

(viii) Take other action warranted by the reported nondelivery.

(2) After two reports by a household of nondelivery in a 6 month period the State agency shall utilize other issuance methods for that household. The State agency shall keep the household on the alternate issuance system for the length of time that the State agency determines to be necessary. The State agency may return the household to the regular issuance system if the State agency finds that the circumstances leading to the loss have changed and the risk of loss has lessened. Alternate issuance methods include:

(i) Using certified mail;

(ii) Arranging for the household to pick up its coupon allotment at a specified location; or

(iii) Moving the household from a mail issuance system to a regular over-the-counter system.

\* \* \* \* \*

(4) Replacement coupons which are stolen shall not be replaced.

\* \* \* \* \*

91 Stat. 958 (7 U.S.C. 2011-2027)  
(Catalog of Federal Domestic Assistance  
Program No. 10551, Food Stamps)

Dated: January 16, 1981.

Robert Greenstein,  
*Administrator.*

[FR Doc. 81-2651 Filed 1-26-81; 8:45 am]

BILLING CODE 3410-30-M

# **federal register**

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Tuesday  
January 27, 1981

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## **Part IX**

### **Health and Human Services Department**

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**Food and Drug Administration**

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**Protection of Human Subjects; Informed  
Consent; Standards for Institutional  
Review Boards for Clinical Investigations;  
and Clinical Investigations Which May Be  
Reviewed Through Expedited Review  
Procedure**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

21 CFR Parts 50, 71, 171, 180, 310, 312, 314, 320, 330, 361, 430, 431, 601, 630, 812, 813, 1003, 1010

[Docket No. 78N-0400]

### Protection of Human Subjects; Informed Consent

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

**SUMMARY:** The Food and Drug Administration (FDA) is issuing regulations to provide protection for human subjects of clinical investigations conducted pursuant to requirements for prior submission to FDA or conducted in support of applications for permission to conduct further research or to market regulated products. The regulations clarify existing FDA requirements governing informed consent and provide protection of the rights and welfare of human subjects involved in research activities that fall within FDA's jurisdiction.

**EFFECTIVE DATE:** July 27, 1981.

**FOR FURTHER INFORMATION CONTACT:** John C. Petricciani, Office of the Commissioner (HFB-4), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301-496-9320.

#### SUPPLEMENTARY INFORMATION:

In the Federal Register of August 14, 1979 (44 FR 47713), the Commissioner of Food and Drugs proposed regulations concerning standards of informed consent. FDA believed that a complete revision of its requirements relating to informed consent is needed because (1) current regulations had not been comprehensively reviewed in 12 years; (2) actions by the Department of Health and Human Services (HHS) and the Congress suggested 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) wherever possible, informed consent requirements adopted by FDA should be identical to, or compatible with, HHS 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) FDA's Bioresearch Monitoring Program could be conducted

more efficiently and effectively with uniform, agency-wide requirements for informed consent; and (7) FDA regulations should take into account the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) regarding institutional review boards (IRB's) and informed consent, published in the Federal Register of November 30, 1978 (43 FR 56174).

FDA allowed 90 days for comment on the proposal of August 14, 1979 (44 FR 47713). In addition, FDA held three open hearings to give the public an opportunity to comment on both the informed consent proposal and the IRB proposal that was repropounded in the same issue of the Federal Register (44 FR 47699). The hearings were held in Bethesda, MD, on September 18, 1979, San Francisco, CA, on October 2, 1979, and Houston, TX, on October 16, 1979. The comments received at the hearings and the hearing transcripts were made a part of the record of this regulation and are on file in the Dockets Management Branch (formerly the Hearing Clerk's office) along with the written comments received in response to the proposal. Comments were received from clinical investigators, institutional review boards, trade associations, professional societies, drug companies, and private citizens. The substantive comments received and FDA's conclusions about them are discussed below.

#### General Comments

1. Many comments suggested that FDA's informed consent requirements should be identical to the informed consent requirements adopted by HHS.

FDA agrees that uniformity of requirements is desirable and that uniform requirements would be less confusing to investigators who frequently may conduct both research funded by HHS and research involving FDA-regulated products. The substance of the informed consent requirements of the two regulations, with minor differences, therefore, is identical. The minor differences in wording reflect that (1) Part 50 is an interlocking but separate part of FDA's bioresearch monitoring regulations (2) purely behavioral research is not regulated by FDA, and (3) HHS has promulgated its IRB and informed consent requirements together in one subpart which was published in the January 26, 1981 issue of the Federal Register. FDA's bioresearch monitoring regulations when complete will contain separate requirements for and clarify the responsibilities of IRB's, clinical investigators, sponsors and monitors,

and nonclinical testing laboratories. FDA does not anticipate that clinical investigators will find the informed consent requirements contained in 21 CFR Part 50 confusing in relationship to the informed consent requirements contained in 45 CFR Part 46.

2. The preamble to the FDA proposal of August 14, 1979 (44 FR 47713) contains an extensive discussion of the history and evolution of the concept of informed consent. FDA pointed out in that discussion that the informed consent provisions for investigational drugs and antibiotics contained in sections 505(i) and 507(d)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i) and 357(d)(3)) (the act) differed from the provisions for investigational devices contained in section 520(g)(3)(D) of the act (21 U.S.C. 360(g)(3)(D)).

The majority of comments received in response to FDA's proposal to establish uniform requirements patterned upon section 520(g)(3)(d) of the act were in favor of uniformity. In fact, most comments favored uniform requirements not only for FDA-regulated research but for all research subject to the regulations of either FDA or HHS. One comment, however, questioned FDA's legal authority to conform the statutory requirements of sections 505, 507, and 520 of the act, but commended it, stating that the application of a uniform set of standards for informed consent for all clinical investigations would eliminate some of the confusion which has resulted from the promulgation of varying and sometimes inconsistent policies. Another comment stated that absent a single set of regulations, regulatory chaos would result, unintentional noncompliance would be likely, and the aims of subject protection would be defeated. Two comments argued that because the act established standards for investigations involving drugs that differ from the standards established for investigations involving devices, FDA should perpetuate the different standards in its informed consent regulation. Neither of these comments argued that the concept of informed consent had not changed since the Drug Amendments were enacted in 1962, and neither comment offered any particular investigational situation in which they thought an investigator might reasonably determine, as provided in sections 505(i) and 507(d) of the act, that obtaining informed consent would not be "feasible" or "in an investigator's professional judgment, [would be] contrary to [a subject's] best interests."

Only one of the comments objecting to the promulgation of a single standard

offered any extensive rationale for the objection raised. This comment argued that FDA should perpetuate in its informed consent regulation, the "therapeutic privilege" exemption provided by Congress when it enacted the 1962 Drug Amendments. This comment stated that in choosing to disregard the "therapeutic privilege" exemption, FDA was intruding into both the realm of congressional prerogative and the practice of medicine.

According to this comment, the circumstances in which the "therapeutic privilege" ought to apply, were as follows:

\* \* \* A departure from the absolute requirement of informed consent is necessitated when "patient psychology" is such that a physician must be free to use a new therapeutic measure, without obtaining the patient's informed consent, if in his judgment it offers help of saving life, re-establishing health, or alleviating suffering. When a drug is being used in a clinical investigation primarily for treatment, the circumstances call for the standards pertinent to the traditional physician-patient relationship, instead of those applicable to pure research. (Emphasis added.)

Basically, this comment assumes that a clinical investigation which involves an investigational article used primarily for treatment is not really an "investigation" at all, but is simply "the practice of medicine," and the basic objection expressed seems to be that obtaining informed consent could unjustifiably frighten patients away from participation in an investigational study that might provide significant benefits for that individual and/or society as a whole, while presenting little or no risk to the individual participant.

FDA has considered the objections raised by these comments, has conducted an extensive review of the current legal requirements for informed consent in the treatment as opposed to the investigational/experimental setting, and finds, for the reasons discussed below, that the uniform approach proposed is justified.

The "therapeutic privilege" in the context of experimentation has been subject to increased criticism in recent years. In a paper on the Law of Informed Consent prepared for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Ref. 1), the authors concluded that nondisclosure based upon a physician's judgment that it is not in the patient's best interest to know, should never be allowed in the experimental setting.

The authors of this report, who surveyed international, Federal, and

local standards of informed consent, concluded that because the purpose of the "therapeutic privilege" doctrine was to make sure that patients get treatment that physicians believe they need, it could have no application to nontherapeutic experimentation where no treatment is involved. The authors also concluded that,

\* \* \* Because of the great potential for abuse, e.g., the withholding of information for convenience or to assure the patient will not reject the treatment, and because the probability of success with an experimental treatment is either not known or very low, this exception should also not be permitted in the case of therapeutic experimentation. Indeed, as has been noted by a number of commentators, in this situation the physician-experimenter may have much more ability to obtain consent for an experiment than he would have from a normal volunteer who neither has an established dependency relation with him nor expects that the proposed experiment might be personally beneficial to him. As Professor Alexander Capron has observed: The "normal volunteer" solicited for an experiment is in a good position to consider the physical, psychological, and monetary risks and benefits to him when he consents to participate. How much harder that is for the patient to whom an experimental technique is offered during a course of treatment! The man proposing the experiment is one to whom the patient may be deeply indebted for past care (emotionally as well as financially) and on whom he is probably dependent for his future well-being. The procedure may be offered, despite unknown risks, because more conventional methods have proved ineffective. Even when a successful but slow recovery is being made, patients offered new therapy often have eyes only for its novelty and not for the risks.

In order to protect self-determination and promote rational decision-making, more, not less, information should probably be required to be disclosed in the experimental therapy situation than in the purely experimental setting with a normal volunteer (Ref. 1).

FDA agrees with the findings contained in the special report on the Law of Informed Consent. The standard of practice regarding informed consent promulgated by Congress in the Drug Amendments of 1962 was the standard that prevailed at that time. It is not the standard of practice today. FDA is concerned that research subjects be adequately protected from abuses of the kind that have taken place in the past (44 FR 47713-17); and is convinced that one way to protect research subjects against abuse is to ensure that they have the opportunity to be adequately informed before they consent to participate.

FDA does not believe that promulgating a single standard that reflects both current congressional thinking and current standards

regarding the practice of medicine represents an unreasonable encroachment upon the prerogatives of either Congress or the medical community. Congress expressly recognized at the time the Medical Device Amendments of 1976 were passed that, in view of changing social policy and advancing biomedical technology, the informed consent provisions of the Medical Device Amendments should be implemented through regulations based upon the recommendations to be made by the National Commission (Ref. 2). Indeed, the very purpose for which Congress established the National Commission was to assure a thorough review of the basic ethical principles underlying the conduct of biomedical and behavioral research (44 FR 47716).

FDA believes that the regulation does not encroach upon the prerogatives of the medical community because a review of court decisions which have involved informed consent casts doubt on whether the so-called "therapeutic privilege" to dispense with informed consent has any continued viability even in the standard practice of medicine. With increasing frequency, courts have held that when a patient is harmed by a treatment to which he or she might not have consented had he or she been adequately informed of the risks involved in that treatment, the doctor's failure to obtain informed consent may result in a finding of liability for negligence. In *Cobbs v. Grant*, 8 Cal. 3d 229, 502 P.2d 1 (1972), the California Supreme Court discussed at length the thesis that medical doctors are invested with discretion to withhold information from their patients and found that discretion to be extremely limited, stating that, "it is the prerogative of the patient, not the physician, to determine for himself the direction in which he believes his interests lie. To enable the patient to chart his course knowledgeably, reasonable familiarity with the therapeutic alternatives and their hazards becomes essential." *Cobbs, supra*, at 242-243. The California Court held that a duty of reasonable disclosure of the available choices with respect to proposed therapy and of the dangers inherently and potentially involved in each choice was an "integral part of the physician's overall obligation to the patient." *Cobbs, supra*, at 243. Under the *Cobbs* rationale, a patient's informed consent is an absolute requirement except in an emergency situation or in a situation in which the patient is a child or incompetent, in which case consent is either implied or sought from a legal

guardian. Thus, in *Cobbs*, the California Court found that consent of the quality required by this regulation should have been obtained from the patient and that it was the patient's prerogative to make the treatment decision based upon adequate information, not the physician's prerogative to limit the patient's choices by limiting the information provided. See generally, *Pharmaceutical Manufacturers v. Food Drug Administration*, 484 F. Supp. 1179, 1188 (D. Del. 1980).

The subject of negligence and informed consent is also discussed at length in *Canterbury v. Spence*, 464 F.2d 772 (D.C. Cir. 1972), cert. denied, 409 U.S. 1064 (1972), an action involving, among other things, the sufficiency of the information provided to a patient. Beginning with the fundamental premise that, "every human being of adult years and sound mind has a right to determine what shall be done with his own body," the *Canterbury* court defines "true consent" as the informed exercise of a choice that, in turn, entails an opportunity to evaluate knowledgeably the options available and the risks attendant upon each. *Canterbury, supra*, at 780. The *Canterbury* court flatly rejected the suggestion that disclosure of risk be discretionary with the physician, stating that any definition of the scope of disclosure purely in terms of a "professional standard" would be "at odds with the patient's prerogative to decide on projected therapy himself." *Canterbury, supra*, at 786. The *Canterbury* court discussed two exceptions to the general rule of disclosure—(1) when the patient is unconscious or otherwise incapable of consenting and (2) when risk-disclosure would be so detrimental as to be unfeasible from a medical point of view. The latter exception, according to the court, must be carefully circumscribed, "for otherwise it might devour the disclosure rule itself. The privilege does not accept the paternalistic notion that the physician may remain silent simply because divulgence might prompt the patient to forego therapy the physician feels the patient really needs." *Canterbury, supra*, at 789. The court did not further elucidate the second exception to disclosure other than to limit it to situations in which the patient's reaction to risk information is "menacing." *Id.* What, precisely, the court meant by "menacing" is not clear. A Massachusetts Court, however, has found that although disclosure of the potential side-effects of a medication might be "frightening" to a mental patient, that fact alone would not justify

a failure to inform. See *Rogers v. Okin*, 478 F. Supp. 1342, 1387 (D. Mass. 1979).

Both *Cobbs* and *Canterbury* were decided in 1972. Since 1972 it has become increasingly clear that a lack of informed consent will result in actionable negligence where injury results, and that the physician's duty to inform includes a duty to impart information sufficient to enable a patient to make an informed decision. The courts recognize that standard of informed consent has evolved and that the standard now requires full disclosure in all but the exceptional case. See *Dessi v. United States*, 489 F. Supp. 722 (E.D. Va. 1980); *Rogers v. Okin*, 478 F. Supp. 1342 (D. Mass. 1979).

It is not for the medical profession to establish a criterion for the dissemination of information to the patient based upon what doctors feel the patient should be told. See *Lambert v. Park*, 597 F.2d 236, 239 n.7 (10th Cir. 1979). According to *Lambert*, a standard that requires all material risks to be divulged,

\*\*\* Insures the important social policy underlying informed consent, that is, a physician should be required to disclose to his patients all material risks of a proposed procedure even if other doctors in the community or specialty would not have made so full a disclosure. This is simply an application of the well-known tort doctrine that proof of compliance with the applicable "industry" standard will not insulate a defendant from liability when the standard itself is inadequate. *Id.* at 238-239.

It seems clear that the current standard of care as defined by case law requires disclosure in the ordinary case of exactly the kind required by this regulation. If such full disclosure is required for nonexperimental treatment, it can hardly be argued that it can be dispensed with when the treatment is experimental. See *Ahern v. Veterans Administration*, 537 F. 2d 1098 (10th Cir. 1976). The agency, therefore, reaffirms its proposal of a uniform standard governing informed consent.

3. Several comments questioned the applicability of these regulations to studies conducted outside the United States. A few comments stated that standards of protection for human subjects may vary from country to country, and that the United States should not impose its standards on other countries when the human subjects come from those foreign countries in which the studies are being conducted.

FDA agrees with the comments, and notes that its policy regarding investigational studies involving drugs and biological products is set out in § 312.20 *Clinical data generated outside the United States and not subject to a*

*"Notice of Claimed Investigational Exemption for a New Drug"* (21 CFR 312.20). The policy regarding foreign studies and the background to § 312.20 was set out in detail in the preambles to the proposed and final regulation. See 38 FR 24220; September 6, 1973, and 40 FR 16053; April 9, 1975. The agency's policy regarding studies of investigational devices conducted outside the United States is similar to that for drugs and biological products and is discussed in the preamble to the recent proposal to establish procedures for the premarket approval of medical devices (PMA), published in the Federal Register of December 12, 1980 (45 FR 81769). Proposed § 814.15 of the PMA proposal states the agency policy concerning devices.

#### *The Proposed Regulation*

Part 50 will apply to all clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 520(g) of the act, as well as to clinical investigations that support applications for research or marketing permits for products regulated by FDA. These provisions are contained in § 50.1 (21 CFR 50.1) which was promulgated with Subpart C—Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects published in the Federal Register of May 30, 1980 (45 FR 36386). When complete, Part 50 will contain all of FDA's regulations concerning the Protection of Human Subjects.

The August 14, 1979 proposal contains all of the definitions applicable to Part 50. The definition of "application for research or marketing permit" (21 CFR 50.3(b)) was made final at the same time as Subpart C—Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects (45 FR 36396), and therefore, is not included here. The definition of that term also may be found as part of Part 56 on Institutional Review Boards (IRB's) which is published elsewhere in this issue of the Federal Register. The definitions made final here are congruent with those made final with Part 56, and many of the comments received in response to the IRB proposals were similar to the comments received in response to the Informed Consent proposal. A discussion of the definitions other than "application for research and marketing permit," and comments received in response to this and to the prisoner research proposal follow:

4. Several comments suggested that the proposed definition of clinical investigator in § 50.3(c) was too broad and should be limited through the explicit exclusion of particular kinds of

research such as that involving minimal risk.

FDA disagrees. The National Commission stated that even in no-risk or low-risk studies, respect for the rights and dignity of human subjects would require informed consent before participation in any clinical investigation. Informed consent is, as stated in § 50.20, required in all research subject to these regulations.

5. Two comments suggested that the proposed wording of § 50.3(d) defining "investigator" should be amended to include the primary investigator who might not be the person who actually conducts the investigation or gives immediate direction to those administering or dispensing the test article.

The agency agrees that an investigation may be conducted by several investigators and has modified the language of § 50.3(d) to define the term more broadly. Added to the definition is the language " \* \* \* in the event of an investigation conducted by a team of individuals, is the responsible leader of that team."

6. On its own initiative, FDA has deleted proposed § 50.3(e) defining "person" because the only time that it is used in these regulations is to refer to a living individual. Although additional definitions for the term are applicable to other FDA regulations, they are not applicable to informed consent.

7. One comment stated that proposed § 50.3(h) defining "subject" could be interpreted to deny the administration of a placebo or other control to an unhealthy human.

The agency did not intend the definition of subject to be ambiguous and § 50.3(g) has been slightly modified in this final rule. The definition now clearly states that a subject participates in a clinical investigation either as a recipient of the test article or as a control.

8. Section 50.3(h) defining "institution" replaces § 50.3(i) from the proposed regulations. The revised definition is consistent with the HHS definition and includes any entity including manufacturers, hospitals, and nursing homes.

9. The proposed definition of "institutionalized subject" has been deleted from the final regulations. Because the scope of coverage extends to human subjects, whether or not institutionalized, there is no need for a separate definition for institutionalized subjects at this time.

10. One comment questioned inclusion of cosmetics in proposed § 50.3(k) because cosmetics are not subject to premarket approval and therefore

should not be included in the definition of "test article."

The agency agrees and has deleted the term from § 50.3(k) of the final rule, defining "test article." Because cosmetic studies are not submitted to FDA in support of an application for research or marketing permit, they are not subject to Part 50.

11. One comment suggested that FDA adopt the HHS definition of "minimal risk."

FDA agrees with the comment, and has revised the definition in § 50.3(l) accordingly. This definition takes into account the fact that the risks in the daily life of a patient are not the same as those of a healthy individual, and uses the risks in daily life as the standards for minimal risk.

12. Section 50.3(m) defining "legally authorized representative" has been revised slightly from the definition proposed by FDA so that it is identical to the HHS definition.

13. One comment on proposed § 50.20 suggested that incomprehensible consent forms would be useless to human subjects and that FDA should require that information be communicated to subjects in language they can understand.

FDA agrees that information given to human subjects should be in language they can understand, and notes that the National Commission also made this recommendation. Section 50.20 has been reworded to require that information given to the subject or the subject's legally authorized representative be in language that is understandable to the subject or the representative.

14. One comment suggested that all minimal risk studies be exempted from the requirements for informed consent.

The agency does not agree. Both the HHS regulations and the FDA regulations reflect the belief that even minimal risk studies require the informed consent of human subjects before they may participate in a research study. Informed consent is, therefore, a uniform requirement for all investigational studies, no matter how low risk an investigator may believe them to be.

15. One comment suggested that the IRB should determine when informed consent would be necessary. Another comment suggested that low-risk and no-risk studies be exempted from the requirement of informed consent.

FDA disagrees and rejects the comments. Sections 505(i), 507(d) and 520(g) of the act (21 U.S.C. 355(i), 357(d) and 360(j)) require that FDA promulgate regulations for the exemption of drugs and devices for investigational use. These sections of

the act direct FDA to promulgate regulations that will ensure that informed consent will be obtained from each subject or each subject's legally authorized representative as a condition to the issuance of the exemption. The National Commission stated that even in no-risk or low-risk studies, respect for the rights and dignity of human subjects would require informed consent before participation in any clinical investigation. FDA agrees with this position and requires that informed consent be obtained from each subject or representative before a subject may participate in a clinical investigation. The only exception from the requirement which applies to individual situations and not to categories of studies as a whole, is the provision in § 50.23 for emergency use of a test article.

16. One comment stated that FDA lacked the authority to reject a study if the requirement for informed consent were not followed. The comment further stated that in order for FDA to reject a study, the noncompliance with the regulatory requirements must affect the scientific validity of the data generated.

FDA disagrees with the comment. The Federal Food, Drug, and Cosmetic Act also requires that these regulations have due regard for the interests of patients (21 U.S.C. 355(j)(1) and 21 U.S.C. 357(g)(1)) or be consistent with ethical standards (21 U.S.C. 360(j)(1)). Therefore, FDA believes it possesses the necessary statutory authority to reject studies where informed consent has not been obtained even though the scientific validity of the data generated may not have been affected, and it reserves the right to do so where circumstances so warrant.

17. Several comments argued that the proposed requirements of § 50.21 concerning the effective date of the regulations were too complicated, too burdensome, and not really necessary for the great number of studies. These comments suggested that the revised informed consent requirements apply only to individuals entering a clinical investigation after the effective date of the regulation.

The agency has considered these comments and agrees that only prospective application of the new uniform informed consent provisions will be required. The requirements of both Part 50 and Part 58 will become effective at the same time, that is, July 27, 1981, and will be applicable only to clinical investigations that begin on or after this date.

In determining that the requirements need apply only prospectively, the agency has taken a number of factors

into account. It has balanced the cost of compliance against the possible added protections to be gained by research subjects, and has determined that the potential cost of imposing the requirements retroactively outweighs the potential gain. The informed consent regulations that will continue to be in effect until the effective date of Part 50 have assured that at least minimum standards of informed consent have been met in studies initiated before the effective date of this regulation. In addition, the agency believes that where an inspection reveals deficiencies in the informed consent obtained in a particular ongoing study, correction can be obtained administratively. Further, at the time an IRB performs its continuing review, the IRB may require correction of deficiencies if, in its judgment, such correction is required. The agency believes, therefore, that prospective application will be sufficient.

18. One comment on proposed § 50.23(a)(2), the exception provided for situations in which communication with the subject is not possible, stated that, as written, the section could apply when a subject spoke only a foreign language.

The agency does not agree. For the exception to apply, all four requirements of the subsection must be met. Inability to communicate in the context of § 50.23(a) clearly means that the subject is in a coma or unconscious. The exception is to be invoked only in emergency situations.

19. One comment stated that the exception requirements of proposed § 50.23 were too restrictive and should be modified to allow an investigator to proceed without consent in a nonlife-threatening but "serious" emergency.

The agency does not agree. The requirements of § 50.23 are based on section 520(g)(3)(D) of the act. Those requirements are quite explicit and allow that consent be dispensed with only if the emergency situation is "life threatening." The comment is rejected.

#### Elements of Informed Consent

Many comments were received on the eleven basic and five additional items proposed in § 50.25 as the elements of informed consent. Many of these comments suggested that there were too many elements proposed, that they were duplicative, and that they would simply confuse research subjects. Other comments suggested that the elements proposed were too few and suggested the addition of other items of information to the list of elements proposed. The individual comments are discussed below.

20. Several comments said that the statement that an IRB had approved the

solicitation of subjects to participate in the research, required by proposed § 50.25(a)(1), could mislead human subjects into thinking that because the study had been approved by an IRB there was no need for them to evaluate for themselves whether or not they should participate in the study.

FDA agrees with these comments and has deleted this requirement from the final regulations. Proposed § 50.25(a)(1) and (2) have been combined.

21. Several comments stated that the proposed requirements contained in § 50.25(a)(2), regarding the scope and aims of the research would require explanations that were both too complex and too lengthy to be meaningful to subjects. Another comment asserted that the word "scope" was too vague as to be meaningless while "aims" was synonymous with "purposes." All of these comments suggested that § 50.25(a)(2) should be simplified so that subjects receive only meaningful information.

The agency agrees with the comments and has rewritten the section for clarity. The requirement now reads: "an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of those procedures which are experimental."

22. Several comments on proposed § 50.25(a)(3) (renumbered as § 50.25(a)(2) in the final rule) objected to including a statement of the likely results if an experimental treatment should prove ineffective. A few comments pointed out that in some studies involving cancer chemotherapies, it would be unkind to include such a statement in the informed consent document because the likely result of ineffective treatment would be death. Other comments pointed out that an explanation of the likely results of an ineffective treatment would not be applicable in a study of normal, healthy volunteers because there would be no difference to them if the treatment failed.

FDA agrees with the comments and has deleted the specific language regarding ineffective treatment from the regulation. The agency points out, however, that if an ineffective treatment would result in either a foreseeable risk or discomfort it would have to be described in any case under § 50.25(a)(2).

23. One comment on proposed § 50.25(a)(3), (4), and (5) suggested that investigators should be required, where possible, to give test subjects quantified comparative estimates of risks and

benefits of experimental and alternative treatments.

FDA agrees that, were it always possible to quantify the risks, benefits, and comparative treatments for purposes of estimation, such quantification would be required. The basis elements represented by § 50.25(a)(2), (3), and (4), do require that human subjects be given a description of any reasonably foreseeable risks or discomforts, benefits, and a disclosure of appropriate alternative procedures or courses of treatment. FDA believes that where such descriptions or disclosures can contain quantified comparative estimates of risks and benefits, they should do so. Where such well-defined estimates are not possible, however, the agency believes that the information required to be disclosed will be sufficient. The agency does not believe that imposing such a strict requirement for every case would be realistic or appropriate.

24. One comment stated that FDA's preliminary assessments of an experimental drug's therapeutic significance should routinely be made available to subjects of drug testing and that this should be included as a basic element of informed consent.

FDA does not agree. FDA's preliminary assessment of the therapeutic significance of an experimental drug or device is based on the same data that are available to an IRB at the time of its initial or continuing review. To the extent that an IRB believes that preliminary data assessment is appropriate to include in a consent form, it may so require.

25. One comment on proposed § 50.25(a)(4) (§ 50.25(a)(3) in the final rule) urged the agency to add a specific requirement that a subject be told if it is reasonably anticipated that the study will neither improve nor relieve his or her condition.

The agency does not agree that such specific language need be added. Adequate disclosure of risks (§ 50.25(a)(2)), benefits (§ 50.25(a)(3)), and appropriate alternative treatments (§ 50.25(a)(4)) will provide sufficient information to a subject to enable the subject to decide whether or not to participate. When use of a test article clearly will not benefit a particular condition, that fact should be made known as a reasonably foreseeable risk.

26. One comment stated that the requirement that benefits be described would be meaningless to normal, healthy volunteers because they would receive no benefit, and therefore, suggested that this requirement be deleted from § 50.25(a) and included in

§ 50.25(b). *Additional elements of informed consent.*

FDA rejects the comment. The agency believes that even if subjects receive no personal benefit from the study, others may receive some benefit, and, where it may reasonably be expected that others may benefit, that information should be disclosed.

27. One comment on proposed § 50.25(a)(5) (§ 50.25(a)(4) in the final rule) stated that a mere disclosure of appropriate alternative treatments would not be sufficient, and suggested that an investigator should have to describe the risks and benefits of such alternatives.

The agency believes that the requirement, as worded, is sufficient. Any explanation of "appropriate alternative treatments" that did not contain some explanation of the risks and benefits of the alternatives would not be a true "disclosure." The agency believes that the full description sought by the comment is required by the element as written.

28. Another comment on proposed § 50.25(a)(5) suggested that the consent form should merely state that alternative treatments are available.

FDA disagrees and rejects the comment because it is important for a human subject to have specific information about alternative treatments in order to evaluate the risks and benefits of experimental treatment. Therefore, except for being renumbered, § 50.25(a)(4) remains unchanged in the final regulation.

29. Several comments on proposed § 50.25(a)(6) suggested that a statement that "new information" developed during the course of the research be provided to the subject, would not be appropriate in every study. In particular, these comments stated that such a statement would be irrelevant to either a single-dose clinical study or a study of extremely short duration.

FDA agrees that the statement should not be required in every case and has, therefore, made this provision an "additional" element to be required when appropriate and is issuing it as § 50.25(b)(5) in the final rule. When appropriate, in this case, will mean in every study of sufficient duration, which the agency believes can be decided by the IRB.

30. Several comments on proposed § 50.25(a)(6) stated that the term "new information" is too all-encompassing and would be extremely difficult to interpret. A few comments suggested that "significant new findings" would be an appropriate substitute for "new information."

FDA agrees with the comments and has substituted "significant new findings" for "new information." Thus, only relevant substantive information that might affect a subject's willingness to continue participation in the study need be communicated.

31. One comment stated that proposed § 50.25(a)(6) was unnecessary because it is implicit in every clinical investigation that an ethical and conscientious researcher would inform subjects if new risks or side effects were noted. One comment suggested that the requirement was unnecessary because other regulations require prompt notification and withdrawal of treatment following the occurrence of serious adverse reactions.

FDA disagrees with these comments. FDA believes that an investigator should be required to advise subjects of new risks or adverse reactions that may affect the subject's willing and continued participation in the study. Therefore, even though an ethical investigator would notify subjects of newly determined risks or adverse reactions, and other regulations require prompt reporting to the IRB and FDA of these findings, FDA believes that the investigator should be explicitly required to tell subjects of significant new findings, when necessary and appropriate. The comments are rejected.

32. A number of comments objected to the requirement, contained in proposed § 50.25(a)(7) (§ 50.25(a)(5) in the final rule), that research subjects be informed in advance of their participation in an investigation that FDA may inspect the subject's records. Several of these comments asserted that if subjects were so informed they would refuse to participate in FDA-related investigations.

The agency does not believe that telling subjects that their records might be inspected by FDA will be a serious deterrent to subject participation. Medical records are frequently subject to third party review (e.g., insurance companies) and, although it may be true that informing potential subjects that study records may be inspected by FDA may deter some subjects from participation, that fact can scarcely be cited as a reason not to inform. Indeed, it is particularly important that any subject who feels strongly that his or her study records ought not be seen by anyone other than the clinical investigator be told ahead of time that an expectation of total privacy is not realistic in the context of clinical research being conducted for submission to FDA.

As discussed in the preamble to the proposal, FDA believes in the protection

of subject privacy, and FDA does not routinely inspect subject records. However, the agency must inspect such records when it has reason to believe that the consent of the subjects was not obtained or when there is reason to believe that the study records do not represent actual studies or do not represent actual results obtained. Where 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 (e.g., Freedom of Information Act and Privacy Act) and the law enforcement responsibilities of the agency. Clinical studies are submitted to FDA to obtain an approval to market a regulated product, and the agency must be able to verify the basis for an approval whenever either a question of validity of results or subject rights arises. Moreover, not all raw data produced in the course of a clinical investigation involves "patient records" of the kind envisioned by many of the comments. Many clinical investigations are short-term and involve subjects who may or may not be patients. There may or may not be a doctor-patient relationship between the clinical investigator and the subject and there may or may not be an expectation on the part of the subject that the records of his or her participation in the investigation will be treated as confidential. Subjects who participate in clinical investigations are frequently paid to participate, and, in such cases, the relationship between the investigator and the subject will be a contractual one. For example, in those cases in which a sponsor or monitor will review the subjects' records, the subjects should be so informed. It is particularly important that any subject who has an expectation of privacy regarding the subject's records of participation in FDA-regulated research be informed about the extent to which these records will be kept confidential so that any subject who feels strongly about the records may refuse to participate. The agency believes that providing this information to a subject is both fair and necessary. The motivation of subjects who participate in clinical research varies widely, and the agency does not believe that providing this information will prevent vast numbers of subjects from agreeing to participate. The comments do not require any change in § 50.25(a)(5).

33. Several of the comments on proposed § 50.25(a)(7) objected that the requirement of a notice in the consent document that FDA might inspect subject records constituted a request that subjects waive their legal rights to privacy as a condition to giving their informed consent. One comment stated that proposed § 50.20 prohibits inclusion in informed consent documents of exculpatory language that waives or appears to waive a subject's legal rights. As an alternative to proposed § 50.25(a)(7), several comments suggested that the regulation be revised to provide that FDA would seek permission from individual patients to inspect or copy their records if the need arose.

The agency rejects all of these comments. The basis of FDA's right to inspect subject records was discussed both in the preamble to the proposal (44 FR 47721) and in the response to comment 32 in this preamble. The agency is not requiring any subject to "waive" a legal right. Rather, the agency is requiring that subjects be informed that the "legal right" to privacy that they might expect in other contexts does not apply in the context of regulated research. FDA need not "seek permission" when the need to inspect such records arises because to do so would, in essence, delegate improperly an authority vested in the agency by Congress.

34. Two comments noted that because FDA states in the preamble to the proposal that it has the right to copy medical records containing the names of research subjects when there is reason to believe that consent was not obtained, or there is doubt that the records represent actual studies or actual results obtained, proposed § 50.25(a)(7) should provide that the consent form also inform the research subject that identifying information may be inspected and copied by FDA.

FDA believes that the required statement, as phrased, is sufficient. The language, therefore, as issued in § 50.25(a)(5) of this final rule is unchanged.

35. One comment stated that many institutions would not wish to include the notice required by § 50.25(a)(5) on all their consent forms. Therefore, there would have to be a separate consent form for FDA-regulated research. This comment suggested that this requirement be deleted.

FDA rejects the suggestion. While it may be true that some institutions do not wish to have the notice of possible FDA inspection of subject records on all of their consent forms, the agency believes it is important that human

subjects included in FDA-regulated research be aware that FDA might need to see their records. FDA believes that consent forms should be individualized for each study in any case, because standardized consent forms could not possibly take into account all the elements necessary to obtain adequate informed consent for every clinical investigation.

36. Several comments on proposed § 50.25(a)(9) (§ 50.25(a)(6) in the final rule) stated that because of the possibility of unanticipated injuries, it would be impossible to describe in advance the nature of any compensation and medical treatment for injury that might occur as a result of the study. Several comments stated that it would be difficult, if not impossible, to distinguish between those injuries that are compensable and those that are not.

These comments misunderstand the requirement. All that is required is a statement that compensation or medical treatment are or are not available if unanticipated injuries occur and of what they consist. Such a statement will be adequate if it merely states that medical care will or will not be provided in the event of injury and describes the extent of available compensation, if any. Compensation for injury may vary with the extent of the injury or may be limited. A description so stating will be adequate.

37. One comment suggested that because proposed § 50.25(a)(10) was merely an extension of § 50.25(a)(8), they should be combined.

The agency agrees. Proposed § 50.25(a)(8) required an offer to answer any questions the subject or the subject's representative might have about the research, the subject's rights, or related matters. Proposed § 50.25(a)(10) required that the subject be told whom he or she should contact if harm occurred or if there were questions. These two requirements have been combined and published in this final rule as § 50.25(a)(7). This provision requires that subjects be given an explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.

38. One comment on proposed § 50.25(a)(8) stated that although the clinical investigator could respond to questions concerning the research, the clinical investigator was not necessarily the appropriate person to answer questions about the subject's rights.

While the comment may be true, the final regulation issued as § 50.25(a)(7) does not require that one particular person answer all questions raised by

the subject. Rather, the regulation requires that a subject be told whom to contact regarding particular problems. Where one person cannot respond to all the questions, more may and should be designated. The agency believes that the final regulation clarifies this provision.

39. One comment suggested that the information regarding whom to contact was merely a procedural item and that it should, therefore, not be a "basic" element of § 50.25(a) but should be made an "additional" element of proposed § 50.25(b).

FDA disagrees. The items of information required to be disclosed under "additional elements," § 50.25(b)(1) through (6), are those items that are either irrelevant to some categories of research (i.e., single-dose studies) or items that are discretionary and that may be required by the IRB. The information regarding whom to contact is equally important in all studies, should be required to be provided in every case, and therefore is retained in § 50.25(a)(7) of this final rule.

40. Two comments suggested that proposed § 50.25(a)(11) (§ 50.25(a)(8) in the final rule), as worded, might be interpreted to mean that a subject who was being paid to participate in a clinical investigation could receive full payment even if he or she dropped out. These comments suggested that the provision be revised to state that a subject could discontinue participation "without loss of already earned benefit."

The agency does not agree that the provision should be revised. In any study in which a subject is paid, the contractual agreement may specify the basis of compensation and, therefore, the degree of "entitlement." If, in such a case, full payment requires completion of the study, and a subject fails to complete the study, he or she will not be "entitled" to full compensation. All that is required is that a full explanation be provided. The agency does not find that the wording of § 50.25(a)(8) is ambiguous on this point and the comments are rejected.

41. One comment on proposed § 50.25(b) stated that the regulations could allow IRB's and investigators to deny human subjects information necessary for informed consent because that information was listed under "Additional elements."

FDA disagrees with this interpretation. The elements of informed consent listed as "additional" are not needed in every clinical investigation. However, when any of those additional elements would be appropriate, § 50.25(b) requires that the additional information be provided to the subject.

42. Several comments suggested that the "Additional elements" of proposed § 50.25(b) be required as basic because they are all material to informed consent.

FDA disagrees with the suggestion. The elements listed as "additional" are not material to every clinical investigation. For example, the requirement of § 50.25(b)(5) in the final rule that significant new findings be communicated to the subject if those findings might affect the patient's willingness to continue participation in the study, is not relevant to single-dose studies.

43. One comment on proposed § 50.25(b)(1) suggested that this "additional" element as written was overbroad.

The agency does not agree that the element is overbroad. However, for clarity, § 50.25(b)(1) has been revised and has been shortened by deleting the second sentence.

44. Two comments suggested that proposed § 50.25(b)(2) be deleted. The comments argued that the required disclosure of foreseeable risks or discomforts and that providing information about foreseeable circumstances under which a subject's participation may be terminated would be impractical because such possible circumstances were "infinite."

The agency disagrees. Not every hypothetical circumstance in which a subject's participation might be terminated need be disclosed. The regulation requires only a discussion of anticipated circumstances. It might well be sufficient to state that a subject's participation might be terminated when, in the judgment of the clinical investigator, it is in the subject's best interests although in such a case some illustrative situations should be provided. For clarity, the word "anticipated" has been substituted for the word "foreseeable" as used in the proposed regulation to describe circumstances.

45. One comment on proposed § 50.25(b)(3) suggested that the requirement that information on possible additional costs "to others" besides the subject be provided was unclear, would have infrequent application, and could be misleading because it might refer to additional costs to the investigator or the sponsor.

The agency agrees and has deleted the words "to others." Section 50.25(b)(3) now requires that information be provided only on possible resulting additional costs to the subject.

46. One comment on proposed § 50.25(b)(5) (§ 50.25(b)(4) in the final

rule) stated that providing information on the consequences of a decision to withdraw from a study was unnecessary because the information would duplicate the requirements of other sections of the informed consent regulations.

The agency does not agree. There may be studies in which specific information on the consequences of a decision to withdraw will be of particular importance. The information need only be provided in those cases. IRB review should help identify those studies in which the information would be appropriate.

47. As discussed in responses to comments 29 through 31, the proposed requirement of § 50.25(a)(6) to provide to all subjects in any investigation, a statement regarding new "information" has been determined to be more appropriately an additional element of consent and included in the final rule as § 50.25(b)(5).

48. A number of comments on proposed § 50.25(b)(4) (§ 50.25(b)(6) in the final rule) stated that disclosing the name of the sponsor, the responsible institution, and who was funding the study would add nothing to the quality of a subject's consent because none of the items of information were likely to be important to a subject's decision to participate in research.

The agency agrees that, for the most part, the items of information proposed need not be specifically provided and has, therefore, deleted the language regarding funding, responsible institution, and sponsor. Because the approximate number of subjects participating may have a bearing on a subject's decision to participate, however, that requirement is retained in § 50.25(b)(6). Where multi-institutional studies are involved, an indication of the number of institutions and the approximate number of subjects will be sufficient.

49. On the agency's own initiative, two new paragraphs have been added to § 50.25. Section 50.25(c), which states that the requirements of these regulations are not intended to preempt any applicable Federal, state, or local laws which require additional information to be disclosed, is added to make the policy clear and to conform to the HHS language. Section 50.25(d), which states that these regulations are not intended to limit the authority of a physician to provide emergency medical care to the extent permitted under other applicable statutes, was initially proposed as § 50.23(d). It has been finalized without change and moved to conform to the HHS placement.

50. Section 50.27 requiring an investigator to document informed consent has been revised and shortened. The language of the section conforms to the language of the HHS regulation.

51. Several comments stated that to require a long, detailed consent form would be confusing and would detract from the intended purpose of the regulation that relevant information about a study be conveyed to the human subject.

The agency, as noted in responses to comments on proposed § 50.25, has simplified the informational requirements of the regulation and has required that the information given to a subject be in understandable language. FDA recognizes that the documentation of informed consent represents only one part of the entire consent process. The consent form itself is merely an aid to assure that a required minimum of information is provided to the subject and that the subject consents. The entire informed consent process involves giving the subject all the information concerning the study that the subject would reasonably want to know; assuring that the subject has comprehended this information; and finally, obtaining the subject's consent to participate. The process, to be meaningful, should involve an opportunity for both parties, the investigator and the subject, to exchange information and ask questions. The consent form, thus, should not be viewed as an end point. Rather, it is the beginning. The agency concludes that the comments do not justify any specific changes to § 50.27, although, as stated in comment 50, the regulation has for other reasons been revised and shortened.

52. One comment stated that the documentation of informed consent by a short form will not ensure that subjects understand the oral explanations. The comment further stated that subjects would have to rely solely on the interpretation given to them by the investigator.

FDA disagrees with the comment. The same quantum and quality of information, i.e., that information required by § 50.25, must be provided to a subject whether a long form, a short form, or no form is used (see also § 56.109(c)). The fact that a short form is used to document informed consent does not mean that the subject will get less information than if handed a long, detailed written document. When a "short form" is used, the IRB must first approve a written summary of what is to be said, and a witness must be present to attest to the adequacy of the consent process and to the voluntariness of the

subject's consent. Section 50.27(b)(2) also requires that a copy of that summary be given to the subject. FDA believes that in many cases an oral presentation and written summary will be an effective method of disclosing necessary information. All the "form" provides, in either case, is evidence that the information required by § 50.25 has been provided to a prospective subject. The "form" itself cannot substitute for the communicative process that it represents and, as noted in response to comment 51, it is not intended to.

53. The agency received no comments on the proposed conforming amendments and except for combining the proposed amendments relating to Parts 50 and 56, they are issued as proposed.

54. On its own initiative, the agency is revising 21 CFR 312.20(b)(1)(iv) by replacing the 1964 Declaration of Helsinki with the revised version adopted by the World Medical Assembly in 1975. The Declaration, first adopted by the World Medical Assembly in 1964 (see 44 FR 47715), was revised by that group, and the revision adopted at the 29th World Medical Assembly held in Tokyo, in October 1975. The revision includes a number of new requirements, among them the requirement that a research protocol be reviewed by a specially appointed independent committee.

55. On its own initiative, the agency is also adopting amendments to the Investigational Device Exemptions (IDE) regulations (21 CFR Part 812) to conform them to Part 50. The IDE regulations were promulgated by FDA on January 18, 1980 (45 FR 3732) after the August 14, 1979 proposal of these regulations.

#### References

The following material has been placed on file in the Dockets Management Branch, Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

1. Annas, G. J., "The Law of Informed Consent to Human Experimentation: An Introduction with Specific Reference to the Hospital Patient and the Normal Volunteer," prepared for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, NIH Contract No. NO1-HU-6-2120, June 1976.

2. H.R. Rept. No. 94-1090, 94th Cong., 2d Sess. (1976).

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701(a), 706, and 8901, 52 Stat. 1049-1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 52

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, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 301, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 241, 262, 263b-263n)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

#### SUBCHAPTER A—GENERAL

#### PART 50—PROTECTION OF HUMAN SUBJECTS

##### 1. In Part 50:

a. In § 50.3 by adding paragraphs (a) and (c) through (m), to read as follows:

##### § 50.3 Definitions.

(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)).

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

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

(e) "Sponsor" means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or

more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

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

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

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

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

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

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

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

(m) "Legally authorized representative" means an individual or

judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

b. By adding new Subpart B to read as follows:

**Subpart B—Informed Consent of Human Subjects**

Sec.

50.20 General requirements for informed consent.

50.21 Effective date.

50.23 Exception from general requirements.

50.25 Elements of informed consent.

50.27 Documentation of informed consent.

**Subpart B—Informed Consent of Human Subjects**

**§ 50.20 General requirements for informed consent.**

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

**§ 50.21 Effective date.**

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

**§ 50.23 Exception from general requirements.**

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

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

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

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

**§ 50.25 Elements of informed consent.**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**§ 50.27 Documentation of informed consent.**

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

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

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

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

#### PART 71—COLOR ADDITIVE PETITIONS

2. Part 71 is amended:

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 statements 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 §§ 56.104 or 56.105, and 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 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 §§ 56.104 or 56.105, and 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 (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 statements 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 §§ 56.104 or 56.105, and 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 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 §§ 56.104 or 56.105, and 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)(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, statement that the investigation 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 §§ 56.104 or 56.105, and that it 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 removing and reserving paragraph (i).

##### § 310.102 [Removed]

6. Part 310 is amended by removing § 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:

a. In § 312.1 by revising paragraph (a)(2) item c of Form FD-1571, item 3 of Form FD-1572, and item 2a of Form FD-1573, and redesignating paragraph (d)(11) and (12) as (d)(12) and (13), respectively, and adding new paragraph (d)(11) to read as follows:

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

(a) \* \* \*

(2) \* \* \*

c. *Institutional review board (IRB)*. The sponsor must give assurance that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The sponsor must also provide assurance that the investigators will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that the investigators will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to the human subjects. FDA will regard the signing of the Form FD-1571 as providing the necessary assurances above.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the

additional phase or phases is submitted before such additional phases begin. A limitation on an exemption does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records maintained for each subject to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given, and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

3. The investigator assures that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator also assures that he/she will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research that would increase the risks to human subjects without IRB approval. FDA will regard the signing of the Form FD-1572 as providing the necessary assurances stated above.

2a. The investigator assures that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator also assures that he/she will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research that would increase the risks to human subjects without IRB approval. FDA will regard the signing of the Form FD-1573 as

providing the necessary assurances stated above.

(d) \* \* \*

(11) The clinical investigations are not being conducted in compliance with the requirements regarding institutional review set forth in this part or in Part 56 of this chapter, or informed consent set forth in Part 50 of this chapter; or

b. In § 312.20(b)(1)(iv) by replacing the 1964 "Declaration of Helsinki" with the revised version to read as follows:

**§ 312.20 Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational Exemption for a New Drug."**

(b) \* \* \*

(1) \* \* \*

(iv) \* \* \*

**Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects**

*I. Basic Principles*

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

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

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the

hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

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

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

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

*II. Medical Research Combined With Professional Care (Clinical Research)*

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic methods.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

*III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)*

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

**PART 314—NEW DRUG APPLICATIONS**

8. Part 314 is amended:

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

**§ 314.1 Applications.**

(c) \* \* \*

(2) \* \* \*

Form FD-356H—Rev. 1974:

17. *Conduct of clinical investigations.* Statements contained in the application 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, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

(f) \* \* \*

(7) Statements contained in the application 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, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and 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 (n) to read as follows:

**§ 314.8 Supplemental applications.**

(n) A supplemental application that contains clinical investigations involving human subjects shall include statements 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, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and 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 (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 statements 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, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and 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 (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 informed consent set forth in Part 50 of this chapter either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it 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.**

(a) \* \* \*

(11) The applicant fails to include in the application statements 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, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and 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)(11) to read as follows:

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

(a) \* \* \*

(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, or 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)(7) to read as follows:

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

(c) \* \* \*

(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, or informed consent set forth in Part 50 of this chapter was not conducted in compliance with such requirements.

**PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS**

g. Part 320 is amended:

a. In § 320.31 by adding 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, and 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 (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**

10. 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 and informed consent.* Information and data submitted under this section after (July 27, 1981) shall include statements 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, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and 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 review and approval of an institutional review board that conforms to the requirements of Part 56 of this chapter, 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 (g) to read as follows:

§ 430.20 **Procedure 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 involving human subjects on which the issuance or amendment of the regulation is based 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 §§ 56.104 or 56.105, and 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 (l) to read as follows:

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

(l) Statements 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 §§ 56.104 or 56.105, and 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 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 §§ 56.104 or 56.105, and was conducted in compliance with 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 (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 designed 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 institutional review set forth in Part 56 of this chapter, unless it is not subject to such requirements in accordance with §§ 56.104 or 56.105, and 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.

(1) *Institutional review and informed consent.* Information and data submitted under this section after July 27, 1981 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 §§ 56.104 or 56.105, and 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 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 50, 56 unless exempted under § 56.104 as granted a waiver under § 56.105, 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 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and 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 Part 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and 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 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and 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 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and 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 meet 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 § 56.104 or granted a waiver under § 56.105, and 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. \* \* \*

**PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS**

16. Part 812 is amended:

a. In § 812.2 by revising paragraph (b)(1)(iii) to read as follows:

**§ 812.21 Applicability.**

(b) \* \* \*  
(1) \* \* \*

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under Part 50 and documents it, unless documentation is waived by an IRB under § 56.109(c).

b. In § 812.3 by revising paragraph (f) to read as follows:

**§ 812.3 Definitions.**

(f) "Institutional review board" (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated, and functioning in conformance with Part 56. The term has the same meaning as "institutional review committee" in section 520(g) of the act.

c. In § 812.20 by removing paragraph (a)(2), and by redesignating (a)(3) as (a)(2) and revising it, and by redesignating (a)(4) as (a)(3) as follows:

**§ 812.20 Application.**

(a) \* \* \*

(2) A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.

d. In § 812.35 by revising paragraphs (a) and (b) to read as follows:

**§ 812.35 Supplemental applications.**

(a) *Changes in investigational plan.* A sponsor shall: (1) Submit to FDA a supplemental application if the sponsor or an investigator proposes a change in the investigational plan and (2) obtain IRB approval (see § 56.110(b)) and FDA approval of the change before implementation.

(b) *IRB approval.* A sponsor shall submit to FDA, in a supplemental application, the certification of any IRB approval of an investigation or a part of an investigation not included in the IDE application.

e. By adding new § 812.42 to read as follows:

**§ 812.42 FDA and IRB approval.**

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

f. By revising the heading of Subpart D to read as follows:

**Subpart D—IRB Review and Approval**

g. By revising § 812.60 to read as follows:

**§ 812.60 IRB composition, duties, and functions.**

An IRB reviewing and approving investigations under this part shall comply with the requirements of Part 56 in all respects, including its composition, duties, and functions.

h. In § 812.62 by revising the section heading and the section to read as follows:

**§ 812.62 IRB approval.**

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all investigations covered by this part.

(b) If no IRB exists or if FDA finds that an IRB's review is inadequate, a sponsor may submit an application to FDA.

i. By adding new § 812.64 to read as follows:

**§ 812.64 IRB's continuing review.**

The IRB shall conduct its continuing review of an investigation in accordance with Part 56.

j. By adding new § 812.66 to read as follows:

**§ 812.66 Significant risk device determinations.**

If an IRB determines that an investigation, presented for approval under § 812.2(b)(1)(ii), involves a significant risk device, it shall so notify

the investigator and, where appropriate, the sponsor. A sponsor may not begin the investigation except as provided in § 812.30(a).

k. In § 812.100 by revising the second sentence to read as follows:

**§ 812.100 General responsibilities of investigators.**

\* \* \* An investigator also is responsible for ensuring that informed consent is obtained in accordance with Part 50 of this chapter. \* \* \*

**Subpart F [Removed]**

l. Part 812 is amended by removing Subpart F—*Informed Consent* and marking it "Reserved."

m. In § 812.140 by revising paragraphs (c), (d), and (e) to read as follows:

**§ 812.140 Records**

(c) *IRB records.* An IRB shall maintain records in accordance with Part 56 of this chapter.

(d) *Retention period.* An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

(e) *Records custody.* An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of § 812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

n. In § 812.150 by revising paragraph (a)(4) to read as follows:

**§ 812.150 Reports.**

(a) \* \* \*

(4) *Deviations from the investigational plan.* An investigator shall notify the sponsor and the reviewing IRB (see § 56.108(a)(3) and (4) of any deviation from the investigational plan. In the case of an emergency to protect the life or physical well being of a subject, the investigator shall notify the reviewing IRB within 48 hours. Prior approval by the sponsor is required for changes in, or deviations from, a plan. FDA approval under § 812.35(a) is also required.

**PART 813—INVESTIGATIONAL EXEMPTIONS FOR INTRAOCULAR LENSES****Subpart F [Removed]**

17. Part 813 is amended by removing Subpart F—*Informed Consent of Human Subjects* and marking it "Reserved."

**SUBCHAPTER J—RADIOLOGICAL HEALTH****PART 1003—NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY**

18. 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 generic 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 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 §§ 56.104 or 56.105, and a statement that each investigations was conducted in compliance with the requirements set forth in Part 50 of this chapter.

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

19. Part 1010 is amended:  
a. In § 1010.4 by adding new 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, is subject to the requirements for institutional review set forth in Part 56 of this chapter, 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, 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 §§ 56.104 or 56.105 and a statement that each investigation was conducted in compliance with the requirements set forth in Part 50 of this chapter.

*Effective date.* This regulation shall become effective July 27, 1981.

(Secs. 406, 406, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701(a), 706, and 801, 52 Stat. 1049-1053 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, 371(a), 376, and 381); secs. 215, 301, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 241, 262, 263b-263n))

Dated: January 19, 1981.

Jere E. Goyan,

Commissioner of Food and Drugs.

(FR Doc. 81-2567 Filed 1-21-81; 8:45 am)

BILLING CODE 4110-03-M

21 CFR Parts 16 and 56

[Docket No. 77N-0350]

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

AGENCY: Food and Drug Administration.

ACTION: Final rule.

**SUMMARY:** The Food and Drug Administration (FDA or agency) is establishing standards governing the composition, operation, and responsibility of institutional review boards (IRBs) that review clinical investigations, involving human subjects, conducted pursuant to requirements for prior submission to FDA or conducted in support of applications for permission to conduct further research or to market regulated products. These regulations and the protection of human research subjects regulations adopted by the Department of Health and Human Services (HHS or Department) published in the January 26, 1981 issue of the *Federal Register*, establish a common framework for the operation of IRBs that review research funded by HHS and research conducted under FDA regulatory requirements. Compliance with these regulations is intended to provide protection of the rights and welfare of human subjects involved in clinical investigations.

**EFFECTIVE DATE:** July 27, 1981.

**FOR FURTHER INFORMATION CONTACT:** John C. Petricciani, Office of the Commissioner (HFB-4), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301-496-9320.

**SUPPLEMENTARY INFORMATION:** In the *Federal Register* of August 8, 1978 (43 FR 35186), FDA published proposed standards for IRBs for clinical investigations. 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), FDA extended the comment period to June 6, 1979. During the comment period, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) submitted its report and recommendations on IRBs 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 revision of the current HHS IRB regulations (45 CFR Part 46). On August 14, 1979 (44 FR 46799), FDA withdrew the August 8, 1978 proposal and published a revised proposal that it had developed in conjunction with HHS in response to the recommendations made by the National Commission.

In addition, the agency held three hearings under § 15.1(a) (21 CFR 15.1(a)) of the administrative practices and procedures regulations in: (1) Bethesda, Maryland, on September 18, 1979; (2) San Francisco, California, on October 2, 1979; and (3) Houston, Texas, on October 16, 1979. These hearings were

intended to provide an open forum to present views on the regulations and to foster greater consideration of the proposal among the scientific community, regulated industry, and the public. (Transcripts of these hearings are on file with the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA-305), FDA.)

For the reasons set forth in paragraph 1, the sections of the regulation have been reorganized and renumbered to be parallel with the Department's regulations. The following table correlates the new sections with those proposed.

New section	Old section
56.101	56.1
56.102	56.3
56.103	56.5
56.104	No corresponding section.
56.105	56.6
56.107	56.21, 56.25, 56.26, and 56.34.
56.108	56.80, 56.81, and 56.87.
56.109	56.82 and 56.87.
56.110	56.83.
56.111	56.88.
56.112	56.8, 56.9, 56.87, and 56.90.
56.113	56.90.
56.114	56.9.
56.115	56.15, 56.21, 56.25, 56.185, and 56.195.
56.120	No corresponding section.
56.121	56.202, 56.206, and 56.210.
56.122	56.213.
56.123	56.219.
56.124	56.215.

FDA will seek Office of Management and Budget (OMB) clearance of the reporting and recordkeeping requirements contained in these regulations prior to the effective date. If OMB does not approve the reporting and recordkeeping requirements without change, the agency will revise the regulations to comply with OMB's recommendations.

The agency received 145 comments on the original proposal and 179 comments on the reproposal. In addition, approximately 100 people appeared at the three public hearings. Following is a summary of the significant comments received and FDA's response to them:

**General Comments**

1. One of the overriding themes in the comments was that the agency should adopt the same final regulations as the Department.

FDA agrees that the Department's and the agency's regulations should be as consistent as possible, and it recognizes that if such consistency is achieved, IRBs that deal with both FDA and other HHS components will be able to follow a uniform standard. Therefore, FDA participated with other components of the Public Health Service in an intra-departmental task force whose goal was to achieve the maximum degree of

consistency possible in the Department's and the agency's IRB and informed consent regulations. Drawing heavily on the comments received by both HHS and FDA, the task force made substantial progress toward achieving its goal.

As a result, the structural and functional requirements for IRBs in FDA's regulations are identical to those in the Department's regulation. FDA and HHS have adopted the same definitions for "institution" (§ 56.102(d)) and "minimal risk" (§ 56.102(h)), and identical provisions relating to IRB membership (§ 56.107), IRB functions and operations (§ 56.108), IRB review of research (§ 56.109), expedited review (§ 56.110), criteria for IRB approval of research (§ 56.111), review by an institution (§ 56.112), suspension or termination of IRB approval of research (§ 56.113), cooperative research (§ 56.114), and records (§ 56.115). In addition, the organization of the two sets of IRB regulations is now consistent.

While exact congruity between the Department's and the agency's regulations is not possible because of differences in statutory authority and scope of activity, FDA believes that these regulations are as identical as possible with the regulations that are being adopted by HHS for the protection of human subjects who participate in research funded by the Department.

2. Several comments suggested that FDA adopt the assurance mechanism that is contained in the Department's regulations.

FDA has decided not to adopt this mechanism. Although consistency with the Department's regulations is important, the agency finds that other factors make adoption of the assurance mechanism inappropriate. FDA has determined that the benefits of the entrance into the assurance process of the IRBs that are subject to FDA jurisdiction, but not otherwise to HHS jurisdiction, do not justify the increased administrative burdens that would be placed on institution by requiring them to submit assurance materials to the Department's Office of Protection from Research Risks (OPRR), or the increased burden on the Government of processing those assurance submissions. FDA will rely instead on the dissemination of these regulations and on appropriate educational efforts, together with inspections of IRBs, to assure compliance by IRBs with these regulations.

3. One comment stated that while there should be an organized group to establish guidelines, standards, procedures, and educational activities

that assure the high quality and performance of IRBs, that group should not come from within the Government. The comment stated that institutions themselves, or other interested parties independent of the Federal Government, would organize for these purposes.

While FDA would welcome such an organization, the agency points out that none presently exists. As discussed in paragraph 8 of this preamble, FDA has been charged by Congress with the responsibility of protecting the rights and welfare of human subjects who participate in research that comes within the agency's jurisdiction. Therefore, it is necessary for the agency to publish these regulations to fulfill that responsibility.

4. Three comments stated that FDA does not have legal authority to adopt these regulations. Two comments stated that section 701(a) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 371(a)) cannot be used as a grant of authority to regulate any subject the agency selects. The comments argued that the subject matter of regulations must be within the substantive authority of the agency, and that there is no mention anywhere in the act that the agency can require that clinical investigations be reviewed by an IRB. Two comments suggested that the proposed regulations should therefore be republished as guidelines.

FDA rejects these comments. The agency presented a thorough discussion of its authority to require IRB review in the preamble to the August 8, 1978 proposal at 43 FR 35197. As the agency pointed out in that preamble, its authority to adopt these regulations is derived from several sections of the act.

In section 520(g)(3)(A)(i) of the act (21 U.S.C. 360(j)(3)(A)(i)), congress directed the agency to include in its investigational device exemption (IDE) regulations (21 CFR Part 812) a requirement that an applicant for an IDE submit the plan for research to the local "institutional review committee" that " \* \* \* has been established in accordance with regulations of the [Commissioner] \* \* \* ." Under § 56.102(e) of these regulations, "institutional review committee" is synonymous with "institutional review board."

Although there are no corresponding explicit provisions with regard to the other clinical investigations covered by these regulations, the Supreme Court has recognized in *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973), that FDA has authority that "is implicit in the regulatory scheme, not spelled out in *haec verba*" in the statute.

As stated in *Morrow v. Clayton*, 326 F.2d 36, 44 (10th Cir. 1963):

However, it is a fundamental principle of administrative law that the powers of an administrative agency are not limited to those expressly granted by the statutes, but include, also, all of the powers that may be fairly implied therefrom.

See *Mourning v. Family Publications Service, Inc.*, 411 U.S. 356 (1973); see also *National Petroleum Refiners Association v. FTC*, 482 F.2d 672 (D.C. Cir. 1973).

Sections 505(i), 507(d), and 520(g) of the act (21 U.S.C. 355(i), 357(d), and 360(j)(g)) require that the agency issue regulations that establish the conditions under which drugs and devices will be available for investigational use. Those sections of the act direct the agency to issue regulations to protect the public health in those investigations. FDA has determined (43 FR 35197) that a requirement of IRB review of an investigation is essential to safeguard the rights and welfare, and consequently, the health, of the human subjects involved in the study.

In addition, sections 505(j)(1) and 507(e) of the act require that the regulations adopted under sections 505(i) and 507(d) reflect due regard for the ethics of the medical profession and the interests of patients. There is a similar requirement in section 520(g)(1) of the act that the investigations conducted under that section be consistent with ethical standards. Because IRB review is intended to focus on the ethical acceptability of studies and on the protection of human subjects, FDA believes that the requirement of IRB review will ensure that there is due regard for the ethics of the medical profession and for the interests of patients in the investigations covered by these regulations.

Finally, under section 701(a) of the act, the agency is empowered to issue regulations for the efficient enforcement of the act. In assessing the validity of regulations issued under section 701(a), the basic question is whether the statutory scheme as a whole justifies promulgation of the regulation. *National Confectioners Association v. Califano*, 569 F.2d 690, 693 (D.C. Cir. 1978). As explained in the preamble to the August 8, 1978 proposal, IRB review is very important in helping FDA to assure that the rights and welfare of human subjects are protected in clinical investigations regulated by the agency because IRBs require modifications in or disapproval of those clinical investigations that present unreasonable risk in relation to the benefits and knowledge to be gained. See also 43 FR 35197. Therefore,

the agency has determined that these regulations are essential to enforcement of the agency's responsibilities under sections 406, 409, 501, 502, 505, 506, 507, 510, 513, 514, 515, 516, 518, 519, 520, 706, and 801 of the act, as well as the responsibilities of FDA under sections 301, 351 and 354-360F of the Public Health Service Act.

5. Several comments questioned how the regulations would affect the interaction in clinical investigations of IRBs, sponsors, monitors, and investigators. One comment stated that these regulations may make an IRB feel liable for tasks that are the responsibility of a sponsor.

The IRB regulation is one of five regulatory elements in FDA's bioresearch Monitoring Program. That program is designed to assure the quality and integrity of the research that is subject to the agency's jurisdiction. In addition to the two FDA regulations published in this issue, the Bioresearch Monitoring Program includes proposed regulations to establish obligations of clinical investigators (proposed August 8, 1978 (43 FR 35210)), obligations of sponsors and monitors of clinical investigations (proposed September 27, 1977 (42 FR 49612)), and good laboratory practice regulations (21 CFR Part 58).

The agency has attempted to include in each bioresearch monitoring regulation only the specific obligations of the entity that the regulation covers. Although the IRB regulations obviously include matters of interest to both sponsors and clinical investigators, an IRB should have no problem determining the boundaries of its obligations.

The agency recognizes, however, that the bioresearch monitoring entities are intimately related and interdependent, and that there are certain well-established relationships among IRBs, clinical investigators, and sponsors of clinical investigations. Consequently, the agency believes that it should not impose any unnecessary requirements that would disrupt those relationships. For example, because IRBs usually do not have any direct contact with sponsors, FDA has eliminated from these regulations any requirement that an IRB contact a sponsor. The clinical investigator has the responsibility of keeping the sponsor informed of IRB actions.

6. Several comments claimed that the proposed regulations contained unnecessary, irrelevant, and repetitive rules which would serve as a deterrent to research.

These regulations are intended to establish the basic framework for IRBs and their parent institutions. They differ from those proposed in 1978 and 1979 in

that FDA has included in the final regulations only the essential organizational and procedural requirements for IRBs and has not specified in detail how those requirements are to be met. Because of the great diversity in institutions, research activities, and organizational structures covered by these regulations, FDA has decided that there must be sufficient flexibility in the regulations to allow IRBs and their parent institutions to meet these requirements in a manner that best suits their organizational needs. As a result of this approach, FDA has accepted the thrust of the comments and, as detailed in responses to comments regarding specific sections of the proposal, has deleted a number of the proposed provisions from these final regulations.

7. Several comments suggested that the proposed regulations be withdrawn because they offer no real protection to anyone.

FDA rejects this suggestion. These rules provide minimum standards for review of clinical investigations by IRBs to ensure that the rights and welfare of human subjects will be protected in the investigation. Once these regulations are adopted, if institutions select reasonable and appropriate individuals for the IRBs, the IRB review process will provide a significant safeguard for human subjects in research.

8. Other comments suggested that the objectives of these regulations could be achieved through existing common law and State regulations.

FDA disagrees with these comments. Congress has charged the agency with the responsibility of protecting the rights and welfare of human subjects who participate in research that comes within FDA's jurisdiction. Consequently, the agency cannot rely on existing common law or State regulations. The only way the agency can assure that adequate protections exist nationally is by adopting regulations that define what protections are necessary and that require that those protections be extended to all human subjects in research within the agency's jurisdiction. FDA is adopting these regulations because only through properly constituted and well-functioning IRBs can the agency be assured that the rights and welfare of human subjects are being protected before a study starts, and that the study is ethically acceptable.

9. One comment stated that Congressional and FDA investigations have amply demonstrated that some IRBs, if left free from systematic oversight, will not adequately carry out their obligations. Several other

comments stated that what is needed is an open and trusting relationship between FDA and IRBs.

FDA believes that these regulations, when coupled with FDA's inspection program, strike the appropriate balance between the conflicting approaches to the regulation of IRBs presented by these contrasting comments. The Federal Government cannot bear alone the burden of protecting the rights and welfare of human subjects. Investigators, institutions, and sponsors must share in this responsibility. If IRBs follow these regulations, they will protect human subjects. However, if the agency finds serious deficiencies in the IRB review process at a particular institution, the agency will take appropriate action, as provided for in these regulations.

10. A few comments raised questions about the costs of IRB review. The comments pointed out that there are administrative costs associated with an IRB, and they raised questions about who would pay those costs. One comment stated that a sponsor should be able to provide compensation to IRBs, provided that it does not participate in the selection of IRB members.

FDA recognizes that there are administrative costs associated with IRB review. Because, under these regulations, there is no single administrative model, for example, a single institution may have multiple IRBs, or a single IRB may review studies for several institutions, FDA believes that it is inappropriate for it to prescribe a method for reimbursement for administrative costs, and that the parties themselves should resolve this matter. FDA's statement in the preamble to the August 8, 1978 proposal regarding proposed § 56.26(a) that IRB members should not be compensated for services did not mean that administrative costs such as consultation fees, travel expenses, typing services, paper and supplies, meeting rooms, etc., could not be paid by the sponsor or institution.

11. One comment suggested that institutional review would significantly increase the costs of clinical investigations.

The agency rejects this comment. FDA estimates the cost of IRB review of a clinical investigation to be approximately \$100. Consequently, compared to the total costs of a clinical investigation, the costs of IRB review are insignificant.

12. One comment criticized the absence of data in the Economic Impact Assessment (EIA) of the proposed regulation, but did not dispute the

agency's conclusion that the regulation would not cause a major impact.

The EIA stated that the IRB regulation would "provide for extension of an IRB concept to areas where it has not previously been used" (i.e., to studies involving noninstitutionalized subjects) and increase some of the review group's administrative activities, but that these additional costs would not approach the \$100 million cost threshold for a major impact. The data underlying that conclusion follow.

The agency estimates that 2,000 IRBs are reviewing or have reviewed studies submitted for FDA approval. Approximately 500 of these IRBs have submitted a *General Assurance* to HHS that they are in compliance with departmental regulations. An agency study (Office of Planning and Evaluation Study 47, "Results of the Institutional Review Board's Pilot Compliance Program," April 1978) found that these IRBs review an average of 11 studies per month, amounting to a total of 66,000 reviews annually. The study also found that IRBs that had not submitted a *General Assurance* to HHS review an average of five studies per month, amounting to a total of 90,000 reviews annually, and that more than 50 percent of these IRBs were already in compliance with the administrative and procedural requirements.

Institutional Review boards will incur some additional costs, in part for more thorough review and followup of investigations and in part because there will be additional studies subject to IRB review. FDA estimates that the incremental costs will be \$7.5 million. This estimate was derived by assuming that the expansion of IRB review to studies using noninstitutionalized subjects will add one-third, or \$52,000, more reviews. According to one estimate, a review by an IRB with a *General Assurance* now costs about \$100 (William A. Check, "Protecting and Informing Human Research Subjects," *JAMA*, 243 (1980), 1985-1993.) Thus, the costs of the added reviews are \$5.2 million. If we further assume that the average IRB without a *General Assurance* now spends \$75 per review, the added cost to bring their reviews into compliance with agency regulations is \$2.3 million. This \$75 average cost derives from the assumption that the IRBs already in compliance (50%) spend \$100 per review and the generous assumption that the remaining IRBs (50%) will double their present review costs to come into compliance.

The EIA also attributed potential agency compliance costs to the regulation. However, there will be little,

if any, incremental costs to the agency, given present budgetary constraints.

13. One comment requested that these regulations grant IRB members limited liability in the case of malpractice suits.

FDA lacks the authority to grant limited liability to IRB's or their members. That authority resides in Congress and in the State legislatures. Although it is impossible to limit liability or to ensure against law suits, the agency believes that the chances for a successful suit against an IRB or its members are greatly diminished if the IRB has complied with these regulations and any applicable State law in reviewing the proposed research. See, e.g., *Davis v. Marathon Oil Co.*, 64 Ill. 2d 380, 356 W.E. 2d 93 (1976).

14. Several comments questioned the applicability of these regulations to studies conducted outside the United States. A few comments stated that standards of protection for human subjects may and do vary from country to country, and that the United States should not impose its standards on other countries when the human subjects come from those foreign countries in which the studies are being conducted.

FDA agrees with the comments and notes that its policy regarding investigational studies involving drugs and biological products is set forth in § 312.20 *Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational exemption for a New Drug"* (21 CFR 312.20). The policy regarding foreign studies and the background to § 312.20 was set forth in detail in the preambles to the proposed and final regulations. See 38 FR 24220 (September 6, 1973) and 40 FR 16053 (April 9, 1975). The agency's policy regarding studies of investigational devices conducted outside the United States is similar to that for drugs and biological products and is discussed in the preamble to the recent proposal entitled "Proposed Procedures for the Premarket Approval of Medical Devices," published in the *Federal Register* of December 12, 1980 (45 FR 81769). Section 814.15 of that proposal states the agency's policy concerning devices.

#### The Proposed Regulation

15. Numerous comments objected to the statement in proposed § 56.1 *Scope* (§ 56.101 in the final regulations) that compliance with these regulations would help to assure the quality and integrity of data submitted to FDA. These comments argued that it is neither the responsibility nor within the competence of an IRB to assure the quality and integrity of data. The comments stated that the primary

functions of an IRB are to assure the ethical acceptability of a particular study and to assure that human subjects are adequately protected. One comment argued that IRBs would be converted into consultants for sponsors if they were required to review the quality and integrity of data. A number of comments asserted that review of the validity and integrity of data on an ongoing basis would be an undue burden on IRBs. A number of comments objected on similar grounds to including review of research methods among the criteria for approval of a clinical investigation. The comments argued that the IRB should focus on its primary task of risk assessment, and that the scientific evaluation, validation, and justification necessary for a study should be the obligation of the clinical investigator responsible for the study and of the sponsor.

During the process of reviewing the comments and developing IRB regulations with other components of the Department, FDA became convinced that a number of IRB obligations included in the 1978 and 1979 proposals were inconsistent with the generally accepted view of the scope of IRB review. Consequently, the agency decided to reconsider whether to impose those obligations. One of the obligations most difficult to delineate was the extent to which an IRB must consider the scientific aspects of a research proposal. FDA acknowledges that the primary responsibilities of an IRB are to assure that human subjects are adequately protected, are not exposed to unnecessary risks, and are provided with enough information about a study so that they can give effective informed consent. However, the agency believes that it is impossible to divorce completely considerations of science from those of ethical acceptability and of protection of human subjects. Some type of scientific review is necessary to determine whether the risk to which subjects are exposed is reasonable.

Thus, FDA has decided to delete from § 56.101 all references to any responsibility on the part of IRBs to assure the validity and reliability of data, because the agency is concerned that reference to such an obligation could be interpreted as imposing on IRBs the obligation to exercise primary scientific review responsibilities for clinical studies. IRBs have no such obligation. However, FDA believes that the IRB, the institution, and the clinical investigator share an obligation to assure that a review of the scientific merits of a proposal is conducted. FDA believes that an IRB cannot reasonably

review a study or make a valid risk assessment, unless there has been a positive assessment of the scientific merits of the research.

16. Numerous comments objected that proposed § 56.1 did not limit the scope of IRB review of clinical investigations to exclude those that are conducted outside of an institution. These comments suggested that the other elements of FDA's Bioresearch Monitoring Program provide sufficient protection for human subjects who are not institutionalized.

FDA rejects these comments and declines to change § 56.101 in response to them. Human subjects, whether institutionalized or not, are entitled to the protections that these regulations offer. The agency agrees that the other elements of the Bioresearch Monitoring Program provide important protections to human subjects. However, as the agency pointed out in paragraph 5, the elements of that program are closely related and interdependent. IRB review is necessary to ensure that the rights and welfare of human subjects are protected, and that the subjects are adequately informed prior to the start of a study.

17. One comment questioned whether these regulations would require physicians practicing in their offices to obtain IRB review of their proposed clinical investigations. Another comment suggested that physicians practicing in their offices should have a centrally located IRB available for their use.

Physicians who practice in their offices and who wish to conduct clinical investigations for a sponsor or as sponsor-investigators are required to comply with these regulations to obtain a research permit. The agency recognizes, however, that in some instances such physicians (and other health professionals who would otherwise qualify for a research permit) may not be affiliated with an institution or have direct access to an IRB. In those instances, FDA advises that several options are available to the physician. A sponsor-investigator who is unaffiliated with an institution with an IRB can comply with this requirement by obtaining review at an institution whose IRB conforms with these regulations or by submitting the research proposal to an IRB created under the auspices of a local or State government health agency, a community hospital, a private or public medical school, a county or State medical society, the State medical licensing board, an independent nonprofit group such as a foundation or society interested in a particular health concern, e.g., kidney disease or family

planning, or an organization involved in intergroup communications, e.g., the American Arbitration Association. A private physician who wants to conduct clinical research for a sponsor, in addition to these options, may use an IRB created by the sponsor.

18. One comment suggested that optometrists in private practice be exempted from the requirements of these regulations.

FDA rejects this suggestion. The agency believes that human subjects involved in any clinical investigation subject to FDA jurisdiction (except for those specifically exempted) need the protections that these regulations afford, regardless of whether the study is being conducted by optometrists, medical doctors, dentists, or other health professionals.

19. Several comments objected to the inclusion of cosmetic studies within the scope of these regulations. These comments pointed out that cosmetic studies are not subject to submission to the agency for premarket approval and therefore should not be subject to a requirement of IRB review.

FDA agrees with the comments and has modified § 56.101 to exclude cosmetic studies from the scope of the IRB regulations.

20. Several comments urged that FDA not include over-the-counter (OTC) drugs in the scope of Part 56.

In the preamble to the 1978 proposal at 43 FR 35189, FDA announced:

The Commissioner believes the purposes and processes of IRB review are now so widely accepted, and its value so generally recognized, that all clinical investigations should undergo such review unless circumstances clearly make it unnecessary, or infeasible, or contrary to the patient's interest.

Consistent with that determination, FDA has decided to require IRB review of all clinical investigations (except those exempted under § 56.104 or for which a waiver has been obtained under § 56.105) of test articles that are intended to be submitted to the agency in support of an initial or supplemental research or marketing permit. However, because the agency recognizes the lower risk associated with studies of marketed OTC drugs, and because the agency wishes to minimize the administrative burden created by these regulations, FDA has decided to include studies with marketed OTC drugs, and other drug or biologic studies for which an IND is not required (e.g., bioavailability studies with a marketed drug), on the list of procedures that can receive expedited review.

21. One comment argued that FDA has no authority to require IRB review of

OTC drugs because OTC drugs are not unapproved new drugs within the meaning of section 505(i) of the act.

That an OTC drug is being reviewed under the procedures established in 21 CFR Part 330 does not mean that the drug is not an unapproved new drug under section 505 of the act. One of the purposes of establishing the OTC review was to make certain scientific and legal determinations with regard to a drug's status under section 505 of the act. In making those determinations, under OTC review procedures, the agency will consider data on a drug ingredient that interested persons may submit. To develop these data, investigators may conduct tests for submission to the agency that may present risks to human subjects. These tests should therefore be subject to review by IRB's. As discussed in paragraph 4 of this preamble, the agency has authority under section 701(a) of the act to promulgate regulations to implement section 505 (as well as other sections of the act) that requires such review of these studies. Therefore, it is within the legal authority of the agency to include investigations of drugs under consideration in the OTC review within these regulations.

22. A few comments objected to the inclusion of low risk or no risk studies within the scope of these regulations. The comments suggested that because risk is so low in these studies, and because FDA has rules governing informed consent, no IRB review is needed. A few comments argued that IRB review would not add any protections for human subjects in low risk studies.

FDA believes IRBs should review studies even when there is minimal risk, to assure that (1) there is, in fact, only minimal risk; (2) adequate information is given to the subject or a legally authorized representative, so that effective informed consent can be given; (3) the study is ethically acceptable; and (4) the study complies with the requirements in these regulations. FDA also points out that it has modified these regulations to provide for expedited review of certain studies involving minimal risk (§ 56.109). A notice listing the eligible categories of studies is published elsewhere in this issue of the *Federal Register*.

23. One comment suggested that use of an investigational drug in an emergency situation should be exempted from IRB review.

The agency recognizes that there is a practical need to provide a mechanism for the emergency use of a test article in a single patient. After examining various options, FDA has elected to exempt the emergency use of test articles from the

IRB review requirement and so provides in new § 56.104(c). The agency advises, however, that it views emergency use of a test article as being an uncommon occurrence, and that it will examine the circumstances of emergency use on a case-by-case basis to assure that emergency procedures are not being used to circumvent IRB review. FDA also points out that it has conditioned this exemption on a report of the emergency use to the IRB within 5 working days of its occurrence. FDA would expect that the IRB that receives the report by a clinical investigator on an emergency use, as required by § 56.104(c) and § 50.23(c), will examine each case to assure itself and the institution that the emergency use of the test article was justified. FDA also advises that while it has exempted emergency use of test articles from the requirement of prospective IRB review, this exemption does not release the clinical investigator from any other obligation imposed by other regulations or by the institution in which the emergency use is undertaken. Finally, the agency advises that a "subsequent use," as referred to in the regulation, would be any use of the test article that occurs more than 5 days after its initial emergency use.

24. On its own initiative, FDA has eliminated proposed § 56.3(f) defining "institutionalized subject" because that term does not appear anywhere in Part 56. FDA has eliminated the definition of "person" in proposed § 56.3(i) because that term is used in these regulations only to denote an individual.

25. Several comments stated that the proposed definition of "clinical investigation" in proposed § 56.3(c) (now § 56.102(c)) is too broad and confusing.

FDA disagrees. The definition was drafted to include all studies within FDA's jurisdiction that are subject to the requirements of prior submission to the agency or that may be submitted to the agency in support of a research or marketing permit. The comments are rejected.

26. One comment stated that proposed § 56.3(c) should clearly state that a clinical investigation is always medical in nature and always involves human subjects.

FDA has attempted, whenever possible, to make the IRB regulations identical with those of the Department. To facilitate this goal, FDA has not defined "clinical investigation" to include only those studies that are medical in nature. As a result, this term is interchangeable with the term "research" as that term is defined by HHS. Because these terms are

interchangeable, the same wording can be used in provisions in both FDA's and the Department's regulations. Section 56.102(c) in the final regulations is revised to clarify this fact and to conform with the HHS regulations.

FDA points out that § 56.102(c) already states that human subjects must be involved in a "clinical investigation."

27. Two comments stated that proposed § 56.3(d) defining "institution" was too broad.

As stated in paragraph 1 of this preamble, FDA has revised § 56.102(d) to conform its definition of "institution" with that of the Department. "Institution" is now defined as any public or private entity. Although this definition is perhaps even broader than the proposed definition, the definition itself does not define the scope of those regulations. That scope is clearly set out in § 56.101. IRB review will now be required for all clinical investigations that support applications for research or marketing permits for products regulated by FDA. As noted in the 1978 proposal, it may no longer be strictly appropriate to call the process "institutional review" because the process is no longer tied to "institutions" as they were previously defined (43 FR 35188). Because the concept of institutional review is well understood by the research community, and because no better terminology has been suggested, the terminology has been retained.

28. One comment suggested that contract laboratories should be added to the proposed definition of "institution."

The revised definition of "institution" in § 56.102(d) includes any entity. A contract laboratory clearly would come within the purview of the regulations.

29. Two comments expressed concern about including manufacturers in the definition of "institution." One comment stated that the definition would include manufacturers who use their employees as subjects in the course of routine product testing, even though the manufacturers did not intend to use the data from that testing in support of a research or marketing permit.

The intent of these regulations is to protect human subjects in clinical investigations that are subject to FDA jurisdiction. Therefore, the definition of "institution" must be broad enough to include manufacturers who use employees as test subjects in such research. However, only clinical investigations that are regulated by FDA under sections 505(i), 507(d), and 520(g) of the act or that are intended to support applications for research or marketing permits for products regulated by FDA are within FDA jurisdiction. Therefore, routine product testing, in which the

data are not intended to be used in support of a research or marketing permit or to support the safety and effectiveness of a regulated article, would not be subject to these regulations.

30. On its own initiative, FDA has modified the definition of "institutional review board" in proposed § 56.3(e) (now § 56.102(g)) to clarify that the primary purpose of an IRB is to assure the protection of the rights and welfare of human subjects.

31. One comment stated that HHS and FDA should have a common suitable definition of "institutional review board."

FDA points out that HHS has chosen not to include a definition of "institutional review board" in its regulations. FDA believes, however, that the agency's definition is compatible with the traditional use of the term by HHS and the biomedical community. FDA concludes that its definition of "institutional review board" in § 56.102(g) is suitable.

32. One comment suggested that FDA and HHS should collaborate on common terminology and definitions for the terms "subject" and "human subject."

The scope of research supported by the Department includes behavioral research that FDA does not regulate. At the same time, the scope of research regulated by FDA includes veterinary research that HHS, other than FDA, does not regulate and that, for obvious reasons, are not subject to these regulations. Therefore, it is appropriate for FDA to use the term "human subject" to clarify the scope of the regulation, and to define the scope of the term "human subject" as in § 56.102(e) more narrowly than has HHS. Section 56.102(e) has been revised to relate specifically to the types of research that are subject to FDA jurisdiction.

33. One comment stated that proposed § 56.3(l) could be read to require that there must be a therapeutic benefit for all subjects who participate in an investigation and thus to eliminate all Phase I studies. The comment asked that this confusion be clarified.

The revised definition of "human subject" § 56.102(e) establishes that no therapeutic benefit for the participant from the research is required. The revision clarifies that these regulations do not eliminate Phase I studies.

34. One comment suggested that the proposed definition of "subject" be used in all regulations and guidelines dealing with clinical investigations.

Whenever possible, FDA has tried to use consistent definitions in each of its bioresearch monitoring regulations.

35. One comment stated that a definition of "informed consent" is needed in Part 56. FDA does not believe that the concept of informed consent can be adequately defined in a single "definition." Because the concept of informed consent is complex and should apply to any clinical investigation, FDA is publishing its provisions concerning informed consent separately in Part 50 to apply to all aspects of biomedical research in human subjects.

36. Several comments pointed out that an investigator may not always conduct an investigation or provide immediate direction under which a test article is administered, even though the investigator does exercise a supervisory role. These comments suggested a number of modifications in the proposed definition of "investigator" in § 56.3(g) (now § 56.102(h)).

FDA recognizes that a single investigator does not always immediately direct the administration of the test article. Therefore, FDA has revised § 56.102(h) to reflect more accurately the functions of investigators.

37. Several comments stated that the proposed definition of "minimal risk" in § 56.3(h) (now § 56.102(i)) should be the same as the HHS definition. One comment stated that the proposed FDA definition was too narrow.

FDA agrees with the comments and has rewritten § 56.102(i) to match the revised HHS definition. The definition in these final regulations takes into account the fact that risks encountered in the daily lives of healthy individuals may not be the same as risks encountered in the daily lives of others, and that "minimal" risk should mean that no risk in addition to that already encountered in the daily life of the individual will arise from the study.

FDA points out to those IRB's and investigators involved with medical devices that the term "minimal risk" used in Part 56 is different from the term "non significant risk" that is used in the IDE regulations. "Non significant risk" is used to describe a medical device. "Minimal risk" is used to describe an investigation and involves different criteria from the ones used to determine that a device poses a "non significant risk." Thus, IRB's and investigators cannot assume that an investigation with a "non significant risk" device poses only a "minimal risk" for the purpose of Part 56.

38. One comment stated that cosmetics should not be included in proposed § 56.3(n), which defined "test article."

As stated in paragraph 19 of this preamble, cosmetics are excluded from the scope of the IRB regulations. The

word "cosmetic" is deleted from § 56.102(1).

39. One comment stated that a definition of "substantial risk" is needed in the IRB regulations.

FDA disagrees with this comment. Having defined "minimal risk," there is no need to demarcate the levels of risk any further. All studies with greater than minimal risk are treated the same under these regulations.

40. Many comments on proposed § 56.5 (now § 56.103) objected to the requirement of IRB review of clinical investigations that are conducted outside of an institution.

Most of these comments overlap with or are identical to comments on § 56.101 Scope. The agency responded to these comments in paragraphs 15 through 18 of this preamble. The general objections will not be discussed further here.

41. Several comments on proposed § 56.5 stated that to require IRB review of studies involving non-institutionalized subjects will result in a tremendous additional burden on IRBs. One comment argued that, as a result of the regulations, it might become necessary for institutions to employ full-time reviewers, which would decrease the quality of persons serving on IRBs.

FDA disagrees with these comments. The agency does not expect that any existing IRBs will be overwhelmed with new studies. FDA has exempted all studies that begin before the effective date of these regulations from the requirement of IRB review (see § 56.104). Also, as discussed in paragraph 17 of this preamble, the agency anticipates that where the need arises to accommodate studies with non-institutionalized subjects, new IRBs will be formed by professional societies, local medical societies, etc.

42. One comment on proposed § 56.5 stated that IRBs formed to review research conducted by physicians in their private practices will pose a large problem because sponsors will be reluctant to deal with them out of fear that the IRBs will not properly review studies under these regulations, and, as a result, FDA will refuse to accept studies that the IRBs review.

FDA rejects this comment. The agency has made every effort to make these regulations as clear and precise as possible. The agency stands ready to answer any question an IRB may have about these regulations. Consequently, there should be no reason for an IRB to be seriously out of compliance with Part 56. FDA emphasizes that the agency expects it to be a rare occurrence for studies reviewed by an IRB to be rejected because of the IRB's noncompliance with these regulations.

This expectation is discussed further in paragraph 46 of this preamble.

43. Another comment on proposed § 56.5 suggested that device manufacturers should be allowed to set up IRBs to review protocols and patient consent forms for use by individual clinical investigators.

FDA agrees and points out that these regulations allow any manufacturer to set up an IRB. The agency advises, however, that one of the primary responsibilities of an IRB is to be sensitive to the concerns of the community in which the study will be conducted. Therefore, an IRB formed by a manufacturer or a sponsor must be aware of, and give full consideration to, those concerns.

44. Two comments stated that provision should be made in the final regulations for FDA to accept studies without IRB review where no IRB exists.

FDA rejects these comments. All human subjects of FDA regulated research (except for human subjects of the research specifically exempted by § 56.104 or for which a waiver has been granted under § 56.105 of these regulations) are entitled to the protection of IRB review. FDA is not willing to permit human subjects to be deprived of this protection simply because an IRB is not available locally. Although local review is preferable, FDA has never established local review as a rigid requirement. If an IRB is not available locally, review can be sought at an IRB established in any of the ways discussed in paragraphs 17 and 41 of this preamble.

45. A number of comments objected to proposed § 56.5(a) (now § 56.103(a)) because of the requirement that an application for a research permit must be reviewed and approved by an IRB before it could be accepted by FDA. One comment stated that it was wasteful to require IRB review of a study when FDA may later reject the application. Several comments stated that IRB review should take place after FDA has given its approval or, at a minimum, be concurrent with FDA review.

The agency has considered these comments and has modified § 56.103(a) to respond to the concerns. IRB review and approval will be required before any human subjects may enter into a clinical investigation. However, the IRB may review the study before, during, or after FDA conducts its review.

46. Two comments on proposed § 56.5(b) (now § 56.103(b)) suggested that data from a clinical investigation that were not subject to initial review by an IRB might be acceptable despite the absence of a review. One comment argued that if the agency does not

consider the data, it might deprive members of the public of the opportunity to use a test device that will benefit them. This comment suggested that the problem could be dealt with by permitting an investigation to be approved by an IRB after the fact.

FDA rejects these comments. Post hoc review by an IRB is contrary to the purposes of IRB review. FDA believes it possesses the statutory authority to reject the data from a study, even though the scientific validity of the data generated may not have been affected, when the clinical investigation did not receive IRB review, or when the clinical investigation was under the review of a disqualified IRB or was conducted at a disqualified institution. Although the agency may not reject the data in every case, it reserves the right to do so when circumstances so warrant, and § 56.103(b) has been modified accordingly. The agency will consider, among other factors, the risks to human subjects that would be created if it rejected the data and required that the study be redone.

47. One comment stated that FDA should not require IRB approval for studies being conducted after premarket approval of a regulated article has been granted by the agency.

The comment misunderstands the scope of these regulations, as stated in § 56.101. These regulations govern studies of regulated articles that are conducted for submission to FDA. Studies that are not intended to be submitted in support of an initial or supplemental research or marketing permit do not fall within the purview of these regulations. The agency believes, however, that the best protection for human subjects would be for all clinical studies to be reviewed by an IRB.

48. Many comments objected to the provision in proposed § 56.6 that would have waived the requirement for IRB review of clinical investigations begun prior to the effective date of these regulations only if those studies were completed within 1 year of the effective date. Some comments suggested that studies should be exempted if they were completed within 2 years. Others suggested that studies be exempted if completed within 3 years. Ten comments urged that the regulations should apply only to studies begun after the effective date.

FDA has decided to exempt all studies that were begun before the effective date of these regulations and that were not otherwise subject to a requirement of IRB review under FDA regulations before that date, and § 56.104(b) so provides. The agency believes that the administrative burden that would be

created by requiring IRB review of studies that were begun before the effective date of Part 56 far outweighs any benefits to human subjects that might be created. If the requirement was extended, the large number of studies that IRBs would suddenly have to review would prevent them from reviewing new proposals and from undertaking their continuing review of previously approved research. FDA believes that IRBs should be free to concentrate on the latter two types of research.

However, FDA advises that any expansion of a study that would otherwise be exempt under § 56.104 (a) or (b) to include a new institution will be subject to IRB review. Thus, if a new institution is added to a multicentered study of an investigational drug or device after the effective date of these regulations, IRB review must be conducted at the new institution.

49. FDA received numerous comments about proposed § 56.6(b), which would have established the circumstances in which the requirement of IRB review could be waived. Several comments objected to this provision on the ground that human subjects would not be adequately protected if a waiver were granted.

FDA is in substantial agreement with the latter comments. However, the agency recognizes that there may be circumstances in which a waiver would be appropriate. Therefore, FDA has revised the waiver provision (§ 56.105) to provide a sponsor or a sponsor-investigator with an opportunity to request that the agency waive some or all of the IRB requirements. A waiver may be granted by the responsible Bureau. The agency cautions, however, that it anticipates using the waiver provision only in special circumstances, upon a showing that a waiver is in the interest of patients who are subjects, and that an alternate mechanism for assuring the protection of human subjects is available. FDA also advises that, at the present time, it will consider applications for a waiver for those investigational new drug applications that have been commonly termed "compassionate INDs" or "treatment INDs" or for the distribution of investigational drugs under an investigational new drug exemption for the treatment of patients when alternate therapy is not available or is less effective. FDA also points out that because the statute requires IRB review of device studies, the agency will not waive the requirement of IRB review in those cases.

50. One comment suggested that the FDA regulations concerning membership

of an IRB should be identical to the HHS regulations.

FDA agrees, and the agency has rewritten proposed §§ 56.21, 56.25, 56.26, and 56.34 (now § 56.107) to conform to the revised HHS requirements.

51. Several comments stated that FDA should not require racial and cultural diversity of IRB members because this requirement may be inappropriate to the community that the IRB serves, and because this requirement has no relevance to the competence of persons who serve on an IRB. One comment stated that the IRB regulations are an inappropriate place to implement affirmative action plans.

These comments misinterpret § 56.107(a). The regulation does not require racial and cultural diversity in all cases. It requires that the racial and cultural backgrounds of the members be sufficiently diverse to assure that the IRB will be sensitive to the attitudes and concerns of the community and to the human subject population.

52. One comment suggested that it would be helpful if the term "cultural background" was defined.

FDA has used the term "cultural background" in § 56.107(a) to encompass such socio-economic characteristics as age, economic status, and ethnic origin.

53. One comment suggested that provision be made in the regulations for an IRB to include alternate members.

Although § 56.107(a) does not explicitly provide for alternate members, it would allow an IRB to adopt written procedures (see § 56.108) for using alternate members in the IRB's deliberations in case one of the regular members is absent or is disqualified from considering a proposal because of a conflict of interest. FDA points out, however, that the names of any alternate members must be included on the list of IRB members required by § 56.115(a)(5).

54. Several comments stated that there was no basis for requiring an IRB to have members of both sexes. Two comments suggested that a balance of men and women might not always be possible, and therefore, the requirement should be amended to read, "if possible."

FDA rejects these comments. The agency believes that to achieve a reasonable ethical perspective, IRB membership should be comprised of both men and women. Section 56.107(b) does not require that the number of men and women be equal. Rather, it requires that the IRB not be made up only of men or only of women. FDA points out that this requirement does not mean that members of both sexes are required to

be present for a quorum. No comments pointed to any specific situations in which it would not be possible to find competent men and competent women to serve on an IRB.

55. Several comments stated that the standards for IRB membership in the proposed regulations were too restrictive. The comments urged that FDA adopt more flexible requirements on the make-up of an IRB. Three comments pointed out that it would not always be appropriate to have a physician or to have a scientist on a five-member board. In contrast, one comment stated that the proposed requirements for IRB composition were too vague.

FDA recognizes that it cannot specify in detail the composition of an IRB that would be appropriated to review each of the diverse types of studies that are included within FDA jurisdiction. Therefore, FDA has rewritten § 56.107 to allow an institution great flexibility in the make-up of its IRB. The regulation sets forth the minimum requirements that FDA believes must be met if an IRB's advice and counsel are to receive respect. In addition to the racial and cultural diversity discussed in paragraph 51 of this preamble, an IRB must possess the professional competence to review the research activities it considers (§ 56.107(a)). It may not be made up of members of one profession (§ 56.107(b)). An IRB must include at least one member whose primary concerns are in nonscientific areas (§ 56.107(c)), and at least one member must have no connection to the institution except for his or her membership on the IRB (§ 56.107(d)). FDA has eliminated the requirement that an IRB must include at least one physician and one scientist in all cases. This change was made in consultation with HHS to achieve identical requirements and takes into consideration the need for some flexibility in the make-up of IRBs that review FDA-regulated research. However, FDA emphasizes that § 56.107(a) requires that IRBs have as members persons with the professional competence necessary to review the proposed research. For example, FDA would expect that an IRB that reviews investigational new drug studies will include at least one physician.

56. One comment suggested that it would be helpful if the term "nonscientist" was defined.

FDA believes that the examples given in § 56.107(c) of the types of individuals "whose primary concerns are in nonscientific areas" adequately explain this term.

57. One comment stated that in spite of the recommendation of the National

Commission that an IRB that regularly reviews research that has an impact on vulnerable subjects should include persons who are primarily concerned with the welfare of those subjects, no provision for special representation of vulnerable subjects was contained in the proposed regulations.

FDA disagrees with this comment. Such a requirement is contained in § 56.107(a).

58. One comment recommended that rather than setting out a specific number of lay persons to serve on an IRB, the regulation should establish a minimum proportion of the membership that is to be nonscientists.

FDA disagrees with the comment. The standards set forth in these regulations are minimum standards that must be met by an IRB. If an institution or IRB wishes to exceed these standards and have a certain proportion of the IRB members be nonscientists, it is free to do so. However, an IRB must retain the necessary expertise to effectively review any protocol submitted to it, and therefore, it may need a number of scientists (whether medical doctors, dentists, technical staff, or others) on the IRB. FDA believes that, except for minimum standards, it should not dictate how many people should be from a specific profession.

59. One comment objected to the exclusion from membership on an IRB of immediate family members of a person affiliated with the institution. This comment stated this requirement would put severe restraints on recruiting IRB members in academic communities.

FDA points out that § 56.107(d) does not exclude members of the immediate family of a person affiliated with an institution from being members of an IRB. However, none of those family members may serve as the nonaffiliated member of the IRB. This rule is consistent with the National Commission's recommendation. FDA believes that even in small academic communities in IRB can find at least one person willing to serve on the IRB who is not affiliated with the institution and who is not the immediate family member of a person affiliated with the institution.

60. Many comments stated that under proposed § 56.26 (now § 56.107(e)), members of an IRB who selected other members would be precluded from conducting research. Several comments stated that the requirement should only be that an IRB member may not participate in the IRB's initial or continuing review of a clinical investigation in which the member has a conflicting interest. One comment suggested that the section should be

modified so that no investigator would select IRB members solely to review his or her own investigation. One comment stated that IRBs at larger institutions had sufficient numbers of members to permit members to disqualify themselves if they felt there was a conflict of interest.

FDA agrees that revision is needed and has rewritten § 56.107(e) to coincide with the corresponding section in the Department's regulations. This requirement now provides that no member of an IRB may participate in the IRB's initial or continuing review of any clinical investigation in which the member has a conflicting interest. FDA believes that the IRB or the institution should determine what constitutes a conflicting interest.

61. One comment suggested that for each local IRB to seek consultative opinions on studies proposed for many research centers is redundant and would hinder the timely initiation of important research.

FDA agrees with this comment. Cooperative review of multi-institutional studies is expressly authorized by § 56.114. Expert technical opinion can be provided by a central source, so that each IRB can use that opinion to evaluate the study in light of the ethical standards of the local community.

62. One comment on proposed § 56.34 (now § 56.107(f)) suggested that consultants be allowed to vote with an IRB.

FDA rejects this comment. The decision of an IRB must represent the judgment of the members of the IRB. Although consultants should provide information about the ethical acceptability of a study, FDA believes it would be a distortion of their function to permit them to vote. Therefore, § 56.107(f) prohibits consultants from voting.

63. One comment on proposed § 56.80 (Now § 56.108(a)) suggested that the requirement in the 1978 proposal that an IRB adopt written procedures for the initial and continuing review and monitoring of clinical investigations be modified to delete the requirement of "Monitoring." The comment argued that the sponsor was primarily responsible for monitoring.

FDA deleted the term "monitoring" from repropoed § 56.80 in the August 14, 1979 document. FDA has further rewritten § 56.108(a) in these final regulations to match the HHS section. However, FDA points out that IRBs are responsible for the continuing review of a study to ensure that the rights and welfare of human subjects are protected. Therefore, FDA would expect IRBs to review studies at a frequency consistent

with the risks and to consider those data that bear on the rights and welfare of the human subjects. (See paragraph 89 below.)

64. One comment stated that instead of uniformity among IRBs, there will probably be diversity because each IRB will be able to establish its own regulations within the loose Federal framework.

FDA agrees that each IRB will be able to establish its own procedures within the Federal framework, which represents minimum standards. An institution or IRB is free to impose greater standards of protection for human subjects than those required by these regulations. As stated previously, FDA does not believe that it should provide detailed directions to IRBs on how they are to comply with these regulations. How the IRBs meet the general standards should be left to each individual IRB and institution.

65. A few comments stated that IRBs are being forced into a "police role" as opposed to an ethical review in an atmosphere of trust and cooperation.

FDA disagrees with the comments. There is no requirement that IRBs treat investigators with less cooperation than in the past. However, it is up to the IRB to assure itself, by whatever method it deems appropriate, and to assure FDA that the rights and welfare of human subjects are being protected. FDA encourages IRBs and clinical investigators to cooperate and interact with each other in a nonadversarial manner. Nevertheless, FDA considers it an appropriate requirement that IRBs develop procedures to determine whether there is a need for verification, from sources other than the investigators, that there has been no material change in certain protocols since their previous review. Verification is not required by FDA but should be an available avenue when, in the opinion of the IRB, verification will provide necessary protections for subjects involved in greater than minimal risk research.

66. Several comments on proposed § 56.81 objected to defining a quorum in terms of specific professional groups that must be represented. These comments asserted that such a requirement could have the effect of giving one member of the IRB the power to prevent the IRB from meeting by refusing to appear. A few comments suggested possible remedies to this situation, including adopting a rule that any member who missed two consecutive meetings of an IRB without good cause would automatically be dismissed.

As stated previously, FDA believes that, within the framework of these regulations, each institution or IRB should set up its own rules and procedures governing IRB membership and attendance. However, FDA believes that it is important that a person whose primary concerns are in nonscientific areas be present when the IRB conducts its business because that member represents an important element of diversity. Therefore, FDA has retained in § 56.108(b) the requirement that the nonscientific member must be present for there to be a quorum. To ensure that a nonscientific member will be present, an IRB may wish to have more than one member whose primary concerns are in nonscientific areas.

67. Several comments stated that FDA should allow meetings to take place by conference calls. These comments argued that effective dialogue can occur between IRB members on conference calls without forcing the members to be physically present in one room.

Although FDA, like HHS, encourages meetings to take place with members physically present in the room, FDA also recognizes that in some cases time and commuting expense would favor conference calls. As long as each IRB member can actively participate in any discussion of a protocol and has all pertinent material before the call, FDA has no objection to allowing meetings to occur in such a fashion and will consider meetings that take place by conference call to be "convened" meetings. These meetings must follow the same requirements (minutes, etc.) as meetings with members physically present.

68. One comment stated that the proposed requirement in § 56.87(b) (now § 56.108(c)) that an IRB report any serious or continuing noncompliance by investigators with the IRB's determinations to the institution and to FDA extends beyond the intended role of an IRB.

FDA rejects this comment. During the course of its continuing review of a study, an IRB may become aware that a clinical investigator has not complied with its requirements or determinations. If the noncompliance is serious enough, an IRB may withdraw its approval of the investigation. Disciplinary action against the investigator may also be in order. Consequently, FDA has required in § 56.108(c) that the IRB report an investigator's serious noncompliance to the bodies that have authority to take action against the investigator—the institution and FDA.

69. One comment on proposed § 56.87(b) agreed that it was appropriate for IRBs to report any noncompliance

with the requirements of the IRB to FDA, but the comment stated that IRBs should also have authority to suspend the investigator until the situation is reviewed by FDA.

Under § 56.113, the IRB is authorized to suspend or terminate its approval of any research that is not being conducted in accordance with the IRB's requirements or that has resulted in unexpected serious harm to human subjects. Where appropriate, action against a clinical investigator may be taken by FDA, or by the institution either directly or through the IRB if that authority is delegated to the IRB by the institution.

70. One comment stated that it was unclear in proposed § 56.82 whether a complete review of a proposed investigation is necessary if minor changes in the protocol, requested by the IRB, are agreed to by the investigator and the sponsor.

FDA believes that it is up to each individual IRB to decide whether it wants to review the study completely or merely to note that the requested changes have been made. However, the IRB must maintain documentation of changes made (§ 56.115(a)(2)). FDA has rewritten § 56.109(a) to match the corresponding section in the Department's regulations. This section provides that the IRB shall review and shall have authority to approve, to require modifications in, or to disapprove all research within FDA's jurisdiction.

71. Many comments objected to proposed § 56.82(a) because they interpreted the proposed regulations to require IRBs to conduct a scientific review of pertinent prior animal and human studies with the test article, as well as ethical review. A few comments stated that IRBs may not wish to see the complete animal studies but may wish to see only the conclusions from those studies.

FDA has deleted the requirement of review of prior studies from § 56.109(a). FDA emphasizes that it would not expect an IRB to conduct a scientific review of a study except to the extent necessary for the IRB to assure itself that the human subjects will not be needlessly placed at risk. However, an IRB is free to review prior studies, in whole or through summaries.

72. On its own initiative, FDA has added § 56.109 (b) and (c) to these regulations to make explicit an IRB's obligations with regard to the informed consent materials that are to be given to human subjects by the investigator (see Part 50 published elsewhere in this issue of the Federal Register).

73. One comment suggested that FDA explicitly authorize IRBs to require that human subjects in studies involving greater than minimal risk be given a cooling off period in which to consider the information that they have been given as part of the informed consent process.

FDA does not agree that there is a need to make such an explicit authorization. Implicit in the IRB's authority to review the information given to human subjects as part of informed consent is the authority to require that a specific period of time must lapse between when the information is presented to a potential subject, and when the subject must decide whether to participate in the investigation.

74. One comment suggested that informed consent materials be sent to FDA for approval before the start of a study.

FDA disagrees with this suggestion. Because IRB review includes an assessment of the adequacy of informed consent, FDA does not believe that prior approval of informed consent materials by FDA is necessary for all of the clinical investigations submitted to the agency. However, FDA points out that it may review consent materials if they are submitted as part of an application for a research permit or during the course of an inspection of an IRB or clinical investigator.

75. Many comments objected to the requirement in the proposed regulations that the IRB notify the investigator or sponsor in writing that it has received the proposed investigation. A few comments stated that the actual paperwork used by an IRB to conduct its business is its own responsibility. Another comment, however, stated that both the investigator and the sponsor need to be informed of IRB activities, so both should be notified when the study is received for review.

FDA agrees that this requirement should be deleted from the final regulation. The decision of the IRB to approve or not to approve the study, rather than the date of receipt of the study for review, is the information that must be communicated to the investigator (see § 56.109(d)).

76. Several comments suggested that an IRB has no relationship to the sponsor but only to the investigator and the institution. These comments suggested that, consequently, an IRB should not have to communicate at all with the sponsor.

As explained in paragraph 5 of this preamble, FDA agrees with these comments and has deleted from

§ 56.109(d) the requirement that the IRB notify the sponsor.

77. Several comments objected to the requirement contained in the proposed regulations that an IRB must approve or disapprove an investigation as soon as possible after receipt of the proposal. These comments suggested that this requirement could be interpreted to mandate that special meetings be convened merely because a study was submitted or could lead to confusion about what "as soon as possible" meant.

FDA agrees with these comments and has deleted this requirement from the final regulations.

78. One comment on proposed § 56.87 (now § 56.109(c)) stated that it was unclear how often an IRB should review research covered by these regulations.

Section 56.109(c) explicitly states that review shall occur at intervals appropriate to the degree of risk but not less than once per year.

79. Several comments stated that in the provisions for continuing review of research by an IRB, FDA is attempting to delegate its authority to enforce the act to a group of private citizens. One comment stated that this provision would make the IRB into an investigator for FDA. These comments stated that the act does not grant FDA authority to make such a delegation.

FDA rejects these comments. FDA is not delegating its authority to enforce the act. However, unanticipated risks are sometimes discovered during the course of an investigation, and new information sometimes comes to light showing that the risks in a study are not justified. Periodic review will assure that these risks are promptly brought to the IRB's attention and will provide extra protection to subjects. Consequently, FDA believes periodic review by an IRB is essential if an IRB is to adequately protect the rights and welfare of the human subjects involved in a clinical investigation. In paragraph 4 of this preamble, FDA already discussed its authority to adopt requirements that protect human subjects and there is no need to repeat that discussion here.

80. One comment suggested that these regulations should authorize IRBs to require investigators to provide human subjects with any new knowledge about a test article that is developed during the course of a study.

FDA and HHS have both provided as an additional element of informed consent that significant new findings developed during the course of the research that may affect the human subject's willingness to continue to participate must be provided to the subjects. Section 50.25(b)(5) of FDA's

informed consent regulations published elsewhere in this issue of the Federal Register so provides for investigations that fall within the jurisdiction of FDA. The comment does not require any change in Part 56.

81. Several comments on proposed § 56.83 (now § 56.110) offered suggestions of different types of studies that should receive expedited review.

FDA has carefully reviewed these comments, along with the comments on expedited review received by HHS, and has developed a list of procedures that, if they involve no more than minimal risk, can receive expedited review. Publication of the list is provided for in new § 56.110. FDA had decided that expedited review should play a much more important role under the final regulations than the agency originally proposed. After reviewing the comments, FDA believes that it is unnecessary to require that a full IRB meet to consider every study. For studies that present minimal risk, expedited review strikes the appropriate balance between protection of patient and minimizing the burdens imposed by these regulations.

The expedited review list has been separated from the text of these regulations and is published as a notice elsewhere in this issue of the Federal Register. FDA views this list as being subject to change and encourages public comment on what additional classes of research should be included in this list. The agency will publish appropriate revisions of the list in the Federal Register as the need arises. FDA also points out that the Department is publishing a slightly different list, but the differences are caused by the fact that HHS funds many types of studies that do not fall within FDA jurisdiction.

82. One comment on proposed § 56.83 suggested that because some changes in protocol are universally accepted as minor, they should be listed in the regulations. Another comment suggested that "minor change" should be specified to avoid confusion.

FDA disagrees with these suggestions. The scope of investigations regulated by FDA is so broad that FDA does not believe that it is feasible for the agency to list all of the different changes that might be considered to be minor. The agency advises that it considers that changes that result in increased risk to human subjects are not minor. However, FDA is unable to generalize about whether changes that apparently do not entail increased risk are minor. For example, the agency recognizes that a substantial increase in the number of human subjects above that originally approved by the IRB might be

considered to be a minor change in some clinical studies but a major change in others. Therefore, FDA believes that it is up to the IRB to determine on a case-by-case basis whether a proposed change in a protocol is minor. The agency intends to provide additional guidance on this issue in the educational program that it will conduct with the Department. The comments are rejected.

83. On its own initiative, FDA has added new § 56.110(c), which matches the HHS requirement, so that all members of an IRB will be kept informed of the studies approved under the expedited review procedure. FDA believes that it is important that all IRB members know what studies are being approved at that institution. An IRB is free to adopt specific procedures for keeping individual members informed.

New § 56.110(d), which is also identical to the HHS provision, permits FDA to suspend an IRB's use of expedited review when it becomes necessary to protect the rights or welfare of the human subjects involved in a study. Although it is unlikely that this provision will be used by the agency except in the most unusual circumstances, FDA believes that it is important, to protect human subjects, to retain this flexibility in the regulation.

84. Several comments on proposed § 56.86(a) (now § 56.111(a)(1)) objected to IRB review of research methods, stating that IRBs are not qualified to conduct such review, and that IRB's primary responsibility is not to determine the scientific merit of the study.

FDA agrees with these comments. It has drafted § 56.111(a)(1) to focus on the risks to subjects. FDA reemphasizes that IRBs need not conduct scientific reviews of clinical investigations except to the extent necessary to determine that human subjects will not be exposed unnecessarily to risk.

85. One comment on proposed § 56.86(c) asserted that the meaning of the phrase "safest procedures" is unclear.

FDA agrees and has revised § 56.111(a)(1)(i) to clarify the intent of the regulations with respect to risk.

86. One comment suggested that FDA adopt the HHS language on use of procedures being performed for diagnostic or treatment purposes, when these procedures are appropriate.

FDA agrees with the comment and has adopted language in § 56.111(a)(1)(ii) to match the HHS requirement. The IRB should ensure that if procedures that are to be used in a study are already being used on a human subject for diagnostic or treatment purposes, the research

procedures will be coordinated with the diagnostic or treatment procedures to avoid unnecessary repetition of the procedures.

87. Two comments suggested that proposed § 56.86(d) requiring that "risks to subjects be reasonable" and that "the importance of the knowledge to be gained should be considered" needed clarification.

FDA has rewritten § 56.111(a)(2) to match the HHS requirement. FDA advises that in a placebo-controlled trial, for example, no immediate benefit to the placebo group would be anticipated, so that the risks to that group must be reasonable in relation to the importance of the knowledge to be gained in the research. The regulations now state that the IRB shall not consider possible long-range effects of the knowledge gained in the research as a risk of conducting the research. Only those risks that relate to the particular human subjects involved in the investigation must be considered by the IRB.

88. Two comments on proposed § 56.86(b) (now § 56.111(a)(3)) stated that the term "equitable" was ambiguous and needed further explanation.

FDA disagrees with the comments. Special subgroups of the population should not have to bear a disproportionate amount of the risks of research that benefits others. The subjects of an investigation should not come from any particular group simply because it is convenient for the investigator to draw from that group. Scientific design and alternate human subject populations should be considered in assessing whether the selection of subjects is "equitable." For example, the IRB should require that the investigator justify the proposed involvement in the study of hospitalized patients, of other institutionalized persons, or of disproportionate numbers of racial or ethnic minorities or persons of low socioeconomic status. The comments are rejected, and § 56.111(a)(3) is published as proposed.

89. One comment questioned the meaning of the requirement in proposed § 56.86(g) (now § 56.111(a)(6)) that, where appropriate, data be monitored.

Where appropriate, IRB's should require that the research plan make adequate provision for monitoring the data collected to ensure the safety of human subjects. This procedure might be an appropriate requirement in large scale clinical trials or in studies with a high degree of risk. The IRB may require the use of data safety monitoring boards in order to meet the requirements of this provision. Thus, if it becomes clear that

risks are greater than anticipated, or that the benefits do not justify the risks of the research, the IRB is informed and can act on the information. This provision matches the HHS requirement.

90. One comment suggested that each IRB should set out guidelines for determining at what point in each experiment one treatment is shown to be safer and more effective than alternate treatments or no treatment.

FDA disagrees with this suggestion. IRBs generally will not have the scientific consistence to make such a judgment. The determination whether and at what point in an investigation a test article has been shown to be safe and effective in accordance with the requirements of the act is a determination that must be made by the investigator, the sponsor, and, ultimately, FDA. The comment does not require any change in the regulations.

91. One comment stated that the regulations should protect vulnerable groups, such as minorities. The comment stated that neither the HHS nor the FDA proposed requirement was sufficient in this regard.

FDA has rewritten § 56.111(b) (and HHS has rewritten the corresponding provision in its regulations) to require that the IRB assure that appropriate additional protections are provided if the human subjects are from a vulnerable group.

92. One comment stated that before exposing human subjects to risk, an IRB should be required to make a determination that treatment is available for injuries that may arise from the research.

FDA disagrees in part with this comment. Section 50.25(a)(6) of the informed consent regulations requires that the subject be told if treatment for injuries is available. It should then be up to the subject to decide if he or she wishes to participate in the study. However, FDA agrees that the IRB should determine whether the investigator has made adequate provision for emergency medical care, if it appears that such emergency care may become necessary during the course of the investigation.

93. One comment suggested that IRB's should follow human subjects after completion of the study, unless the investigator can show that it is not necessary to do so.

FDA disagrees and rejects the suggestion. If anyone should follow subjects after completion of the study, it is the investigator or the sponsor. IRBs are generally not in a position to follow human subjects. If an IRB believes that it is necessary to do so to protect the subjects, it can require as part of the

protocol that the investigator follow subjects after the completion of the study.

94. Several comments on proposed § 56.8 stated that a means is needed for an investigator, a sponsor, or an institution to appeal an IRB ruling.

FDA has renumbered § 56.8 as § 56.112 in the final regulations to conform with those issued by HHS. The National Commission did not recommend that there be a mechanism for appeal from IRB determinations. However, there is nothing in § 56.112 that would prevent an institution from formulating an appeals mechanism, so long as the final ruling body is an IRB that satisfies the requirements of Part 56. Appeal of an adverse IRB determination to other institutional bodies that do not meet the requirements of Part 56 is not allowed under the regulation.

95. One comment questioned why officials at an institution could overrule IRB approval but not IRB disapproval of a study. Another comment stated that § 56.8 might abrogate the authority of the head of an institution.

Review and approval of a proposed clinical investigation by an IRB should not preclude a subsequent decision by the institution itself to reject the investigation. Officials of the institution take into account factors other than ethical acceptability and patient protection in deciding whether to authorize a particular investigation. For example, IRBs do not make decisions regarding the priority of funding studies or policy on whether to conduct a certain type of study at the institution. Therefore, FDA believes that institutional officials should have the authority to overrule an IRB's decision to approve a study. At the same time, FDA has decided not to authorize an institution to overrule and IRB's rejection of a study. If an institution had that authority, and IRB would become merely advisory, and its responsibilities would be eliminated. The comments do not warrant any change in the regulations.

96. Several comments on proposed § 56.92 stated that the sponsor should be given notice of a decision by an IRB either to suspend or to terminate approval of a clinical investigation.

FDA rejects these comments for the reasons explained in paragraphs 5 and 76 of this preamble.

97. One comment on proposed § 56.92 (now § 56.113) stated that once FDA has acted on an application for a research permit, it would be unfair to allow an IRB to suspend its approval of a particular clinical investigation.

FDA disagrees with the comment. An IRB focuses on different factors in its review of a proposed investigation than the agency considers in deciding whether to grant a research permit. Consequently, approval of a proposed investigation by either an IRB or FDA does not preclude the other entity from suspending or terminating the approval of the investigation at a later date.

98. FDA has deleted from the final regulations the criteria for disapproval and suspension or termination of approval of a clinical investigation that were proposed in § 56.90. Section 56.113 now states that an IRB may suspend or terminate its approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. This section now conforms to the HHS provision. The agency believes that the section, as revised, adequately specifies general criteria for the suspension or termination of the IRB's approval of an ongoing study. The section also requires that the IRB promptly notify FDA of its actions. Where necessary, FDA can, in turn, take any steps necessary to assure that the subjects are protected.

99. Several comments objected to the requirement in proposed § 56.90 that, after suspending or terminating approval of an investigation, the IRB make recommendations to FDA about the care of the human subjects of that investigation. The comments argued that it was the responsibility of a physician, and not an IRB, to make such recommendations.

FDA agrees with the comments and has deleted this requirement from the final regulations. The agency believes that this requirement inappropriately imposed medical responsibilities on an IRB. The responsibility for human subjects in a study for which IRB approval has been suspended or terminated is more properly shared by the clinical investigator, the institution, and the sponsor.

100. Section 56.114 in the final regulations was proposed as § 56.9. That section has been rewritten for clarity but there is no change in its intent. It is now consistent with the corresponding provision in the HHS regulations. The purpose of this section is to assure IRBs that FDA will accept reasonable methods of joint review. Thus, an IRB need not re-review a study that has already received approval from another IRB, unless it chooses to do so. However, FDA advises that the requirement for the IRB to be sensitive to such factors as community attitudes (§ 56.107(a)) is applicable to § 56.114. The IRB's records must include, either in

the minutes or elsewhere, documentation of agreement that a specific study will be reviewed cooperatively.

101. Two comments on proposed § 56.185 (now § 56.115) suggested that the records of an IRB should be maintained by the institution rather than by the IRB.

FDA agrees that, in some cases, it may be more feasible for an institution to maintain the records of an IRB. Consequently, FDA has rewritten § 56.115(a) to provide that either the institution or the IRB may be responsible for preparing and maintaining adequate records of IRB activities.

102. One comment stated that it is unreasonable to require IRBs to keep records because they lack adequate storage facilities.

FDA advises that if an institution delegates the responsibility to maintain records to an IRB, it must also provide the IRB with adequate facilities to do so. The comment does not justify any change in § 56.115.

103. One comment suggested that proposed § 56.185 should spell out every record that the agency wants an IRB to keep. The comment stated that the proposed requirements were not sufficiently detailed.

FDA disagrees with this comment. Section 56.115(a) in the final regulations sets forth the minimum records that an institution or an IRB must keep to document the activities of the IRB. The IRB or the institution is free to maintain additional records if it chooses. However, FDA does not believe that any more extensive recordkeeping by the IRB or the institution is necessary.

104. Five comments objected that the documentation FDA proposed to require was an unnecessary burden on IRBs. These comments argued that the proposed documentation is not necessary to protect the rights and welfare of human subjects.

FDA rejects these comments. The agency believes that the records that an IRB or an institution must maintain under § 56.115(a) provide significant evidence of whether the procedures utilized by the IRB are adequately protecting the human subjects of the investigations that the IRB is reviewing. For example, when an IRB approves the use of a "short form," for informed consent as provided in § 50.27(b)(2), FDA would expect the IRB to retain in its files a copy of the written summary of the oral presentation of informed consent information that is given to human subjects in the clinical investigation.

105. Several comments stated that proposed § 56.185(d) (now § 56.115(a)(2)), which requires that the minutes of an IRB meeting include a summary of the discussion of substantive issues, is not reasonable.

FDA agrees in part with the comments. The National Commission recommended, and FDA agrees, that it is important to maintain detailed minutes of IRB meetings. However, FDA decided to reduce the burden on IRBs by requiring that the minutes contain: (1) A basis for IRB action only when the research is disapproved or requires modification; and (2) A written summary of the IRB discussion and resolution only when it involves controversial issues.

FDA does not believe that summarizing the discussions of controverted issues in the minutes will have a chilling effect on those discussions because FDA does not require the identification of specific individuals with specific comments in the summaries.

106. One comment suggested that minutes could be kept by an audio tape recording, which would be complete and more accurate than any summary.

FDA agrees that a tape recording is a more complete record of the meeting. However, FDA advises that retention of complete recordings of meetings does not relieve an IRB of its obligation under § 56.115(a)(2) to keep at least brief written summaries of its meetings that must be available for inspection.

107. A few comments stated that the voting records of individual members should not be kept. The comments stated that this requirement would have a chilling effect on IRB members.

FDA believes the requirement has been misunderstood. Proposed § 56.185 did not include such a requirement nor does § 56.115 of the final regulations. Section 56.115(a)(2) requires only that the number of members voting for and against a study be kept. While the members attending the meeting would also be recorded in the minutes, individual voting records are not required.

108. Three comments objected to any requirement that voting records be kept.

FDA disagrees with these comments. The voting records must be included in the IRB records for FDA to document that a majority of those members present voted in favor of conducting a particular study at that institution.

109. One comment suggested that individual voting records of IRB members should be submitted to FDA, so that even if a member objected to a study but was overruled by the other members, the objection would come to

the attention of FDA. The agency could then take appropriate action.

FDA disagrees with this suggestion. Section 56.115(a)(2) already requires that votes of an IRB be recorded, and that any controverted items discussed be summarized in the minutes of IRB meetings. Consequently, there is no need to record individual members' voting records. In addition, except in the most extreme circumstances, FDA does not believe that it should second guess a properly constituted and well-functioning IRB on the ethical acceptability of a study.

110. Several comments objected that the records about the members of an IRB that were required in the proposed regulations were overly burdensome.

The recordkeeping requirements in § 56.115(a)(5) have been limited to provide that only information that necessarily bears on the IRB's impartiality and expertise must be maintained.

111. One comment stated that the record retention time required by proposed § 56.195 (now § 56.115(b)) disregarded the possibility that problems might not appear for 20 to 30 years.

This comment suggested that the regulations should be changed to require that records be kept 7 years for adults and 25 years for minors and pregnant women.

Although an institution is free to adopt a longer requirement, FDA has decided to match the HHS provision that records must be kept a minimum of 3 years. The agency believes that the 3-year requirement strikes an appropriate balance between the need to retain records and the administrative burdens involved. Although some problems may not become apparent for 20 years or more, those instances are so rare that the agency concludes that they do not justify an absolute requirement that all IRB records be retained for such an extended period of time. In addition, FDA reviews IRBs on a 2-year cycle. Thus, the 3-year requirement will ensure that all of the important records of the IRB will be available for FDA review. If, however, an institution or an IRB believes that in a particular study it would be appropriate to retain the IRB records longer to protect the human subjects involved, the institution or the IRB is of course free to do so.

112. One comment stated that the period that IRBs or institutions are required to retain records should be consistent with the record retention requirements in the proposed regulations regarding obligations of sponsors and monitors of clinical investigations and the proposed

regulations regarding obligations of clinical investigators.

FDA rejects this comment. The records covered by these regulations are quite different than those that are proposed to be required under the sponsor-monitor and clinical investigator regulations. Therefore, the agency believes that the three sets of regulations need not be consistent on this point. The agency believes it is more appropriate to keep § 56.115(b) consistent with the corresponding provision in the HHS regulations. FDA believes that the 3-year period satisfies the needs of the agency while not imposing an unreasonable administrative burden on IRBs or their parent institutions.

113. A few comments suggested that records could be maintained by microfiche, microfilm, or other similar photographic method, if the records are properly verified as being accurate reproductions of the original records.

FDA agrees with these comments. There is nothing in these regulations that would prevent records from being reproduced and retained in this manner.

114. Many comments objected to the requirement in proposed § 56.15(a) that FDA be allowed to copy patient medical records during an IRB inspection. Most comments stated that IRBs do not have individual patient records. Other comments questioned whether FDA was requiring IRBs to obtain those records. Many comments stated that there were problems with confidentiality if IRBs were to obtain individual patient medical records and maintain them in the files for 5 years after completion of a clinical investigation to which the IRB records relate. Many comments stated that if this information is needed by the agency, it is available from either the sponsor or clinical investigator and should be obtained through proper legal channels from those persons.

In response to the comments, FDA has deleted from the final regulations any requirement that patient records be maintained by an IRB or that patient records be made available to FDA during an inspection of an IRB. If it becomes necessary for FDA to see the medical records of individual patients, adequate authority exists under the act for FDA to obtain those records from the clinical investigator or sponsor. Also, because IRBs would rarely have individual medical records, FDA wants to assure IRBs that there is no need to obtain individual patient records to comply with the requirements of § 56.115.

115. One comment suggested that IRBs do not have to submit to inspection by

FDA because inspections require warrants.

FDA rejects this comment and declines to change § 56.115(b) to respond to the comment. As discussed in the preamble to the 1978 proposal, FDA has authority to inspect an IRB, in many cases, without the IRB's permission. Under section 704(a) of the act (21 U.S.C. 374(a)), FDA may inspect establishments in which certain drugs or devices are processed or held and may examine research data that would be subject to reporting and inspection under sections 505(i) or (j), 507(d) or (g), 519, or 520(g) of the act. Under section 704(e) (21 U.S.C. 374(e)), FDA may inspect certain required records concerning devices. Thus, most sponsors and many investigators of investigational new drugs and investigational devices, and the institutions at which such studies are conducted, are subject to FDA inspection whether they consent or not.

FDA advises that if an IRB refuses to permit inspection, FDA may, under § 56.115(c), reject the studies conducted under review of that IRB from supporting an application for a research of marketing permit, or the agency may seek a warrant to inspect. However, there is no requirement that FDA obtain a warrant before inspection.

116. Two comments stated that inspections were too long, and that FDA should provide more detail about how inspections are to be conducted.

FDA has recently mailed an information sheet on the inspection process to the approximately 1,500 individuals, institutions, and organizations that have communicated with the agency previously about IRB's. FDA also sponsored a workshop on IRB compliance activities on November 7, 1980 (announced in the *Federal Register* of September 26, 1980; 45 FR 63929). The agency will distribute the transcript of the workshop to interested parties; will evaluate the workshop as well as written comments on it; and will then decide whether to make modifications in the current inspection program. The transcript and the information sheet are on file under Docket No. 80N-0399 in FDA's Dockets Management Branch (HFA-305), Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. The transcript and any comments on it may be seen in that office between 9 a.m. and 4 p.m., Monday through Friday.

The comments do not require any change in the regulation.

117. A few comments on proposed § 56.15(b) (now § 56.115(c)) stated that FDA has no authority to refuse to consider a clinical investigation in support of an application for a research

or marketing permit if the IRB refuses to allow inspection by FDA officials. Some of the comments stated that FDA should have the burden of showing that the validity of the study is adversely affected by the IRB's refusal to allow inspection.

As stated in the preamble to the 1978 proposal, if follows from the authority to issue regulations establishing standards for IRBs that FDA also has the authority to prescribe the terms on which it will accept data generated in a clinical investigation reviewed by an IRB. Therefore, the agency may refuse to consider data from a clinical investigation in support of an application for a research or marketing permit, unless the IRB that reviewed the investigation consents to an inspection by FDA.

The connection between an IRB's refusal to permit an inspection and the agency's refusal to consider data is clear. FDA is charged by statute with the obligation of ensuring the protection of the rights and welfare of the human subjects who participate in clinical investigations involving articles subject to sections 505(i), 507(d), and 520(g) of the act. In performance of that obligation, the agency has adopted these regulations requiring IRB review. However, FDA has a concomitant obligation to ensure that these regulations are observed. FDA must verify that IRBs are operating in accordance with these regulations, and it must have access to the IRBs and their records to do so. When an IRB refuses to permit FDA to inspect its records, FDA cannot verify that the IRB is properly constituted and operating correctly. Consequently, the agency cannot be assured that human subjects have been given the protection that the IRB mechanism is intended to afford, and it may be appropriate for the agency to refuse to accept the data from the studies that the IRB has reviewed.

However, FDA points out two additional facts: First, before rejecting the data from a clinical investigation, the agency will review each study to determine whether the risks created by requiring the study to be re-done outweigh the benefits of rejecting the data.

Second, FDA expects that it will be a very rare occurrence for an IRB to refuse to allow an inspection by FDA personnel. FDA has found that the vast majority of IRBs are cooperative at the time of inspection.

The comments do not justify any change in § 56.115(c) from the regulation as proposed.

118. A few comments stated that it is unfair for the agency to "punish" the

sponsor of a study by refusing to accept the data from a study that was reviewed by an IRB that refused to allow FDA inspection.

FDA has already explained in paragraphs 46 and 117 above that it will not automatically reject data. FDA also points out that, with these regulations (see § 56.120 et seq.), the agency has available more direct administrative actions against institutions and IRBs for noncompliance. Thus, the agency may apply sanctions directly against the entity that refused inspection. However, there may be occasions when it would be appropriate for the agency to also refuse to accept data, and FDA has reserved that option.

119. FDA received numerous comments criticizing the provisions of Subpart K of the proposed regulations (now Subpart E) relating to the disqualification of IRB's.

In response, FDA has simplified and streamlined Subpart E of the final regulations. FDA has also shifted the focus of the administrative sanctions for noncompliance from the IRB to the institution. The agency recognizes that an IRB is created by and is responsible to the institution. Consequently, it is the duty of the institution to assure that its IRB meets the obligations imposed by Federal statute and regulations. FDA believes that when an IRB is found not to be in compliance with the regulations, and the institution to which the IRB is responsible does not take positive steps to correct the deficiencies, the appropriate response is to take action against the institution. However, there are exceptions to this rule. If an IRB is not directly responsible to a single institution, e.g., where an IRB reviews clinical investigations for more than one institution, and the IRB is found not to be in compliance with these regulations, FDA believes it would be appropriate to take action directly against the IRB. A second exception is the situation in which an IRB is one of several directly responsible to a single institution, e.g., where an IRB reviews certain kinds of clinical investigations at the institution, and where an IRB is found not to be in compliance with these regulations. FDA believes that it may not be appropriate to disqualify all the IRBs at the institution because one is out of compliance. Therefore, FDA will take action against the individual IRB, and not against the institution, when the institution has taken all appropriate steps within its power to correct the IRB's deficiencies, but the IRB remains out of compliance.

Section 56.120(c) reflects the agency's shift in focus to the institution. However, the regulation also provides that FDA

may take action against an IRB or a component of the parent institution if the agency determines that it is appropriate to do so under the facts of the particular case.

120. Several comments on proposed § 56.202(c) suggested that the lesser regulatory actions that were referred to in the proposed regulations should be listed.

FDA accepts these comments. Section 56.120(b) has been added to the final rule to set forth the lesser administrative actions that the agency may take if FDA finds deficiencies in the operation of an IRB and to describe the circumstances in which these lesser administrative actions may be used by the agency.

121. Two comments stated that notification of other Federal agencies of a possible IRB disqualification, as provided in the proposed regulations, would presume that IRB is guilty before it had an opportunity for a hearing and would make it difficult to recruit members.

FDA rejects these comments. In most instances, FDA will not advise other Federal or State agencies of deficiencies in the operation of an IRB, unless the agency decides to disqualify the IRB or its parent institution. However, in § 56.120(b)(4), the agency has reserved the right to do so if it finds serious deficiencies in the operation of an IRB during an inspection. In addition, FDA, as an agency of HHS, will share knowledge gained from inspections with other agencies within the Department, including the National Institutes of Health.

122. A few comments stated that FDA should exhaust all other remedies before disqualification. Other comments suggested that the IRB should have an opportunity to correct or refute the deficiencies found by FDA.

Section 56.121(a) of the final regulations provides that disqualification proceedings will not be instituted by the agency, unless the agency determines that grounds for holding a hearing exist, and the institution or the IRB has failed to take adequate steps to correct the deficiencies listed in the letter sent by the agency under § 56.120(a).

123. One comment stated that if FDA decided to retain the disqualification mechanism, the regulations should clearly state that disqualification will be used only in the most extreme cases and not on a routine basis.

FDA agrees with this comment. Disqualification will be used by the agency only when it is necessary to protect the rights and welfare of human subjects, and after the institution or IRB has refused or has continuously failed to

comply with these regulations. FDA hopes never to use this sanction, and, based on the demonstrated willingness of institutions to correct deficiencies in their IRBs, the agency does not expect to use this sanction except in the most extraordinary circumstances. However, the agency believes that it is important to retain the option to disqualify an institution or an IRB if it becomes necessary to do so to protect human subjects.

124. Several comments pointed out that nowhere in the act is disqualification mentioned. These comments consequently concluded that FDA lacks the authority to disqualify IRBs.

FDA disagrees and rejects these comments. FDA has previously discussed its authority to promulgate these regulations (see paragraphs 4 and 117 of this preamble). Inherent in that authority is the authority to enforce these regulations. Disqualification is an essential element of the enforcement mechanism adopted by the agency. Without such an enforcement mechanism, compliance with these regulations would be voluntary, and these regulations would be nothing more than guidelines that would not adequately protect human subjects.

125. A few comments suggested that disqualification of an IRB or an institution would only hurt the sponsor, because studies reviewed by the IRB would not be accepted by FDA. The comments stated that sponsors exert little control over IRBs and have little opportunity to ensure that IRBs comply with these regulations.

FDA believes that it has responded to these concerns in paragraph 118 of this preamble. FDA would suggest that a sponsor assure itself, through the clinical investigator, that the IRB that reviews the clinical investigation protocol meets FDA requirements.

126. Several comments suggested that FDA should send notice of the initiation of proceedings to disqualify an IRB or its parent institution to all investigators and sponsors whose studies are under the review of the IRB.

FDA rejects this suggestion. FDA believes it would be an unreasonable expenditure of agency resources for it to send out such notices prior to a hearing. While a great deal of effort would have to be expended in putting together a list of sponsors and investigators involved with the institution and in sending them notices, the reason for the notice could be easily mooted if the IRB comes into compliance, or if FDA decides against disqualification. The agency believes that its resources are better spent after the hearing, notifying all interested

parties it can identify that the agency has decided to disqualify the institution or the IRB. FDA advises that this notification may require publication of the disqualification decision in the Federal Register.

127. One comment suggested that an additional provision should be inserted into the final regulations to allow the IRB 30 to 60 days to prepare for the hearing, except where the safety of the human subjects requires immediate action.

FDA rejects this suggestion. Hearings under these regulations will be conducted in accordance with the requirements for a regulatory hearing before the FDA set forth in 21 CFR Part 16. Adequate time to prepare for a regulatory hearing is afforded under those regulations.

128. Several comments objected to the grounds for disqualification set forth in proposed § 56.202 (now § 56.121(b)). One comment argued that a blanket statement that disqualification could be based on a failure to comply with any regulations regarding IRBs would open the door to harassment and abuse of this system. Two comments stated that although it would be appropriate to disqualify an IRB if its noncompliance adversely affected the rights and safety of human subjects, it made no sense to disqualify an IRB because its noncompliance affected the validity of a study.

FDA has revised the grounds in § 56.121(b) for disqualification. To assure that the remedy is invoked only when appropriate, § 56.121(b)(1) provides that an IRB's failure to comply must be repeated to be grounds for disqualification (see paragraph 129). Noncompliance that adversely affects the validity of an investigation is no longer a basis for disqualification (§ 56.121(b)(2)).

129. Two comments stated that failure to comply with these regulations should not trigger disqualification. One of these comments stated that FDA should have to show a willful intent not to comply.

FDA disagrees with these comments. Although disqualification will not be used lightly, the agency should not have to show that the IRB or the institution did not intend to comply with the regulations. Repeated failure to comply may or may not indicate a willful intent, but it is sufficient to trigger disqualification. Section 56.121(b)(1) of the final regulations so provides. The important point is that the failure to comply is repeated and not an isolated event. Of course, a flat refusal to comply with these regulations could also trigger disqualification.

130. Three comments stated that the regulations should provide that the agency will advise a sponsor of the disqualification of an IRB that is reviewing studies of that sponsor.

FDA accepts this comment and has revised § 56.121(c) to so provide. The agency will notify any sponsor of which it is aware that has had studies reviewed by the disqualified IRB. This notification may require publication of the disqualification decision in the *Federal Register*.

131. Several comments questioned whether an institution has to replace its IRB after the IRB is disqualified.

Because FDA has shifted the focus of these regulations from the IRB to the institution, disqualification will usually be directed at the institution itself. In order for the IRB of a disqualified institution to be in compliance with these regulations, the institution would have to be reinstated. The situation is somewhat different for institutions with more than one IRB or for institutions whose studies are reviewed by an IRB that serves several institutions. As discussed in paragraph 119 above, FDA may disqualify the IRB rather than the institution in such situations. Those institutions are then free to establish a new IRB, to replace the disqualified IRB, but FDA would not require them to do so. An institution with several IRBs may choose to have another IRB that is competent to assume the responsibilities of the disqualified IRB. For example, the institution would assign an IRB that normally reviews drug studies the responsibility to assume the review of drug studies that were previously under the review of a disqualified IRB. However, FDA would find unacceptable the assignment of those duties to an IRB that normally reviews behavioral research, whose members lack the professional competence necessary to review drug studies.

132. Several comments stated that investigations reviewed by an IRB before disqualification should not automatically be presumed to be unacceptable. A few stated that only the particular studies where deficiencies were found should be unacceptable to FDA.

FDA disagrees in part with the comments. FDA believes that if it is necessary to disqualify an institution or an IRB, the agency cannot be assured that any study conducted at that institution or reviewed by that IRB provided for the rights and welfare of the human subjects. Because disqualification will not be undertaken lightly, the deficiencies that required disqualification are likely to be so pervasive that they had an effect on

more than one study. Therefore, FDA believes that any study reviewed by a disqualified IRB or conducted at a disqualified institution is suspect. However, as stated previously in paragraph 46 of this preamble, the agency will review the studies conducted as a disqualified institution or reviewed by a disqualified IRB to decide on a case-by-case basis whether to reject the data.

133. One comment expressed concern that confidential information would be disclosed to the public during the disqualification process. A few comments stated that no data, clinical reports, or records regarding particular studies ought to be disclosed.

Section 56.122 provides that the determination of the agency to disqualify an institution and the administrative record regarding that determination are disclosable to the public under the agency's public information regulations. Under § 20.61 (21 CFR 20.61), any trade secret or confidential commercial information in the administrative record is exempt from disclosure. Under § 20.63, medical and similar files, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy, are also exempt. Therefore, there is no basis for concern that confidential information will be disclosed, and the comments are rejected.

134. One comment stated that adverse publicity caused by disqualification would make recruitment for IRBs very difficult.

FDA recognizes that some adverse publicity may arise from a disqualification of an IRB or an institution. However, because IRBs play such an important role in the protection of human subjects, and because disqualification will be undertaken only when there has been a serious disregard by an IRB or an institution of its responsibilities, FDA believes it is appropriate to retain the disqualification mechanism and the provisions allowing the agency to publicly disclose the fact of the disqualification at the discretion of the agency.

135. One comment stated that because an IRB is created to serve an institution, any disqualification should be of the institution, and the burden of reinstatement should be placed upon that institution.

FDA generally agrees with these comments and, except for the situations discussed in paragraph 119 of this preamble, has changed the focus of disqualification and reinstatement to the institution. To be reinstated pursuant to § 56.123, an institution must adequately demonstrate to FDA how the concerned

IRB will comply with these regulations. FDA does not believe that it should spell out exactly how the institution should demonstrate how compliance with these regulations will be assured, because institutions may choose different methods of assuring such compliance.

136. Three comments stated that additional sanctions against individual members of an IRB would make it difficult to recruit members to serve on any IRB.

FDA disagrees with these comments. Other sanctions will be used in cases where disqualification of the institution or the IRB might not be the appropriate action, e.g., where individual members of an IRB submit false information to the Federal Government, which is a criminal offense. The agency does not believe that qualified people will be deterred from serving on an IRB by the fact that they will be held accountable if they break the law.

137. One comment stated that in light of the other sanctions referred to in proposed § 56.215 (now § 56.124) disqualifications would be superfluous.

FDA disagrees with this comment. As stated in paragraph 123 of this preamble, while FDA expects to use disqualification only rarely, it is important that the agency retain the option to use it if the need arises. In some situations, disqualification may be a more appropriate remedy than criminal sanctions. In other situations, it may be necessary to institute disqualification proceedings in conjunction with criminal proceedings to assure that human subjects will be adequately protected.

138. FDA is adopting the conforming amendments as proposed. However, in accordance with the principles of common sense, the amendments proposed separately but applicable both to Part 50 and Part 56 have been combined and are included with FDA's informed consent final rule published elsewhere in this issue of the *Federal Register*.

139. On its own initiative, the agency is also adopting amendments to the IDE regulations (21 CFR Part 812) to conform them to Part 56. The IDE regulations were promulgated by FDA after the August 14, 1979 reproposal of these regulations.

However, the agency has decided not to amend the IDE regulations for intraocular lenses (21 CFR Part 813). The ongoing intraocular lens investigations are exempt from the requirements established by these regulations under § 56.104(a). Therefore, it would not be appropriate to modify Part 813 at this time. In addition, the agency is revising Forms FD-1571, 1572, and 1573 in 21 CFR

312.1(a) to conform them to these regulations. FDA stated in the 1978 proposal (43 FR 35198) that it would revise these forms at the time the final IRB regulations were adopted.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 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. 511-518 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 76 Stat. 794-795 as amended, 90 Stat. 540-546, 560, 562-574 (21 U.S.C. 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 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, 241, 262, 263b-263n)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

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

1. In Part 16, § 16.1 is amended by adding a new regulatory provision under paragraph (b)(2) to read as follows:

##### § 16.1 Scope.

- (b) \* \* \*
- (2) \* \* \*

Section 56.121(a), Relating to disqualifying an institutional review board or an institution.

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

#### PART 56—INSTITUTIONAL REVIEW BOARDS

##### Subpart A—General

- Sec.
- 56.101 Scope.
- 56.102 Definitions.
- 56.103 Circumstances in which IRB review is required.
- 56.104 Exemptions from IRB requirement.
- 56.105 Waiver of IRB requirement.

##### Subpart B—Organization and Personnel

- 56.107 IRB membership.

##### Subpart C—IRB Functions and Operations

- 56.108 IRB functions and operations.
- 56.109 IRB review of research.
- 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 56.111 Criteria for IRB approval of research.
- 56.112 Review by institution.
- 56.113 Suspension or termination of IRB approval of research.

Sec.

- 56.114 Cooperative research.

##### Subpart D—Records and Reports

- 56.115 IRB records.

##### Subpart E—Administrative Action for Noncompliance

- 56.120 Lesser administrative actions.
- 56.121 Disqualification of an IRB or an institution.
- 56.122 Public disclosure of information regarding revocation.
- 56.123 Reinstatement of an IRB or an institution.
- 56.124 Actions alternative or additional to disqualification.

Authority: Secs. 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 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. 511-518 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 76 Stat. 794-795 as amended, 90 Stat. 540-546, 560, 562-574 (21 U.S.C. 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371(a), 376, and 381), secs. 215, 301, 351, 354-360f, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 241, 262, 263b-263n).

##### Subpart A—General Provisions

###### § 56.101 Scope.

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

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

###### § 56.102 Definitions.

As used in this part:

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

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

- (1) A color additive petition, described in Part 71.
- (2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as

safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in § 170.35.

(3) A food additive petition, described in Part 171.

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

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

(6) A "Notice of Claimed Investigational Exemption for a New Drug" described in Part 312.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#### § 56.103 Circumstances in which IRB review is required.

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

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

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

#### § 56.104 Exemptions from IRB requirement.

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

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

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

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

#### § 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these

regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

#### Subpart B—Organization and Personnel

##### § 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members' backgrounds including consideration of the racial and cultural backgrounds of members and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, including but not limited to subjects covered by other parts of this chapter, the IRB should include one or more individuals who are primarily concerned with the welfare of these subjects.

(b) No IRB may consist entirely of men, or entirely of women, or entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in nonscientific areas; for example: lawyers, ethicists, members of the clergy.

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

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

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

#### Subpart C—IRB Functions and Operations

##### § 56.108 IRB functions and operations.

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

(a) Follow written procedures (1) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution, (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, (3) for insuring prompt reporting to the IRB of changes in a research activity, (4) for insuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects; and (5) for insuring prompt reporting to the IRB of unanticipated problems involving risks to subjects or others.

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

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

##### § 56.109 IRB review of research.

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

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

(c) An IRB shall require documentation of informed consent in accordance with § 50.27, except that the IRB may, for some or all subjects, waive the requirement that the subject or the subject's legally authorized representative sign a written consent

form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

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

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

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

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

(b) An IRB may review some or all of the research appearing on the list through an expedited review procedure, if the research involves no more than minimal risk. The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 56.108(b).

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

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

**§ 56.111 Criteria for IRB approval of research.**

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

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

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

(3) Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted.

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

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

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

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

(b) Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

**§ 56.112 Review by institution.**

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

**§ 56.113 Suspension or termination of IRB approval of research.**

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

**§ 56.114 Cooperative research.**

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

**Subpart D—Records and Reports**

**§ 56.115 IRB records.**

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

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

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

(3) Records of continuing review activities.

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

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each

member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

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

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

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

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

**Subpart E—Administrative Actions for Noncompliance**

**§ 56.120 Lesser administrative actions.**

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

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

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part;

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or

(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct

interest in the agency's action of the deficiencies in the operation of the IRB.

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

**§ 56.121 Disqualification of an IRB or an institution.**

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

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

- (1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and
- (2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

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

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

unless the IRB or the parent institution is reinstated as provided in § 56.123.

**§ 56.122 Public disclosure of information regarding revocation.**

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

**§ 56.123 Reinstatement of an IRB or an institution.**

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

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

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

*Effective date.* This regulation shall become effective July 27, 1981.

(Secs. 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513-518, 518-520, 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, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371(a) 376, and 381]; secs. 215, 301, 351, as amended [42 U.S.C. 216, 241, 282, 263b-263n])

Dated: January 19, 1981.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 81-2688 Filed 1-28-81; 8:45 am]

BILLING CODE 4110-03-M

**21 CFR Part 50**

[Docket No. 78N-0049]

**Protection of Human Subjects; Prisoners Used as Subjects in Research; Correction**

**AGENCY:** Food and Drug Administration.  
**ACTION:** Correction.

**SUMMARY:** In FR Doc. 80-16578 appearing at page 36386 in the Federal Register of Friday, May 30, 1980, the following correction is made in the first column of page 36391: In § 50.1 *Scope*, in paragraph (a) the word "prisoner" is removed.

**FOR FURTHER INFORMATION CONTACT:** Agnes Black, Federal Register Writer (HFC-11), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2994.

Dated: January 19, 1981.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 81-2688 Filed 1-21-81; 8:45 am]

BILLING CODE 4110-03-M