerable importance," and (3) that any reasonable alternative means for attaining these objectives would be less advantageous to the subjects (45 CFR 46.110(c)). As noted above, FDA's current regulations permit oral consent (with documentation by the investigator) in phase 3 trials and, in exceptional cases, provide for waiver of consent altogether. Fourth, the HEW regulations forbid use of exculpatory language through which the subject is made to waive, or appear to waive, any legal rights, including a release of the investigator from liability for negligence (45 CFR 46.109). FDA has no comparable regulation, although actual agency policy has been similar to the HEW rule.

*National Research Act*

On July 12, 1974, the National Research Act became law. This statute directed the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was to study the basic ethical principles underlying the conduct of biomedical and behavioral research involving human subjects, to develop guidelines that should be followed to ensure that the research is conducted in accordance with these principles, and to recommend administrative actions to the Secretary of HEW to apply the guidelines to the research conducted or supported under programs administered by the Secretary. The Commission was specifically charged with considering "the nature and definition of informed consent in various research settings" (section 202(a)(1)(b)(iv)) and with identifying "the requirements for informed consent to participation in biomedical and behavioral research by children, prisoners, and the institutionalized mentally infirm" (section 202(a)(2)).

Reports issued to date by the Commission and published in the **Federal Register** include—

1. Research on the Fetus (August 8, 1975 (40 FR 33530));
2. Research Involving Prisoners (January 14, 1977 (42 FR 3076));
3. Use of Psychosurgery (May 23, 1977 (42 FR 26318));
4. Research Involving Children (January 13, 1978 (43 FR 2084));
5. Research Involving Those Institutionalized as Mentally Infirm (March 17, 1978 (43 FR 11328));
6. Institutional Review Boards (November 30, 1978 (43 FR 56174));
7. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (April 18, 1979 (44 FR 23192)); and

8. Special Study, Implications of Advances in Biomedical and Behavioral Research (May 25, 1979 (44 FR 30644)).

The agency has reviewed the reports issued by the Commission and has incorporated many of the Commission's recommendations in the proposed regulations published in the **Federal Register** concerning the use of prisoners as subjects of biomedical research (May 5, 1978 (43 FR 19417)); protections pertaining to clinical investigations involving children (April 24, 1979 (44 FR 24106)); standards for institutional review boards for clinical investigations (August 8, 1978 (43 FR 36186)), repropose in this issue of the **Federal Register**; obligations of clinical investigators of regulated articles (August 8, 1978 (43 FR 35210)); and obligations of sponsors and monitors of clinical investigations (September 27, 1977 (42 FR 49612)).

*The Medical Device Amendments*

The Medical Device Amendments of 1976 (Pub. L. 94-295, 90 Stat. 539-583) became law on May 28, 1976. Section 520(g) of the act (21 U.S.C. 360j(g)), which was added by those amendments, concerns investigational devices and contains provisions similar to those governing the investigational use of new drugs, biologics, and antibiotic drugs that are found in sections 505(i) and 507(d)(3) of the act (21 U.S.C. 355(i) and 357(d)(3)).

Although the informed consent provisions of section 520(g) of the act are similar to the informed consent provisions of sections 505(i) and 507(d)(3), they differ in several respects. Section 520(g)(3)(C) provides that the person applying for an exemption to permit the use of an investigational device must obtain and submit to the Secretary signed agreements from each investigator that any testing will be under his or her supervision and that the informed consent requirements of section 520(g)(3)(D) will be met. Section 520(g)(3)(D) provides an exception to the general informed consent requirement that differs from the exceptions provided in sections 505(i) and 507(d)(3) in that informed consent is required unless the clinical investigator makes a written determination that (1) "there exists a life threatening situation involving the human subject of such testing which necessitates the use of such device," and (2) "it is not feasible to obtain informed consent from the subject," and (3) "there is not sufficient time to obtain such consent from his representative." Thus, any exception from the informed consent requirement of the Medical Device Amendments

must rest on the concurrent existence of all three of these requirements. A mere lack of feasibility is not, by itself, enough nor is there any provision that the requirement may be dispensed with if an investigator deems obtaining informed consent to be "contrary to the best interests" of the subject. In addition, the device amendments further provide that a licensed physician who is not involved in the testing must separately agree with the determination that informed consent need not be obtained unless there is not sufficient time. The exceptions set out in section 520(g)(3)(D) are "subject to such conditions as the Secretary may prescribe."

As discussed above, sections 505(i) and 507(d)(3) of the act allow two separate exceptions from the requirement that informed consent be obtained for the use of an investigational drug: (1) when a clinical investigator deems obtaining the consent not feasible; or (2) when, in the professional judgment of the clinical investigator, obtaining the consent would be contrary to the best interest of the subject. Because maintenance of separate systems of informed consent for research on drugs, antibiotics, and devices would serve no purpose and would create confusion, the agency is proposing to follow, in this regulation, the more recently enacted requirements of the Medical Device Amendments with respect to informed consent generally.

Proposed regulations for investigational devices were first issued in the **Federal Register** of August 20, 1976 (41 FR 35282). These proposed regulations contained additional provisions governing informed consent as applied to experimental devices, and the comments that were received in response to the proposal were considered in the preparation of this document. In the **Federal Register** of November 11, 1977, FDA promulgated a new Part 813 (21 CFR Part 813) as a final rule governing the investigational use of intraocular lenses (42 FR 58874). The intraocular lens regulation also contained provisions governing informed consent (Subpart F) that were similar to those proposed for investigational devices on August 20, 1976. The agency did not foresee, however, any case in which the implantation of an intraocular lens would be compelled by a life-threatening emergency and therefore did not include the language providing exceptions from informed consent contained in § 812.123 (21 CFR 812.123) of the investigational device proposal (41 FR 35312-13).

The informed consent provisions contained in this proposal would be uniform agency-wide requirements. Therefore, the agency is proposing, in the conforming amendments, to revoke Subpart F of Part 813. Again, however, the agency foresees no case in which implantation of an intraocular lens without consent might be compelled by a life-threatening emergency.

In the **Federal Register** of May 12, 1978 (43 FR 20726), FDA issued a tentative final regulation on investigational device exemptions that contained, as Subpart F of Part 812, provisions for obtaining informed consent. The agency advises that the informed consent provisions of proposed Subpart B of Part 50 (21 CFR Part 50), when final, will replace the informed consent provisions proposed with Part 812.

### Evolution of the Concept of Informed Consent

Although the statutory history detailed above does demonstrate that, as the concept of informed consent has evolved, the requirements for subject protection have become more complex, it does not fully explain the changes in attitude that have resulted in this increased complexity. The statutory standards established for the use of investigational drugs by Congress in 1962 are inconsistent with the standards established by Congress for the use of investigational devices in 1976. FDA believes that the standards expressed through the regulations now being proposed should be consistent with current thinking. Therefore, FDA is including a brief discussion of how and why the concept has changed.

Before the National Research Act (discussed above) was passed in 1974, informed consent was discussed at length in testimony offered during the course of hearings on human experimentation before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare. Various witnesses testified that human experimentation often occurred in the absence of informed consent and that more stringent safeguards were necessary to protect human subjects of such research. Dr. Henry Simmons, testifying for HEW in 1973, stated:

The Congress, the administration, the scientific community, and the general public are all manifesting an increased sensitivity to the moral and ethical issues associated with the advancement of science.

When humans are the subject of experimentation, the dangers of unintended infringement of the rights of persons involved in the research are real and, therefore, it is incumbent upon society to develop

appropriate guidelines and safeguards so that no investigator—no matter how well intentioned—may transgress the rights of participants \* \* \*. (Quality of Health Care—Human Experimentation: Hearings on S. 974, 93d Cong., 1st Sess., 1458-59 (1973).)

Included in the hearing record is a reprint of an article, "Experimenting with Humans," in which the author, Bernard Barber, discusses the action taken by the New York Board of Regents following the disclosure of an experiment in which live cancer cells were injected into 22 elderly patients who were not clearly informed that the injections were being performed for research and not for treatment purposes. Finding the two doctors involved guilty of "unprofessional conduct," the Regents put forth the following two important principles:

First, "a patient has the right to know he is being asked to volunteer and to refuse to participate in an experiment for any reason, intelligent or otherwise, well-informed, or prejudiced. A physician has no right to withhold from a prospective volunteer any fact which he knows may influence the decision." In short, the patient's right to be "emotional" or "irrational" is his, and not subject to any overriding decision by an experimenting physician.

Second, "the physician, when he is acting as experimenter, cannot claim those rights of doctor-patient relationships that do permit him, in a therapeutic situation, to withhold information when he judges it to be in the best interests of his patient." (Human Experimentation Hearings, *supra*, at 1137-38.)

The last statement reflects an important distinction that was not recognized by Congress in 1962, but that has since been explicitly stated. Both the 1966 AMA Ethical Guidelines and the 1964 Declaration of Helsinki distinguish between therapeutic and nontherapeutic research, and each makes informed consent an absolute requirement in the latter. In addition, there has been growing recognition of the fact that the physician acting as experimenter may respond to pressures different from those that might affect the physician acting as healer. Thus, the National Commission in its 1978 report on IRB's stated:

The Commission's deliberations begin with the premise that investigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others, who are independent of the research, must share this responsibility, because investigators are always in positions of potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of human subjects of their research. (See the **Federal Register** of November 30, 1978 (43 FR 56174).)

### The Need for Revision of FDA Regulations

The concept of informed consent has changed as outlined above. For several years, FDA has been planning to revise substantially the regulations governing drug research under sections 505(i) and 507(d) of the act. Many of the current regulations were, as noted previously, first issued in 1963 under the Drug Amendments of 1962. Current FDA policy regarding consent for use of investigational new drugs on humans was adopted in 1967 and is set forth in § 310.102, although significant discrepancies exist between the regulation and the statements in Forms FD-1572 and FD-1573. Until now, however, there has been no comprehensive review or update of these regulations. The actions of the Congress, the National Commission, and the Department in the area of human experimentation all demonstrate the need for a uniform FDA regulation that covers the investigational use of drugs, devices, and other test articles subject to FDA jurisdiction.

The concept of "informed consent" is not a narrow or technical concept, limited in application to this or that particular kind of research on human subjects. Rather, the concept has a broad sweep; and, like the concepts of "due process of law" and "equal protection of the laws," it reflects fundamental social value judgments about how people should be treated. Like those other concepts, too, the concept of "informed consent" changes and grows in light of increasing experience in its application and more precise identification of problems to be addressed in its articulation.

In principle, there is no reason for requirements of informed consent to differ depending on whether the article administered to the human subjects of research is, a drug, an antibiotic, or a medical device. The basic notions of autonomy and fairness that undergird the concept of "informed consent" apply in the same way to all categories of human biomedical research.

Indeed, on the basis of FDA's experience with the regulation of human biomedical research, the agency strongly believes that maintenance of separate and different systems for informed consent in different categories of research would promote confusion among investigators and institutional review boards, and would frustrate the congressional purpose, reflected in both the Drug Amendments of 1962 and the Medical Device Amendments of 1976, to require that biomedical research be

conducted in accordance with the highest contemporary ethical standards. The same investigators may from time to time do research on drugs and devices. One investigation may include one treatment group receiving a drug and another receiving a device.

The concept of "informed consent" has developed only in the last quarter century. As the history of its development described above makes plain, the concept has changed over the years; most likely, it will continue to change.

The agency recognizes that the language, interpreted literally, of sections 505(i) and 507(d)(3) of the act allows an investigator using experimental drugs greater freedom to dispense with informed consent when, in the exercise of professional judgment, the investigator concludes that obtaining such consent is "not feasible" or is "contrary to the best interests of the patient." This language, as discussed above, does not appear in the informed consent provisions of the Medical Device Amendments. The informed consent regulations adopted by FDA in 1967, and now codified under § 310.102, provide that the exception to the requirement that informed consent be obtained be carefully limited to those situations in which either communications with the patient is not possible and it is imperative to employ the drug without delay, or in which communication of the necessary information would seriously affect the disease state of the patient. Both of these exceptions assume situations in which the patient subject is seriously ill; and, when read in light of the context in which they would actually apply, the exceptions do not differ greatly from the emergency exemptions contained in section 520(g)(3)(D) of the Medical Device Amendments. Thus, the actual policy, which has been followed by the agency since 1967 regarding the investigational use of drugs, is quite similar to the policy that the agency is now proposing.

To the extent that the informed consent provisions of the Drug Amendments differ from those of the Medical Device Amendments, however, FDA is proposing to make the latter applicable to both. In light of the nature of the concept of "informed consent" and its anchorage in ethical values basic to our society, FDA believes that the particular language of the Drug Amendments should not be interpreted literally or strictly or as preventing progress in the evolution of informed consent requirements. Amendments to the act have occurred historically on a

product-by-product basis, and Congress, in enacting the informed consent requirements of the Medical Device Amendments, did not address the fact that the exemption requirements for investigational devices being proposed were different from those previously enacted for investigational drugs. The agency finds that the informed consent requirements contained in section 520(g)(3)(D) of the act represent the most recent congressional thinking regarding the standards required of clinical investigators of FDA-regulated products and, as such, should be the standards applied to all FDA-regulated research, regardless of the regulated product involved. It is fair to assume that each time Congress addressed the issue of informed consent, it intended to adopt the most highly developed and practical informed consent requirements then available. In 1962 there was ample reason to expect that the concept would evolve; and, as discussed above, it has done so. In proposing a uniform system of informed consent applicable to research on all articles regulated by FDA, the agency is seeking to administer the informed consent provisions of the law in the manner that will most effectively carry out the congressional purpose and facilitate the obtaining of informed consent.

### The Proposed Regulations

The agency proposes to make a single set of informed consent requirements applicable to all investigators involved in investigational studies that either require prior FDA review or are later submitted to FDA in support of an application for a research or marketing permit. These regulations, if adopted, may not eliminate the need for additional requirements relevant to a particular article under study, but will reduce the potential for duplicative and inconsistent regulations or interpretations of policy. Proposed Part 50, when complete, will contain all FDA regulations governing the protection of human subjects. Sections covering the scope of Part 50, definitions (Subpart A), and protections pertaining to clinical investigations involving prisoners as subjects (Subpart C), were proposed in the **Federal Register** of May 5, 1978 (43 FR 19417), and a proposed regulation providing protection to children involved as subjects in clinical investigations (Subpart D of Part 50) was published in the **Federal Register** of April 24, 1979 (44 FR 24106).

#### Definitions

Many of the general definitions required to understand Part 50 were



proposed with Subpart C—Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects in the May 5, 1978 document. The agency believes that, because Subpart B is the foundation of all of Part 50, because the comment period on Subpart C has closed, and because all parties affected by this proposal should also have an opportunity to comment on the proposed definitions, the definitions should be repropose. Therefore, FDA is withdrawing the definitions proposed with the prisoner research regulations and repropose them here. Definitions specific to other subparts will be added as needed.

A few editorial changes have been made in the definitions. The definition of "clinical investigation," § 50.3(c) (21 CFR 50.3(c)), has been modified to conform to the definition in the IRB proposal published elsewhere in this issue of the **Federal Register**. This definition more clearly confines "clinical investigation" to studies involving human subjects. The definition of "subject," § 50.3(h), has been modified by the addition, in the last sentence, of the phrase "or a better understanding of a disease or metabolic process." "Institutionalized subject," § 50.3(k), has been modified in paragraph (k)(2) by the addition of the phrase "order, decree, or judgment." These modifications also conform the definitions to those published with the IRB proposal.

Proposed § 50.3 defines a number of terms used in proposed Subpart B. The terms defined as part of this proposal are those needed to fully understand Subpart B. Many of the proposed definitions pertain to terms that can be variably or imprecisely interpreted by persons affected by the proposed regulation. These definitions should provide a common basis of understanding for the agency, investigators, IRB's, the regulated industry, and the general public regarding the terms used in Part 50. In proposed § 50.3(a), the term "act" is limited to the Federal Food, Drug, and Cosmetic Act, as amended. This is consistent with definitions appearing elsewhere in the agency's regulations. Other statutes, when referred to, will be mentioned by name, e.g., the Public Health Service Act (42 U.S.C. 201 et seq.).

The decision to make this proposal agency wide in scope required a term that would include all the various requirements for submission of scientific data and information to the agency under its regulatory jurisdiction, even though in certain cases no permission is technically required from FDA for the

conduct of a proposed activity with a particular product, i.e., carrying out research or continuing to market a product. The term chosen, "application for research or marketing permit," is intended solely as a shorthand way of referring to at least 22 separate categories of information that are now, or in the near future will become, subject to requirements for submission to the agency; the term is defined in proposed § 50.3(b).

To facilitate further the applicability of a single set of regulations to all studies involving products or articles within FDA's purview, the agency is proposing in § 50.3(c) to describe each such study as a "clinical investigation," which is defined as any experiment involving a test article (defined below) and human subjects and either (1) is subject to requirements under section 505(i), 507(d), or 520(g) of the act for prior submission to FDA for review, and in some cases approval, before it can be commenced, or (2) is not subject to requirements for prior submission but whose results are intended to be later submitted to, or held for inspection by, FDA as part of an application for a research or marketing permit. Within the category of clinical research the definition excludes studies that do not use any test articles, or do not use them in a manner that requires prior FDA approval or subsequent FDA review because the studies are not regulated by, or intended to be submitted to, FDA. The definition also excludes studies that do not involve human subjects.

Other proposed definitions include terms to describe the persons who initiate and carry out clinical investigations: "sponsor," "investigator," and "sponsor-investigator." The term "sponsor" is currently defined in §§ 310.3(j) and 510.3(k) (21 CFR 310.3(j) and 510.3(k)), but FDA believes this definition is unsatisfactory because it fails to distinguish the other commonly used term, "investigator," which is not defined. Although these terms are widely understood, their precise meanings are difficult to express. The key distinction seems to lie between the person who initiates the project (the sponsor) and the person who actually conducts the study (the investigator). This distinction has been incorporated in the definitions proposed in § 50.3(d) and (f), together with a further distinction: Investigators must be individuals, but sponsors can be individuals, corporations, institutions, or other legal entities. (The term "person" is defined in paragraph (e) to include an individual, partnership, corporation,

association, scientific or academic establishment, government agency or organizational unit thereof, and any other legal entity.) The agency believes that these distinctions will clarify the participants' respective roles and duties.

Many studies (approximately 45 percent of the investigational new drug applications in the Bureau of Drugs, for example) are initiated and actually conducted by the same individual; this investigator may carry out the study alone or with other investigators responsible to the initiator. FDA considers it important to identify the hybrid role of the sponsor-investigator and, when appropriate, to make special provisions for that role. Thus, this term is defined in proposed § 50.3(g); unlike the term "sponsor," the term "sponsor-investigator" is limited to individuals.

Proposed § 50.3(h) defines "subject" as any individual who is or becomes a participant in a clinical investigation, either as the recipient of the test article or as a control. The term also includes both healthy or normal individuals and patients to whom the test article might offer a therapeutic benefit. This definition is in accord with past FDA policy. The term is limited to human beings.

The terms "institution" and "institutional review board" are defined in proposed § 50.3(i) and (j), respectively. Although since 1971 FDA has had a requirement that clinical drug investigations involving institutionalized subjects be reviewed and monitored by an institutional review committee or board, no guidelines defining the outer limits of these concepts have been issued. FDA proposes that the definition of "institution" include any corporation, scientific or academic establishment, or government agency that engages in the conduct of research on human subjects or in the delivery of medical services to individuals. The term "institution" includes a hospital, a university that performs research with students, a retirement home that primarily provides housing and personal care to the elderly but also cares for health needs of residents, a manufacturer that uses its employees as subjects in the course of product development, or a prison.

The term "institutional review board" is defined in this proposal to mean any board, committee, or other formally organized group created to review research involving human subjects, and to approve the initiation of such research. The use of the word "board" reflects terminology of the National Research Act of 1975, HEW regulations (45 CFR Part 46), and discussions of the National Commission for the Protection

of Human Subjects of Biomedical and Behavioral Research. However, the agency recognizes that, like section 520(g) of the act, existing FDA regulations, e.g., § 312.1, use the term "committee." FDA believes there is no practical difference between the two words and has elected to follow Departmental terminology.

An "institutionalized subject," as defined in proposed § 50.3(k), includes two categories:

1. Any individual who is voluntarily confined on the premises of, and in the care of, an institution for more than one day; outpatients are excluded from the definition in keeping with existing FDA policy.

2. Any individual involuntarily confined by civil commitment for any period of time in an institution such as a penal facility or a hospital.

"Prisoner," as defined in proposed § 50.3(1), follows the definition proposed by HEW and means any individual involuntarily confined or detained in a penal institution. In scope, the term encompasses individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. To some extent, the terms "institutionalized subject" and "prisoner" overlap. The term "prisoner," however, does not include either those persons voluntarily confined or those persons subject to a civil commitment procedure that is not an alternative to criminal prosecution.

"Test article," as defined in § 50.3(m), describes those items being studied that are subject to FDA's jurisdiction and to these regulations. The term includes those new drugs, biologics for human use, and medical devices for human use, studies of which require prior review by FDA under an investigational new drug study or an investigational device study. In addition, the term includes food additives, color additives, drug products, and biological products for human use, electronic products, and medical devices for human use. The broad definition of "test article" is intended to include substances for which clinical investigations are submitted to FDA in support of an application for permission to market a product, but which investigations need not be conducted under an exemption for an investigational new drug (IND) or an investigational device exemption (IDE), e.g., studies on food additives or cosmetics, certain drug bioavailability

studies described in Part 320 (21 CFR Part 320), and studies on medical devices for human use not required to be submitted to FDA for prior review under proposed Part 812 (21 CFR Part 812). A test article is covered by these regulations only if it is used in a clinical investigation involving human subjects.

#### *General Requirements of Informed Consent*

Proposed § 50.20 (21 CFR 50.20) sets forth the general requirements for obtaining informed consent from human subjects.

The subject's consent may be obtained only while he or she is so situated as to be able to comprehend fully the information presented, and the subject's consent must be obtained under circumstances that minimize the possibility of undue influence or coercion. In addition, the information given must be in the primary language of either the subject or the subject's legal representative. No exculpatory language may be included in either written or oral consent. This policy is a restatement of those currently found in 45 CFR 46.109 and proposed 21 CFR 812.130(b).

The agency recognizes that, when confronted with the possibility that the use of a new therapy or test article may result in the improvement of his or her condition, an individual who is seriously ill may not have the ability to exercise unqualified discretion. Regulation of the pressures on a patient's decision that are inherent in his or her medical condition is not the subject of this proposal. Rather, its purpose is to prevent the imposition of external forms of pressure.

#### *Exception from General Requirements*

Proposed § 50.23 (21 CFR 50.23) sets forth two related exceptions from the general requirements of informed consent proposed in § 50.20 to provide for use of test articles in certain life-threatening situations when the investigator complies with specific procedures. The first exception, § 50.23(a), concerns a life-threatening situation in which the use of the test article is necessary, in which it is not possible to obtain informed consent, but which is not so immediate as to prevent the investigator from obtaining a second opinion. Under this exception, both the clinical investigator and a physician not otherwise participating in the clinical investigation must determine in writing, before using the test article, that all of the following factors are present: (1) The subject is confronted by a life-threatening situation necessitating the use of the test article; (2) informed

consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective informed consent from, the subject; (3) time is not sufficient to obtain consent from the subject's legal representative; and (4) there is available no alternative method of approved or generally recognized therapy that may save the life of the subject.

The second exception, contained in § 50.23(b), allows the determinations required by § 50.23(a) to be made after the use of the test article. This exception provides for those situations in which immediate use of the test article is required. The investigator must, under paragraph (b), make the written determinations required in paragraph (a), and a physician who is not participating in the clinical investigation must review and evaluate the determinations in writing within 5 working days after the use of the article.

All but one of the factors that must be present before the informed consent requirement is waived under § 50.23 are drawn from section 520(g)(3)(D) of the act. The requirement that a determination be made as to lack of an available alternative method of therapy that may save the life of the subject has been added to prevent routine reliance on the exception. This additional requirement should provide guidance to investigators regarding those exceptional situations in which informed consent need not be obtained. As noted above, obtaining informed consent has come to be a standard of practice for professional clinical investigators. Defining those circumstances when informed consent need not be obtained should provide a clearer understanding of how to determine when informed consent is "not feasible."

#### *Elements of Informed Consent*

Proposed § 50.25 (21 CFR 50.25) contains both basic and additional elements of informed consent. The information provided must include a complete explanation of pertinent information sufficient to enable the prospective subject or the prospective subject's legal representative to make an informed and intelligent decision concerning participation in the investigational study.

Proposed § 50.25 lists 11 basic items of information to be included in the presentation to the subject. Although this list is drawn, in part, from the National Commission's report on IRB's, current HEW regulations, existing FDA regulations covering the use of investigational new drugs and devices,

and the Conference Report on the Medical Device Amendments of 1976 (H. Rept. No. 1090, 94th Cong., 2d Sess. (1976)), the list of informational items set out in this section represents only the minimum required. The information should be tailored to the needs of the individual subject to ensure that it is sufficient to enable him or her to make an informed and intelligent decision regarding participation. When appropriate, an IRB should ensure that information in addition to that expressly required by proposed § 50.25(a) is provided five such additional items of information are set out in § 50.25(b).

Proposed § 50.25(a) (1) through (6), (8), and (11) restates current FDA or HEW policy. See, e.g., § 310.102(h); § 312.1(a) (12) and (13) (Form FD-1572, item 6g, and Form FD-1573, item 4g); proposed § 812.130(a) (21 CFR 812.130(a)) published in the **Federal Register** of May 12, 1978 (43 FR 20757); and § 46.103(c) of the Departmental regulation (45 CFR 46.103(c)).

Proposed § 50.25(a)(7) requires that a subject be apprised in advance of those situations in which his or her records may be disclosed. The agency believes that FDA should clearly and publicly state when it will request access to the records, and, if access is requested, how FDA will safeguard the privacy of subjects. First, the agency does not need to inspect medical history records routinely. The scientific evaluation of case report forms, and of summary tables proposed from the data in these forms, is the basic mechanism by which FDA assesses data from studies. However, the agency's inspections have uncovered a significant number of errors of omission and commission in information submitted to the agency. For this reason, FDA has initiated an inspectional program that includes the onsite audit of certain data submitted to the agency. During this audit, access to the subject's identification is incidental to the review of the records. When the records are reviewed, as described in current regulations, "the names of the subjects need not be divulged unless the records of the particular subjects require a more detailed study of the cases, or unless there is a reason to believe that the records do not represent actual studies or do not represent actual results obtained" (see Form FD-1572, item 5e, in § 312.1(a)(12) (21 CFR 312.1(a)(12))). The agency invites comment on whether the subjects of a clinical investigation should be informed that FDA may not only inspect but also may copy records that identify the subjects.

To ensure the privacy of individually identifiable medical records, FDA has

implemented clear and extraordinarily exacting guidelines for FDA personnel who conduct inspections of medical records containing the names of individual research subjects. Agency personnel may not copy medical records containing the names of research subjects, and the clinical investigator or the IRB representative is to be given the right to delete any information that could identify an individual subject, except when: (1) the agency has reason to believe that the consent of human subjects was not obtained, or (2) there is reason to believe that the records do not represent actual studies or do not represent actual results obtained. The exceptions to the prohibition against the copying of individually identifiable medical records by FDA personnel rest primarily on the need to determine whether a given research subject in fact exists and whether the research subject in fact participated in the investigation. When an individually identifiable medical record is copied and reviewed by the agency, the record is properly safeguarded within FDA and is used or disseminated under conditions that protect the privacy of the individual to the fullest possible extent, consistent with laws relating to public disclosure of information (Freedom of Information and Privacy Act regulations) and the law enforcement responsibilities of the agency. Both the IRB and the clinical investigator proposals, discussed above, restate these policies.

The requirement of proposed § 50.25(a)(6) that new information that may relate to the willingness of the subject to continue participation be provided to the subject or the subject's legal representative on a continuing basis has not been previously codified. It is included to emphasize that, if new information that might affect the basis of the original decision to participate is discovered, the investigator is obligated to provide that information to the subject or to the subject's legal representative.

Proposed § 50.25(b) includes five additional elements of informed consent. Any of these items of information should be included as appropriate. The appropriateness of an item may be determined by an IRB at the time it reviews a consent form proposed for use in a clinical investigation.

#### *Documentation of Informed Consent*

Proposed § 50.27 (21 CFR 50.27) sets forth the requirements for the documentation of informed consent, which may be by either a long or a short form. The form used must be signed by

either the subject or the subject's legal representative, and, if the short form is used, by an auditor witness as well.

Proposed § 50.27 provides for a written consent form containing the information required by § 50.25. The consent form may be read by or to the subject or the subject's legal representative, but in either case an adequate opportunity to read the form must be provided, and a copy must be offered to the person signing.

Proposed § 50.27(c)(2) provides for the use of a "short form" written consent document. Use of the short form allows the basic information required by § 50.25 to be presented orally to the subject or the subject's legal representative. Written summaries of what is to be said are to be reviewed and approved in advance by the IRB. When consent is obtained in this manner, an auditor witness must be present during the explanation and must also sign the form. The auditor witness should be some one not involved in the conduct of the study. Any additions to the explanation other than those appearing on the approved form must be noted in the summary.

Although no provision for oral informed consent is being proposed, comments are invited on whether, in some limited circumstances, oral informed consent might be adequate to protect human subjects of those clinical investigations regulated by FDA.

#### **Legal Authority**

The results of literally hundred of clinical investigations are submitted to FDA each year by persons seeking regulatory action by the agency. To obtain a marketing license, clinical research data are offered to support the safety and effectiveness or functionality of a product, e.g., a food or color additive, a drug or biologic for human use, or a medical device for human use. Even when a license is not required or has already been issued, the data may be relied upon to demonstrate the bioavailability of a marketed drug, the general recognition of safety of a product, or the absence of any need for premarket approval or a product standard for a device.

In evaluating the enormous volume of clinical investigations filed with FDA, many types of scientific and regulatory review must be devoted to these studies, apart from determining their ethical acceptability, e.g., to interpret the results and to evaluate the status of the affected products in light of the results. Given its limited resources, FDA believes that it must have standards to screen out those clinical investigations that are likely to be unacceptable and

thus should not be authorized by FDA, or that warrant little further evaluation in support of a product application. The promulgation of this proposed regulation would provide one process for making this judgment. Moreover, the regulation reflects principles recognized by the scientific community as essential to sound research involving human subjects. Thus, this proposed regulation would assist FDA in identifying those investigations that cannot be permitted to be carried out or considered in support of an application for a research or marketing permit.

Under section 701(a) of the act (21 U.S.C. 371(a)), the Commissioner of Food and Drugs is empowered to promulgate regulations for the efficient enforcement of the act. Previously, the agency has issued regulations (21 CFR 314.111(a)(5)) for determining whether a clinical investigation of a drug intended for human use, among other things, was scientifically reliable and valid (in the words of the act, "adequate and well-controlled") to support approval of a new drug. These regulations were issued under sections 505 and 701(a) of the act and have been upheld by the Supreme Court (see *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); see also *Upjohn Co. v. Finch*, 422 F.2d 944 (6th Cir. 1970) and *Pharmaceutical Manufacturers Association v. Richardson*, 318 F. Supp. 301 (D.Del. 1970)).

Furthermore, sections 505(i), 507(d), and 520(g) of the act, regarding clinical investigations that require prior FDA authorization, direct the Commissioner to promulgate regulations to protect the public health in the course of the investigations. The proposed regulation is intended to fulfill these mandates.

The agency concludes that legal authority to promulgate this regulation exists under sections 505(i), 507(d), 520(g), and 701(a) of the act as essential to protection of the public health and safety and to enforcement of the agency's responsibilities under sections 406, 409, 502, 503, 505, 506, 507, 510, 513, 514, 515, 518, 519, 520, 601, 706, and 801 of the act (21 U.S.C. 346, 348, 352, 353, 355, 358, 357, 360, 360c-360f, 360h-360j, 361, 376, and 381), as well as the responsibilities of FDA under sections 351 and 354 to 360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

#### Conforming Amendments

The agency intends to revise the IND regulations in § 312.1(a), Forms FD-1571, FD-1572, and FD-1573, to correspond with the clarified requirements regarding informed consent in proposed

Part 50. However, because repeating these provisions in the forms in this proposal might confuse readers and lead to duplicative comments, the agency gives notice that the forms will be revised in the final order to reiterate the requirements proposed here, as modified in light of the comments received.

Also, FDA proposes to add or revise regulations regarding food and color additives, new drug applications, bioavailability and bioequivalence testing requirements, OTC drug products, radioactive drugs, antibiotic drugs, biological product licenses, and electronic products to incorporate appropriate implementing provisions for, and cross-references to, Part 50.

The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b), and consideration by the agency of the need for preparing an environmental impact statement is not required.

#### Effective Date

The agency is proposing that the final rule take effect 90 days after its date of publication in the **Federal Register**. Because the informed consent obtained under current regulations from subjects already participating in ongoing studies may not meet the requirements proposed for Subpart B of Part 50, there will be cases in which a second informed consent that meets Subpart B requirements should be obtained. The agency recognizes, however, that retroactive application of the requirements is neither practical nor necessary in every case.

In addition, the agency realizes that the administrative burden of obtaining a second informed consent from each subject in a continuing study must be balanced against the additional protection that might be afforded to the human subjects involved in studies already ongoing at the time the final order takes effect. A review of the data derived from the agency's IRB pilot inspection program showed that of the 116 IRB's inspected by FDA, 42 percent reviewed from 6 to 30 new protocols per session, and 62 percent met monthly or less frequently. The average IRB inspected for the Bureau of Biologics performed continuing review of 10 FDA-regulated studies per year. Many of the IRB's that review FDA-regulated research also review HEW-funded research, particularly at those institutions holding a general assurance. Because FDA and HEW have agreed to take the same approach for an effective date for informed consent regulations in order to facilitate compliance, FDA must

consider the more general administrative impact on IRB's of the various approaches to an effective date for these regulations.

For FDA to require IRB's to review informed consent forms for all ongoing studies to determine whether or not they meet the new requirements on the effective date of the final order would mean that the average IRB would have to review 10 informed consent forms plus 10 new protocols at its regular monthly meeting. The agency must consider, however, that 54 percent of IRB's with general assurance review between 6 and 30 proposals per session and that there may be from 50 to 400 ongoing studies at any given time at those institutions. Thus, if FDA and HEW were to require that IRB's review informed consent forms for all ongoing studies, many institutions would be faced with having to commit approximately 10 sessions to the review of informed consents, with an inevitable delay in the review of new proposals. Both FDA and HEW view this administrative burden and the delay in the review of new protocols as unreasonable when compared to the modest gains that might be made in protecting the rights of human subjects already involved in most clinical investigations. The agency is proposing instead that the informed consent of ongoing studies be reviewed when those studies would normally undergo continuing review. Thus, the administrative burden will be spread out over time, all informed consents will have been reviewed within 1 year of the effective date of these regulations, and those studies with high risk will have been reviewed sooner because continuing review is required at frequencies appropriate to the degree of risk but not less frequently than once a year.

The agency proposes that IRB's, at the time of continuing review, make a determination whether or not: (1) revised informed consent should be obtained from human subjects already entered into the study; and, (2) revised informed consent should be obtained from human subjects who will enter the study after the continuing review. In making those determinations, the IRB should consider the nature of the study, the degree of risk to human subjects in the study, and the adequacy of the informed consent initially approved. The agency recognizes that most informed consents of ongoing studies may not comply with the new requirements, and that the degree of noncompliance will vary from study to study. A second informed consent from all subjects

continuing in a clinical investigation is therefore required only when the IRB determines that the consent obtained initially was inadequate. The agency proposes to interpret an inadequate consent as one that is grossly deficient, such as a consent that contains exculpatory language, fails to reveal risks to subjects, or fails to reveal the experimental nature of the investigation. In such cases, a second informed consent would be required from those subjects continuing in the study. The agency invites comments on this approach to the revision of consent forms for ongoing studies and on the applicability of those revised forms to both new subjects and subjects already entered into the study.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 601, 701(a), 706, and 801, 52 Stat. 1049–1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–517 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794–795 as amended, 90 Stat. 540–560, 562–574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 361, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 351, 354–360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 262, 263b–283n)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

#### SUBCHAPTER A—GENERAL

#### PART 50—PROTECTION OF HUMAN SUBJECTS

1. Part 50 (as proposed in the **Federal Register** of May 5, 1978 (43 FR 19417)) is amended:

a. By revising and repropounding § 50.3 of Subpart A to read as follows:

##### § 50.3 Definitions.

As used in this part:

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

(b) “Application for research or marketing permit” includes:

(1) A color additive petition, described in Part 71 of this chapter.

(2) A food additive petition described in Part 171 of this chapter.

(3) Data and information regarding a substance, submitted as part of the

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

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

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

(6) A “Notice of Claimed Investigational Exemption for a New Drug,” described in Part 312 of this chapter.

(7) A new drug application, described in Part 314 of this chapter.

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

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

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

(11) Data and information regarding an antibiotic drug, submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs described in Part 430 of this chapter.

(12) An application for a biological product license, described in Part 601 of this chapter.

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

(14) An “Application for an Investigational Device Exemption,” described in Part 812 of this chapter.

(15) Data and information regarding a medical device for human use, submitted as part of the procedures for

classifying such devices, described in section 513 of the act.

(16) Data and information regarding a medical device for human use, submitted as part of the procedures for establishing, amending, or repealing a standard for such devices, described in section 514 of the act.

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

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

(19) Data and information regarding an electronic product, submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act (42 U.S.C. 263f).

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

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

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

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

(d) “Investigator” means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject.

(e) "Person" includes an individual, partnership corporation, association, scientific or academic establishment, government agency or organizational unit thereof, and any other legal entity.

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

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

(h) "Subject" means a human who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject may be either a person in normal health or a patient to whom the test article might offer a therapeutic benefit of provide diagnostic information or a better understanding of a disease or metabolic process.

(i) "Institution" means a person, other than an individual, that engages in research on human subjects or in the delivery of medical services to individuals, as a primary activity or as an adjunct to providing residential or custodial care of humans. The term includes, for example, a hospital, retirement home, prison, academic establishment, and pharmaceutical or device manufacturer. "Facility" as used in section 520(g) of the act is deemed to be synonymous with the term "institution" for purposes of this part.

(j) "Institutional review board" means any board, committee, or other group formally designated by an institution for the purposes of reviewing clinical investigations or other types of biomedical research involving humans as subjects and approving the initiation of the investigations or research. The term has the same meaning as the phrase "institutional review committee" as used in section 520(g) of the act.

(k) "Institutionalized subject" means:

(1) A subject who is voluntarily confined for a period of more than 24 continuous hours on the premises of,

and in the care of, an institution (e.g., a hospital inpatient or a retirement home resident), whether or not that institution is a sponsor of the clinical investigation; and

(2) A subject who is involuntarily confined for any period of time in a penal institution (e.g., jail, workhouse, house of detention, or prison) or another institution (e.g., a hospital) by virtue of a sentence, order, decree, or judgment under a criminal or civil statute, or awaiting arraignment, commitment, trial, or sentencing under such a statute, or by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal facility.

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

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

(n) "Minimal risk" means that risk of harm that is no greater in probability and no greater in magnitude than that risk of harm that is normally encountered in the routine medical examination of healthy individuals.

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

b. By adding new Supart B to read as follows:

**Subpart B—Informed Consent of Human Subjects**

Sec.

50.20 General requirements of informed consent,

50.21 Effective date.

50.23 Exception from general requirements.

50.25 Elements of informed consent.

50.27 Documentation of informed consent.

**§ 50.20 General requirements of informed consent.**

Except as provided in § 50.23, no investigator may involve a human being

as a subject in a clinical investigation regulated by or conducted for submission to the Food and Drug Administration in support of an application for a research or marketing permit 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 prospective subjects (or their legally authorized representatives) sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The investigator seeking informed consent from a prospective subject or his or her legal representative shall provide to such person the information that is to be the basis of the informed consent in the primary language of the subject or the subject's legally authorized representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject waives or appears to waive any of his or her legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

**§ 50.21 Effective date.**

The requirements for informed consent set out in this part apply to all subjects entering a clinical investigation that commences on or after (insert effective date of final regulation). Informed consent obtained from subjects of clinical investigations that commenced before (insert effective date of final regulation) shall be reviewed for adequacy at the time of the continuing review of the study by the responsible institutional review board (as set forth in § 56.87 of this chapter). Where such continuing review results in a finding that the consent obtained initially was inadequate (e.g., the consent contained exculpatory language, failed to reveal the experimental nature of the investigation, or did not reveal the risks to the subject), the investigator shall obtain from each subject a new informed consent as a precondition for the subject's continuing participation in the investigation.

**§ 50.23 Exception from general requirements.**

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

participating in the clinical investigation determine in writing all of the following:

(1) The subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that may save the life of the subject.

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

(c) The documentation required in paragraph (a) or (b) of this section shall be filed with the institutional review board.

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

#### § 50.25 Elements of informed consent.

(a) *Basic elements.* In seeking and obtaining informed consent, an investigator shall provide to each person whose consent is sought or obtained the following information:

(1) A statement that the clinical investigation involves research and that the institutional review board has approved the solicitation of subjects to participate in the research.

(2) An explanation of the scope, aims, and purposes of the research, the procedures to be followed (including identification of any treatments or procedures that are experimental), and the expected duration of the subject's participation.

(3) A description of all reasonably foreseeable risks or discomforts to the subject (including likely results if an experimental treatment should prove ineffective).

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

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

(6) A statement that new information developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject or to the subject's legal representative.

(7) A statement that describes the extent to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration will inspect the records.

(8) An offer to answer any questions the subject (or subject's representative) may have about the research, the subject's rights, or related matters.

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

(10) Whom the subject should contact if harm occurs or if there are questions or problems.

(11) 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 loss of benefits to which the subject is otherwise entitled.

(b) *Additional elements.* When appropriate, an investigator shall also provide to each person whose consent is sought or obtained one or more of the following elements of information:

(1) A statement that the particular treatment or procedure being tested may involve risks to the subject (or fetus, if the subject is or becomes pregnant), which are currently unforeseeable. This statement will often be appropriate in tests that involve experimental drugs, or where the subjects are children, pregnant women, or women of childbearing age.

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

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

(4) Who is conducting the study, the approximate number of subjects involved, the institution responsible for the study, and who is funding it.

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

#### § 50.27 Documentation of informed consent.

(a) An investigator shall document informed consent by the use of a written consent form signed by the subject or the subject's legal representative, and shall give a copy of the consent form to the person signing.

(b) The investigator shall ensure that the consent form demonstrates that the information required by § 50.25 has been presented to the subject or to the subject's legal representative.

(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 legal representative, but, in any event, the investigator shall give either the subject or the subject's legal representative adequate opportunity to read it before it is signed.

(2) A "short form" written consent that states that the elements of informed consent required by § 50.25 have been presented orally to the subject or to the subject's legal representative. If the required information is presented orally, a written summary of the oral presentation shall have been previously approved by the IRB, and the consent form shall also be signed by an auditor who shall witness both the oral presentation and the signing of the form by the subject or the subject's legal representative. The person obtaining consent shall prepare a written summary of the information to be presented orally and a copy of the summary, annotated to show any changes, shall be signed by both the person obtaining consent and the auditor witness.

#### PART 71—COLOR ADDITIVE PETITIONS

2. Part 71 is amended:

a. In § 71.1 by adding new paragraph (j) to read as follows:

##### § 71.1 *Petitions* \* \* \*

(j) If clinical investigations involving human subjects are involved, petitions filed with the Commissioner under section 706(b) of the act shall include statements regarding each such clinical investigation contained in the petition, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

b. In § 71.6 by adding a new sentence at the end of paragraph (b) to read as follows:

**§ 71.6 Extension of time for studying petitions; substantive amendments; withdrawal of petitions without prejudice.**

\* \* \* \*

(b) \* \* \* If clinical investigations involving human subjects are involved, additional information or data submitted in support of filed petitions shall include statements regarding each such clinical investigation from which the information or data are derived, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

\* \* \* \*

**SUBCHAPTER B—FOOD FOR HUMAN CONSUMPTION**

**PART 171—FOOD ADDITIVE PETITIONS**

3. Part 171 is amended:  
a. In § 171.1 by adding new paragraph (n) to read as follows:

**§ 171.1 Petitions.**  
\* \* \* \*

(n) If clinical investigations involving human subjects are involved, petitions filed with the Commissioner under section 409(b) of the act shall include statements regarding each such clinical investigation relied upon in the petition, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

b. In § 171.6 by adding a new sentence at the end of the paragraph to read as follows:

**§ 171.6 Amendment of petition.**

\* \* \* If clinical investigations involving human subjects are involved, additional information and data submitted in support of filed petitions shall include statements regarding each clinical investigation from which the information or data are derived, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

**PART 180—FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS OR IN CONTACT WITH FOOD PENDING ADDITIONAL STUDY**

4. Part 180 is amended in § 180.1 by adding new paragraph (c)(7) to read as follows:

**§ 180.1 General.**  
\* \* \* \*

(c) \* \* \*  
(7) If clinical investigations involving human subjects are involved, such investigations filed with the Commissioner shall include, with

respect to each investigation, a statement that the investigation has been or will be conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

\* \* \* \*

**SUBCHAPTER D—DRUGS FOR HUMAN USE**

**PART 310—NEW DRUGS**

**§ 310.3 [Amended]**

5. Part 310 is amended in § 310.3 *Definitions and interpretations*, by deleting and reserving paragraph (j).

**§ 310.102 [Deleted]**

6. Part 310 is amended by deleting § 310.102 *Consent for use of investigational new drugs (IND) on humans; statement of policy*.

**PART 312—NEW DRUGS FOR INVESTIGATIONAL USE**

7. Part 312 is amended in § 312.1 by redesignating paragraphs (d)(11), (d)(12), and (d)(13) as (d)(12), (d)(13), and (d)(14), respectively, and adding new paragraph (d)(11) to read as follows:

**§ 312.1 Conditions for exemption of new drugs for investigational use.**  
\* \* \* \*

(d) \* \* \*

(11) The clinical investigations are not being conducted in compliance with the requirements regarding informed consent set forth in Part 50 of this chapter; or

\* \* \* \*

**PART 314—NEW DRUG APPLICATIONS**

8. Part 314 is amended:

a. In § 314.1 by adding a new sentence at the end of item 17 of form FD-356H in paragraph (c)(2) and by redesignating paragraph (f)(7), (f)(8), and (f)(9) as (f)(8), (f)(9), and (f)(10) and adding new paragraph (f)(7) to read as follows:

**§ 314.1 Applications.**  
\* \* \* \*

(c) \* \* \*

(2) \* \* \*

Form FD-356H—Rev. 1974;  
\* \* \* \*

17. \* \* \* Statements regarding each clinical investigation involving human subjects contained in the application, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

\* \* \* \*

(f) \* \* \*

(7) Statements regarding each clinical investigation involving human subjects contained in the application, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

\* \* \* \*

b. In § 314.8 by adding new paragraph (o) to read as follows:

**§ 314.8 Supplemental applications.**  
\* \* \* \*

(o) A supplemental application that contains clinical investigations involving human subjects shall include statements by the applicant regarding each such investigation, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

c. In § 314.9 by adding new paragraph (f) to read as follows:

**§ 314.9 Insufficient information in application.**  
\* \* \* \*

(f) The information contained in an application shall be considered insufficient to determine whether a drug is safe and effective for use unless the application includes statements regarding each clinical investigation involving human subjects contained in the application, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

d. In § 314.12 by adding new paragraph (f) to read as follows:

**§ 314.12 Untrue statements in application.**  
\* \* \* \*

(f) Any clinical investigation involving human subjects contained in the application subject to the requirements for informed consent set forth in Part 50 of this chapter was not conducted in compliance with such requirements.

e. In § 314.110 by adding new paragraph (a)(12) to read as follows:

**§ 314.110 Reasons for refusing to file applications.**

(a) \* \* \*

(12) The applicant fails to include in the application statements regarding each clinical investigation involving human subjects contained in the application, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

\* \* \* \*

f. In § 314.111 by adding new paragraph (a)(12) to read as follows:

**§ 314.111 Refusal to approve the application.**

(a) \* \* \*



(12) Any clinical investigation involving human subjects contained in the application subject to the requirements for informed consent set forth in Part 50 of this chapter was not conducted in compliance with such requirements.

\* \* \* \* \*

g. In § 314.115 by adding new paragraph (c)(8) to read as follows:

**§ 314.115 Withdrawal of approval of an application.**

\* \* \* \* \*

(c) \* \* \*

(8) That any clinical investigation involving human subjects contained in the application subject to the requirements for informed consent set forth in Part 50 of this chapter was not conducted in compliance with such requirements.

\* \* \* \* \*

**PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS**

9. Part 320 is amended:

a. In § 320.31 by adding new paragraph (g) to read as follows:

**§ 320.31 Applicability of requirements regarding a "Notice of Claimed Investigational Exemption for a New Drug."**

\* \* \* \* \*

(g) An in vivo bioavailability study in humans shall be conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter, regardless of whether the study is conducted under a "Notice of Claimed Investigational Exemption for a New Drug."

b. In § 320.57 by adding new paragraph (f) to read as follows:

**§ 320.57 Requirements of the conduct of in vivo bioequivalence testing in humans.**

\* \* \* \* \*

(f) If a bioequivalence requirement provides for in vivo testing in humans, any person conducting such testing shall comply with the requirements of § 320.31.

**PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERAL RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED**

10. Part 330 is amended in § 330.10 by adding new paragraph (f) to read as follows:

**§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.**

\* \* \* \* \*

(f) *Informed consent.* Information and data submitted under this section after (insert effective date of this paragraph) shall include statements regarding each clinical investigation involving human subjects, from which the information and data are derived, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

**PART 361—PRESCRIPTION DRUGS FOR HUMAN USE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED DRUGS USED IN RESEARCH**

11. Part 361 is amended in § 361.1 by revising paragraph (d)(5) to read as follows:

**§361.1 Radioactive drugs for certain research uses.**

\* \* \* \* \*

(d) \* \* \*

(5) *Human research subjects.* Each investigator shall select appropriate human subjects and shall obtain the consent of the subjects or their legal representatives in accordance with Part 50 of this chapter. The research subjects shall be at least 18 years of age and legally competent. Exceptions are permitted only in those special situations when it can be demonstrated to the committee that the study presents a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, and is without significant risk to the subject. Studies involving minors shall be supported with review by qualified pediatric consultants to the Radioactive Drug Research Committee. Each female research subject of childbearing potential shall state in writing that she is not pregnant, or, on the basis of a pregnancy test, be confirmed as not pregnant, before she may participate in any study.

\* \* \* \* \*

**PART 430—ANTIBIOTIC DRUGS; GENERAL**

12. Part 430 is amended in § 430.20 by adding new paragraph (h) to read as follows:

**§ 430.20 Procedure for the issuance, amendment, or repeal of regulations.**

\* \* \* \* \*

(h) No regulation providing for the certification of an antibiotic drug for human use shall be issued or amended unless each clinical investigation involving human subjects on which the issuance or amendment of the regulation is based was conducted in compliance with the requirements for informed

consent set forth in Part 50 of this chapter.

**PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS**

13. Part 431 is amended in § 431.17 by adding new paragraph (m) to read as follows:

**§ 431.17 New antibiotic and antibiotic-containing products.**

\* \* \* \* \*

(m) Statements regarding each clinical investigation involving human subjects contained in the request, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

**SUBCHAPTER F—BIOLOGICS**

**PART 601—LICENSING**

14. Part 601 is amended:

a. In § 601.2 by revising paragraph (a) to read as follows:

**§ 601.2 Applications for establishment and product licenses; procedures for filing.**

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations; statements regarding each clinical investigation involving human subjects contained in the application, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent

information and data have been received from the manufacturer by the Bureau of Biologics. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section.

b. In § 601.25 by revising paragraph (h)(1) and adding new paragraph (m) to read as follows:

**§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.**

(h) *Additional studies.* (1) Within 30 days following publication of the final order, each licensee for a biological product designated as requiring further study to justify continued marketing on an interim basis, under paragraph (f)(3) of this section, shall satisfy the Commissioner of Food and Drugs in writing that studies adequate and appropriate to resolve the questions raised about the product have been undertaken, or the Federal government may undertake these studies. Any study involving a clinical investigation that involves human subjects shall be conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter. The Commissioner may extend this 30-day period if necessary, either to review and act on proposed protocols or upon indication from the licensee that the studies will commence at a specified reasonable time. If no such commitment is made, or adequate and appropriate studies are not undertaken, the product licenses shall be revoked.

(m) *Informed consent.* Information and data submitted under this section after (insert effective date of this paragraph) shall include statements regarding each clinical investigation involving human subjects, that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

c. By revising § 601.30 to read as follows:

**§ 601.30 Licenses require products for controlled investigation only.**

Any biological or trivalent organic arsenical manufactured in any foreign country and intended for sale, barter or exchange shall be refused entry by collectors of customs unless manufactured, in an establishment holding an unsuspended and unrevoked

establishment license and license for the product. Unlicensed products that are not imported for sale, barter or exchange and that are intended solely for purposes of controlled investigation are admissible only if the investigation is conducted in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act and the requirements set forth in Parts 50, 58, and 312 of this chapter.

**PART 630—ADDITIONAL STANDARDS FOR VIRAL VACCINES**

15. Part 630 is amended  
a. In § 630.11 by revising the first sentence to read as follows:

**§ 630.11 Clinical trials to qualify for license.**

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with Part 50 of this chapter.

b. In § 630.31 by adding a new sentence at the end of the section to read as follows:

**§ 630.31 Clinical trials to qualify for license.**

Such clinical trials shall be conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

c. By revising § 630.51 to read as follows:

**§ 630.51 Clinical trials to qualify for license.**

To qualify for license, the antigenicity of Mumps Virus Vaccine, Live, shall be determined by clinical trials, conducted in compliance with Part 50 of this chapter, that follow the procedures prescribed in § 630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of mumps-susceptible individuals, each having received the parenteral administration of a virus vaccine dose not greater than that demonstrated to be safe in field studies (§ 630.50(b)) when used under comparable conditions.

d. By revising § 630.61 to read as follows:

**§ 630.61 Clinical trials to qualify for license.**

To qualify for license, the antigenicity of Rubella Virus Vaccine, Live, shall be determined by clinical trials, conducted in compliance with Part 50 of this chapter, that follow the procedures prescribed in § 630.31, except that the

immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of rubella-susceptible individuals, each having received the parenteral administration of a virus vaccine dose not greater than that demonstrated to be safe in field studies when used under comparable conditions.

e. In § 630.81 by revising the first sentence to read as follows:

**§ 630.81 Clinical trials to qualify for license.**

In addition to demonstrating that the measles component meets the requirements of § 630.31, the measles and smallpox antigenicity of the final product shall be determined by clinical trials of adequate statistical design conducted in compliance with Part 50 of this chapter and with three consecutive lots of final vaccine manufactured by the same methods and administered as recommended by the manufacturer.

**SUBCHAPTER H—MEDICAL DEVICES**

**PART 813—INVESTIGATIONAL EXEMPTIONS FOR INTRAOCULAR LENSES**

**Subpart F [Deleted]**

16. Part 813 is amended by deleting Subpart F—*Informed Consent of Human Subjects* and marking it “Reserved.”

**SUBCHAPTER J—RADIOLOGICAL HEALTH**

**PART 1003—NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY**

17. Part 1003 is amended in § 1003.31 by revising paragraph (b) to read as follows:

**§ 1003.31 Granting the exemption.**

(b) Such views and evidence shall be confined to matters relevant to whether the defect in the product or its failure to comply with an applicable Federal standard would create a significant risk to injury, including genetic injury, to any person and shall be presented in writing unless the Secretary determines that an oral presentation is desirable. When such evidence includes clinical investigations involving human subjects, the data submitted shall include, with respect to each clinical investigation, a statement that each investigation was conducted in compliance with the requirements set forth in Part 50 of this chapter.

**PART 1010—PERFORMANCE  
STANDARDS FOR ELECTRONIC  
PRODUCTS: GENERAL**

18. Part 1010 is amended:

a. In § 1010.4 by adding new paragraph (b)(1)(xii) to read as follows:

**§ 1010.4 Variances.**

\* \* \* \* \*

(b) \* \* \*

(1) \* \* \*

(xii) If the electronic product is used in a clinical investigation involving human subjects and is subject to the requirements for informed consent set forth in Part 50 of this chapter, the investigation shall be conducted in compliance with such requirements.

\* \* \* \* \*

b. In § 1010.5 by revising paragraph (c)(12) to read as follows:

**§ 1010.5 Exemptions for products  
intended for United States Government  
use.**

\* \* \* \* \*

(c) \* \* \*

(12) Such other information required by regulation or by the Director, Bureau of Radiological Health, to evaluate and act on the application. Where such information includes nonclinical laboratory studies, the information shall include, with respect to each nonclinical study, either a statement that each study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations. When such information includes clinical investigations involving human subjects, the information shall include, with respect to each clinical investigation, a statement that each investigation was conducted in compliance with the requirements set forth in Part 50 of this chapter.

\* \* \* \* \*

Interested persons may, on or before November 12, 1979, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5800 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

**Note.**— In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: August 6, 1979.

**Sherwin Gardner,**

*Acting Commissioner of Food and Drugs.*

[FR Doc. 79-24787 Filed 8-13-79; 8:45 am]

**BILLING CODE 4110-03-M**

Errata

Corrections to the Department of Health, Education, and Welfare, Office of the Secretary, proposed regulations regarding research involving human subjects which were published in the August 14 Federal Register, Part II (44 FR 47688).

1. On page 47691, second column, under "*HEW Response*" second paragraph, line 1 and 2, change "(4)(F)(I-III)" to "(4)(F)(i-iii)"
2. On page 47691, second column, under "*HEW Response*" third paragraph, line 1, change "(4)(F)(IV)" to "(4)(F)(iv)"
3. On page 47691, second column, under "*HEW Response*" fourth paragraph, line 1, change "(4)(F)(V-VI)" to "(4)(F)(v-vi)"
4. On page 47694, first column, under "§46.105(c)," line 5, change "indications" to "indications"
5. On page 47694, third column, under "§46.106(g)," line 16, change "insufficient detail" to "in detail sufficient"
6. On page 47697, first column, under "§46.112(b)," line 1, change "approved" to "approve"