

TUESDAY, AUGUST 8, 1978
PART IV

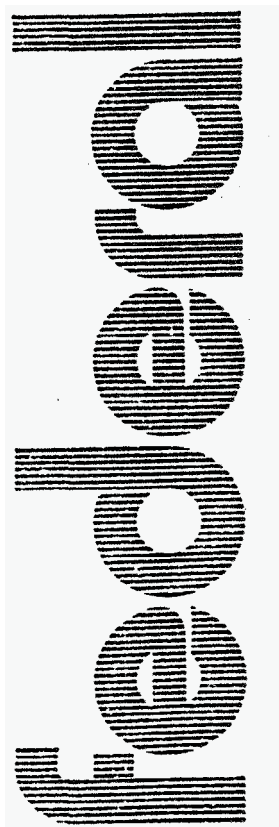


**DEPARTMENT OF
HEALTH,
EDUCATION, AND
WELFARE**

**Food and Drug
Administration**

**STANDARDS FOR
INSTITUTIONAL REVIEW
BOARDS FOR CLINICAL
INVESTIGATIONS**

**Proposed Establishment of
Regulations**



[4110-03]**DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE****Food and Drug Administration**

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

[Docket No. 77N-0350]

**STANDARDS FOR INSTITUTIONAL REVIEW
BOARDS FOR CLINICAL INVESTIGATIONS****Proposed Establishment of Regulations**

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This is a proposal to clarify existing regulations governing the activities of institutional review boards (IRB) that review clinical investigations involving human subjects and new human drug products. The proposed rule would extend these regulations to include IRB's that review clinical investigations involving human subjects and articles other than new human drug products regulated by the Food and Drug Administration (FDA). The proposed regulations are intended to provide greater protection of the rights and safety of subjects involved in clinical investigations and to help assure the quality and integrity of the resulting data that are submitted to FDA in support of applications for permission to conduct further research or to market regulated products.

DATES: Comments by December 6, 1978.

ADDRESS: Written comments, preferably four copies and identified by docket No. 77N-0350, may be submitted to the office of the Hearing Clerk (FHA-305), Food and Drug Administration, room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

**FOR FURTHER INFORMATION
CONTACT:**

John Petricciani, Division of Pathology (HFB-400), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, Md. 20014, 301-496-5491.

SUPPLEMENTARY INFORMATION: Although informed consent is an important part of the protection of human subjects participating in clinical investigations, this proposal is being published without a comprehensive definition of "informed consent" to provide an early opportunity for interested persons to review and comment on the proposed standards and procedures for institutional review. The agency will be publishing shortly

a companion proposal that will define "informed consent."

The agency also intends to hold three open hearings to give the public an opportunity to make oral comments on both proposals. A notice of the date and location of these hearings will be published later with the proposed definitions of "informed consent."

The comment period for this proposal will close on December 6, 1978. However, the Commissioner of Food and Drugs recognizes that it may not be possible to publish the "informed consent" proposal, and schedule and hold the public hearings on both proposals within that time period. The Commissioner advises interested persons that he is prepared to extend the comment period on this proposal as appropriate.

The Commissioner believes that a complete revision of FDA requirements relating to IRB's is needed because: (1) Current regulations have not been comprehensively reviewed in 7 years, (2) actions by the Department of Health, Education, and Welfare (HEW), the Congress, and the World Medical Assembly suggest a need to extend IRB requirements to types of clinical investigations involving human subjects other than those on new human drugs, (3) wherever possible, IRB requirements adopted by FDA should be identical to or compatible with HEW regulations as well as IRB regulations issued by other Federal agencies, (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), provided for IRB's in clinical investigations of devices intended for human use, and (6) the new FDA bio-research monitoring program, designed to assure compliance with FDA requirements to protect human research subjects and reinforce the validity and reliability of clinical data submitted to FDA, can be more efficiently and effectively conducted with the utilization of IRB's and with uniform, agencywide regulatory standards regarding IRB's. Each of these matters is discussed in further detail below.

Since 1971, FDA has required institutional review of clinical investigations subject to regulation by the agency and involving institutionalized human subjects or noninstitutionalized subjects where an institution agrees to assume responsibility for the investigation. The benefits of institutional review include appraisal of local conditions and standards, acquaintance with investigators, subject groups, and the setting in which the investigation is proposed to be conducted, independence from competing interests, and sensitivity to ethical and scientific concerns in the

community and the society at large. In addition, IRB's can review ongoing investigations and oversee the continuing safety of the subjects as well as the adherence of the investigation to the approved protocol and other understandings and regulations. Current FDA requirements for IRB review are set forth in the texts of the forms FD-1571, FD-1572, and FD-1573 used for exemptions for investigational new drug studies (21 CFR 312.1(a)(2), form FD-1571, item 10.c.; 21 CFR 312.1(a)(12), form FD-1572, item 3.; and 21 CFR 312.1(a)(13) form FD-1573, item 2a.). When originally adopted, the agency indicated that it was considering extending these requirements to all other drug investigations under FDA jurisdiction (36 FR 5037; March 11, 1971). The Commissioner has for some time also desired to review and codify existing requirements. Since 1971, several events have indicated increased acceptance of and reliance upon the concept of local, independent review of human research to evaluate the scientific justification for and ethical acceptability of exposing human beings to risk. These developments, which increase the advisability of a substantial revision and extension of current FDA regulations, include:

(1) HEW guidelines on institutional review for research involving human subjects that is supported by HEW grant or contract were codified in 1974 into regulation form, after public notice and extensive comments from interested persons (45 CFR part 46, subpart A; see 39 FR 18914; May 30, 1974). These regulations were subject to technical amendments in 1975 (40 FR 11854; March 13, 1975). These regulations reflected experience that HEW had gathered under earlier guidelines, guidelines which were also the source of FDA's 1971 regulations. The new HEW rules modified and improved upon the older ones, but created certain inconsistencies between FDA's standards regarding regulated research and the Department's standards regarding funded research. Since 1974, the HEW regulations have served as a model for other Federal agencies that support human experimentation. See, e.g. 10 CFR part 745 adopted by the Energy Research and Development Administration in the FEDERAL REGISTER of November 30, 1976 (41 FR 52434) and regulations proposed by the Consumer Product Safety Commission in the FEDERAL REGISTER of September 2, 1976 (41 FR 37120). The Commissioner believes that, wherever possible, FDA's regulations should be compatible with, if not identical to, HEW's and those of other Federal agencies. A multiplicity of dissimilar and inconsistent Federal requirements is burdensome to institu-

tions, IRB's, and the process of clinical investigation.

(2) Congress endorsed the concept of institutional review in section 212(a) of the National Research Act of 1975 (42 U.S.C. 747(a)), which directs the Secretary of HEW to require IRB review of all biomedical and behavioral research involving human subjects conducted at or sponsored by an institution receiving a grant or contract under the Public Health Service Act. Although this includes biomedical research involving human subjects when such research is regulated or reviewed by FDA under the Federal Food, Drug, and Cosmetic Act (the "act") if it is conducted by a Public Health Service grantee or contractor, it does not extend to institutions not receiving such financial support. The Commissioner believes that it would be consistent with the congressional intent for FDA to use its existing statutory authority to apply an IRB review requirement wherever it is both reasonable and feasible.

(3) The Declaration of Helsinki, a set of principles adopted by the World Medical Assembly (an international body of experts concerned with health and scientific matters) was revised in 1975 to recommend that every biomedical research protocol be given "to a specially appointed independent committee for reconsideration, comment, and guidance" (sec. I(2)). (A copy of the amended declaration is on display in the Office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.) The agency has previously acknowledged the declaration as reflecting the most widely accepted standards for biomedical research involving human subjects. (See 38 FR 24220 (Sept. 6, 1973); 40 FR 16053, (Apr. 9, 1975); and 21 CFR 312.20.) Although it might be argued that the process by which FDA reviews the investigational use of new drugs and will, in the future, review certain medical devices fulfills this recommendation, the Commissioner believes the declaration contemplates a committee more closely acquainted with the investigator and the setting in which the clinical investigation will be conducted.

(4) When the Medical Device Amendments of 1976 were enacted, reference to institutional review was incorporated for the first time in the act, in section 520(g) (21 U.S.C. 360j(g)). Congress clearly approved such review as a means of protecting subjects while encouraging research in medical devices for human use. In the FEDERAL REGISTER of August 20, 1976 (41 FR 35282), the Commissioner proposed regulations governing investigational device exemptions (IDE) under section 520(g) of the act, including im-

plementing institutional review requirements. (See 21 CFR part 812, subpart D of that proposal.) Comments filed on that proposal have been reviewed and utilized in preparing this notice. In the FEDERAL REGISTER of May 12, 1978 (43 FR 20726) the Commissioner issued portions of the IDE proposal as a tentative final regulation. Those provisions in the IDE proposal that duplicate or overlap substantially with the requirements proposed in this document have been deleted from the tentative final regulation. The Commissioner will review comments on this proposed rule promptly and will issue in final form at least those proposed provisions that are essential to the promulgation of comprehensive final regulations governing the investigational use of medical devices.

(5) The General Accounting Office (GAO) published a report entitled "Federal Control of New Drug Testing Is Not Adequately Protecting Human Test Subjects and the Public" (July 15, 1976); chapter 4 of this report evaluated institutional review requirements and made recommendations for improvement. A copy of this report is also on display in the Office of the Hearing Clerk, Food and Drug Administration. This proposal is a step in implementing some of the GAO recommendations.

(6) Finally, FDA has recently reassessed its responsibilities, needs, and priorities in the entire area of biomedical research, including safety testing of substances in animals, monitoring of clinical investigations by sponsors, the role of institutional review boards, and the obligations of clinical investigators. The agency, the Congress, and others have recently become concerned about the validity and reliability of scientific data on the safety and effectiveness of products regulated by FDA. Much of the history of this review, with special emphasis on the quality and integrity of safety data derived from nonclinical laboratory studies, is discussed in the preamble to the proposal on good laboratory practices published in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206). Congressional and Presidential action in the summer of 1976 appropriated to FDA \$16.3 million and authorized over 600 new positions to carry out expanded activities in the area of bioresearch monitoring.

In conjunction with this legislative action, the Commissioner has established a "Bioresearch Monitoring Program" to develop and implement an agencywide program for all aspects of preclinical testing and clinical research relating to FDA-regulated products. The program is managed by an intra-agency steering committee that oversees several task forces as-

signed to consider specific matters. The Institutional Review Board Task Force has the responsibility for: (1) Developing an agency strategy to define the responsibilities of IRB's in clinical investigations involving human subjects which are regulated by FDA or which involve products regulated by FDA and (2) assuring that these duties are adequately and reliably performed. To meet these goals, the task force proposed the following:

1. Promulgation of agencywide regulations that would set forth the responsibilities of IRB's and enforcement procedures; these proposed regulations are based upon existing FDA regulations for investigational new drug studies, proposed regulations for investigational use of medical devices and comments received on them, and FDA experience.

2. Issuance of an agencywide compliance program that would include enforcement policies, regular inspections of IRB's, and special inspections initiated by FDA to audit particular investigations.

3. Development of appropriate organizational structures or mechanisms and data systems to be used for planning and scheduling inspections under the compliance program and for reviewing and evaluating the results of individual inspections as well as the overall program.

PURPOSES OF INSTITUTIONAL REVIEW

Institutional review began when a few institutions treating patients or conducting medical research established internal committees to review research grant applications and other proposed clinical investigations, and to advise responsible officials within the institution on whether the proposed projects should be permitted. Reviews and advice originally emphasized scientific aspects of studies, and IRB's were composed principally of physicians and other health scientists; but these professionals, from the beginning, considered the ethical implications of research. Increasingly, officers of institutions found that sensitivity to community standards of ethics, as well as involvement of nonscientists, was important in considering planned studies; as a result, lawyers, the clergy, ethicists, and other nonscientists from outside the institution were added to IRB's. The original concept remained, however, that the board was to advise the officers of the institution on the acceptability of the proposed study within the institution; this advice naturally involved, but was not limited to, the obligations of the institution to its patients and subjects.

In the 1960's, the National Institutes of Health of HEW began requiring IRB review as part of the process of providing grants and contracts for re-

search involving human subjects. The purposes were several: First, such requirement would provide HEW with an assurance that community standards would be considered in determining the acceptability of a proposed investigation, a goal difficult to attain with centralized review at the level of the Federal Government. Second, it would provide patients and subjects additional protection. Specifically, an IRB is generally capable of making a better informed judgment about the potential risks and benefits of the proposed study than an individual subject; thus, IRB review supplements the use of informed consent as a safeguard of the rights and safety of the subject. Third, IRB review would relieve HEW of the burden of reviewing an application that would subsequently be unacceptable within the institution in which the investigation is proposed to be conducted. In addition, the process of IRB review and approval of a study, providing a review anticipating, in part, HEW's review, could substantially improve the quality of a research protocol. To assure a certain degree of independence of the IRB's in reviewing proposed investigations, HEW required outside membership on each IRB (i.e., at least one or more members cannot be associated with the institution other than by virtue of participation on the board) and stated that no application for a research grant or contract would be approved unless it had IRB approval (i.e., the officers of the institution could not overrule a negative decision by a board). In taking these steps, HEW effectively created a new relationship between the IRB's and the government, altered to some degree the relationship between the IRB's and the parent institutions, and implied a special duty on the part of an IRB to protect subjects, in addition to its duties to the institution and to HEW.

These various roles of IRB's have, as noted earlier, become widely accepted among research scientists throughout the world. Such review is now performed for clinical investigations that do not involve institutionalized patients or subjects. Thus, it may no longer be strictly appropriate to call the process "institutional review." Indeed, in many situations other names are used, such as "human experimentation committee" and "clinical investigations review board"; FDA itself conducts review of all human studies funded by the agency through its "Research Involving Human Subjects" or "RIHS" Committee. Committee and boards to review clinical investigations may be created and appointed under 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, or 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. Because of the lack of any consistent terminology in this area, and in view of the widespread current use of the phrase "institutional review," the Commissioner has elected to adopt that phrase in this proposal. However, the Commissioner advises readers not to interpret this usage as limiting the intent of this proposal to research involving institutionalized subjects or conducted by an institution; likewise, the term "institution," as used in this notice, is not limited to hospitals and other health-care establishments. The Commissioner welcomes comments suggesting more understandable and comprehensive terminology for use in subsequent notices and orders.

In addition to the generally accepted purposes for IRB review of clinical investigations involving humans, the Commissioner seeks two new goals in this proposal. First, local IRB review can provide ongoing review of an investigation to assess, for example, conformity with the approved protocol, including any approved amendments. Ongoing review enhances protection of subjects by assuring that any changes in protocol are reviewed and approved in advance. Essential to the decision to authorize exposure of humans to risk is a conclusion on the Potential benefits to the subjects and/or to scientific knowledge. Any action or failure to act during the investigation that adversely affects the ability of the investigation to yield these benefits may, as a consequence, destroy the justification for the risk. Further exposure of humans may no longer be warranted, even though no change in the actual risks has occurred. Thus, ongoing review includes more than evaluating reports of new safety concerns; it may cover other aspects of the conduct of the clinical investigation.

Second, apart from subject protection, continuing review of an ongoing clinical investigation by an IRB can provide FDA with greater confidence in the quality and integrity of the data submitted at the conclusion of the investigation. As noted earlier, and discussed in detail in the preamble to the good laboratory practices proposal, FDA, the Congress, and others have recently become quite concerned about the validity and reliability of scientific data on the safety and effectiveness of products regulated by FDA. Although much of the concern has focused on long-term toxicology testing in animals, the substantial increases in

FDA's budget and operating resources included a mandate that the agency assure the quality and integrity of data generated by studies in humans as well. It immediately appeared, from past experience with IRB's and from the lack of other available local independent processes to examine ongoing research, that IRB's could assist FDA in carrying out this mandate. The Commissioner does not intend, however, that IRB's undertake major new responsibilities to assure data validity. Rather, the agency contemplates that the present activities or IRB's in ascertaining adherence to approved protocols, reviewing proposed modifications in protocols, and considering the capability of individual investigators and of supporting facilities to carry out protocols, will serve as an important adjunct to other programs that FDA is undertaking to increase its assurance of the reliability of clinical scientific data. These programs include development of regulations governing the conduct of clinical investigators and the obligations of sponsors and monitors of clinical investigations proposed in the FEDERAL REGISTER of September 27, 1977 (42 FR 49612), more extensive FDA oversight of ongoing clinical investigations, and more frequent in-depth audits of data presented to the agency.

UNIFORM FDA STANDARDS FOR INSTITUTIONAL REVIEW BOARDS

For the reasons described earlier, the Commissioner has elected to propose a single set of standards applicable to all IRB's involved in the initial review, approval, and continuing review of clinical investigations involving human subjects that require prior FDA review or that are subsequently submitted to FDA in support of an application for a research or marketing permit. This regulation, if adopted, may not eliminate the need in the future to propose additional requirements relevant to the particular article under study, but it will reduce the potential for duplicative and inconsistent regulations or interpretations of policy. The Commissioner recognizes that a single IRB may, at any one time, be reviewing investigations on a variety of products that are regulated by several of the separate bureaus of FDA, e.g., Bureau of Drugs, Bureau of Biologics, and Bureau of Medical Devices. In addition, the IRB may also be reviewing the same or other investigations subject to institutional review requirements of HEW or other Federal departments or agencies. A uniform standard will thus ease the burdens on these boards in complying with the applicable regulations.

To achieve this objective, the Commissioner proposes to add a new Part 56 to Title 21 of the Code of Federal

Regulations to be entitled "Institutional Review Boards." This proposed new part will be codified in "Subchapter A—General Provisions" of FDA's regulations, thereby applying to all regulated products that are involved in human experimentation. This proposal revises and extends current FDA standards on IRB review to most investigations involving human subjects when such investigations are regulated by or submitted to FDA, lists definitions applicable to the part, presents the requirements for the organization and operation of an IRB, and establishes standards and procedures for taking appropriate regulatory actions in the event of noncompliance with these regulations. Additionally, this proposal contains specific amendments needed for conformance to existing FDA regulations.

To assure uniform standards, any clinical investigation required to have IRB review would be within the scope of the part, whether the investigation required the prior review of any of the bureau of FDA, e.g., Drugs, Biologics, or Medical Devices, or whether the investigation did not receive prior FDA review but was subsequently submitted, or held for FDA inspection, in support of an application to one of those bureaus, or to the Bureau of Foods or the Bureau of Radiological Health. This statement of scope is set forth in proposed § 56.1.

The particular requirements in proposed part 56 are based upon: (1) The current regulations regarding institutional review for investigational studies on new drugs (set forth in 21 CFR 312.1(a)(2), form FD-1571, item 10.c.; 21 CFR 312.1(a)(12), form FD-1572, item 3.; and 21 CFR 312.1(a)(13), form FD-1573, item 2a.) (the "IND regulations"), (2) the experience of the Bureau of Drugs and the Bureau of Biologics in administering these regulations, (3) the proposed regulations regarding institutional review for investigational studies on certain medical devices for human use published in the IDE proposal, (4) comments received on the IDE proposal, and (5) regulations regarding institutional review for clinical studies funded or supported by HEW (45 CFR Part 46, Subpart A).

CIRCUMSTANCES IN WHICH AN IRB IS OR IS NOT REQUIRED

Under the IND regulations, IRB review is required whenever the human subjects involved in the clinical investigation are institutionalized or whenever the investigation is conducted by an individual affiliated with an institution that assumes responsibility for the investigation. The IDE proposal followed these two principles and added a third: IRB review is required whenever the investigation is

conducted in an institution that has an IRB meeting FDA standards (proposed § 812.60(a)(3)).

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. Therefore, the Commissioner is proposing in § 56.2(a) to make IRB review and approval a general precondition to an application for a permit to conduct a clinical investigation that is subject to requirements under section 505(i), 507(d), or 520(g) of the act for prior submission to FDA for review, and in some cases approval, before the investigation may be commenced. The Commissioner further proposes in § 56.2(b) that FDA generally will not consider any data or information that has been derived from a clinical investigation in support of an application for a research or marketing permit unless the investigation was conducted under an IRB. This rule would not mean that the results of the investigation need not be submitted to FDA. The usual rule that all data and information relevant to a particular article, e.g., a proposed or marketed product, must be submitted remains in effect. Finding that the investigation is not acceptable in support of an application for a research or marketing permit means that the agency will not authorize further testing or further marketing if the claim for safety or effectiveness of the product is based upon that investigation. This approach reflects current agency policy: even in situations where the scientific validity of an investigational drug study is not in question, FDA may receive data but not use them in support of a decision to approve testing or commercial distribution of a drug because of ethical improprieties in the conduct of the study. (21 CFR 312.20.)

The Commissioner recognizes that there may be situations in which the IRB requirement may be unnecessary, redundant, or contrary to the interests of a subject. For example, a late "phase 3" drug study will frequently involve several investigators treating noninstitutionalized individuals in separate areas under the same protocol; multiple review is extremely burdensome and, by this time, the drug will usually have been studied in several settings employing IRB's. Or, for another example, in an emergency FDA may be asked to add an investigator to a particular investigation to provide the test article to a single patient only; prior IRB review would delay administration of the article and might jeopardize the subject's health. The Commissioner therefore proposes in

§ 56.2(c) to waive the IRB requirement in certain specified situations and to accept an application for waiver in other situations upon a showing that the requirement is not necessary either for protecting the subjects involved or for assuring the validity or reliability of the scientific data. The section provides, however, that the requirement will not be waived in three situations; (1) When the clinical investigation involves institutionalized human subjects; (2) When the clinical investigation is conducted on the premises of, or utilizes personnel or resources of, an institution having an IRB meeting FDA's standards; and (3) When the Commissioner finds that the risk to the subjects in the investigation justify utilizing an IRB review.

The Commissioner is also proposing to waive the requirements for IRB review for all studies that were commenced prior to, and that are to be completed within 1 year following, the effective date of these proposed regulations and were not otherwise required under FDA regulations to have such review. This "grandfather clause" will avoid rejection of studies that would result from a retroactive application of the IRB requirements.

In addition to expanding the types of clinical investigations covered, the Commissioner emphasizes that the major change in this proposal from existing investigational new drug (IND) regulations is to require institutional review prior to submission of a proposed study that is subject to IND or investigational device exemption (IDE) requirements. The current IND requirements merely require an assurance that IRB review will be obtained prior to actual commencement of the investigation. The change is proposed to enable FDA to rely on IRB's to screen out studies that would not be performed even if FDA reviewed them favorably, and to provide FDA with better information on the IRB's being utilized by sponsors and investigators under IND's and IDE's.

DEFINITIONS

Section 56.3 contains proposed definitions for all of the special terms used in part 56. Many technical terms can be variably or imprecisely interpreted by persons affected by the proposed regulations; these terms are defined to provide a common basis of understanding for the agency, clinical investigators, the regulated manufacturers and other sponsors of clinical studies, and the general public. In addition, other definitions have been proposed for more precisely describing the extent and applicability of the proposed regulations.

In Proposed § 56.3(a), the term "act" is limited to the Federal Food, Drug, and Cosmetic Act, as amended. This is

consistent with definitions appearing elsewhere in FDA's regulations. Other statutes, when discussed, will be mentioned by name, e.g., the Public Health Service Act.

A new definition required by the decision to make these proposed regulations agencywide in scope is the term "application for research or marketing permit" in § 56.3(b). This definition includes all of the various requirements for submission of scientific data and information to the agency under its regulatory jurisdiction, even though in certain cases no permission is technically required from FDA for the conduct of a proposed activity with a particular product, i.e., carrying out research or continuing to market a product. The term is intended solely as a shorthand way of referring to at least 22 separate categories of data and information that are now, or in the near future will become, subject to requirements for submission to the agency.

To facilitate further the applicability of a single set of regulations to all studies involving products or articles coming within the agency's purview, the Commissioner is proposing in § 56.3(c) to describe each such study as a "clinical investigation," which is defined as any experiment involving a test article (defined below) which experiment involves human subjects and either: (1) Is subject to requirements under sections 505(i), 507(d), or 520(g) of the act for prior submission to FDA for review, and in some cases approval, before it can be commenced, or (2) is not subject to requirements for prior submission but the results of which are intended to be later submitted to, or held for inspection by, FDA as part of an application for a research or marketing permit. Within the category of clinical research, the definition excludes studies that do not utilize any test articles, or do not utilize them in a manner that requires prior FDA approval or subsequent FDA review because the studies are not regulated by or intended to be submitted to FDA. The definition also excludes studies that do not involve human subjects.

The terms "institution," "institutional review board," and "institutionalized subject" are defined for the first time in proposed § 56.3 (d), (e), and (f). Although since 1971 FDA has had a requirement that clinical drug investigations involving institutionalized subjects be reviewed and monitored by an institutional review committee or board, no guidelines defining the outer limits of these concepts have been issued.

The Commissioner proposes that the definition of "institution" include any corporation, scientific or academic establishment, or government agency that engages in the conduct of re-

search on human subjects or in the delivery of medical services to individuals; this definition would therefore include: a university that performs research with students, a retirement home that primarily provides housing and personal care to the elderly but also cares for health needs of residents, and a manufacturer that uses its employees as subjects in the course of product development.

The term "institutional review board" is defined as any board, committee, or other formally organized group created to review research involving human subjects, approve the initiation of such research, monitor its conduct, and when necessary suspend or terminate the research. The Commissioner notes that the use of the word "board" reflects terminology of the National Research Act of 1975 (Pub. L. 93-348), HEW regulations (45 CFR Part 46), and discussions of the National Commission on the Protection of Human Subjects in Biomedical and Behavioral Research. However, the Commissioner also recognizes that existing FDA regulations, e.g., 21 CFR 312.1, use the term "committee" as does section 520(g) of the act. The Commissioner believes there is no practical difference between the two words and has elected to follow Departmental terminology.

An "institutionalized subject," as defined, includes two categories: First, any individual who is voluntarily confined on the premises of, and in the care of, an institution for more than 1 day; outpatients are excluded from the definition in keeping with existing FDA policy. Second, any individual involuntarily confined for any period of time in an institution such as a penal facility or a hospital by civil commitment. Because of the involuntary nature of the confinement and the general absence of any therapeutic need for an experimental article, the Commissioner believes the IRB protection should apply in every such situation. Thus, these proposed regulations will continue to require institutional review of all clinical investigations involving an institutionalized subject.

Proposed § 56.3(k) defines "subject" as any individual who is or becomes a participant in a clinical investigation, either as the recipient of the test article or as a control. The term also includes both healthy or normal individuals and patients to whom the test article might offer a therapeutic benefit. This definition is in accord with past FDA policy. The term is limited to human beings.

Other proposed definitions include terms to describe those who initiate and carry out clinical investigations: "sponsor," "investigator," and "sponsor-investigator." The word "sponsor" is currently defined in 21 CFR 310.3(j)

and 510.3(k), but the Commissioner believes this definition is unsatisfactory in that it fails to distinguish the other commonly used word "investigator," which is not defined. While these terms are widely understood, their precise meanings are difficult to express. The key distinctions seem to lie between one who initiates the project (the sponsor) and one who actually conducts the study (the investigator). These distinctions have been incorporated in the proposed definitions, in proposed § 56.3 (g), (h), and (i), together with a further distinction: investigators must be individuals, while sponsors are defined as "persons," which term includes an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit thereof, and any other legal entity. The Commissioner believes that these distinctions will clarify the participants' respective roles and duties.

Many studies, approximately 45 percent of IND's in the Bureau of Drugs, for example, are initiated and actually conducted by the same individual; this investigator may personally carry out the study or may do so with other investigators responsible to him or her. The Commissioner believes it important to identify the hybrid role of the "sponsor-investigator" and, where appropriate in FDA's regulations regarding clinical investigations, to allow special provisions for that role. Thus, proposed § 56.3(j) defines this term. Unlike the term "sponsor," the term "sponsor-investigator" is limited to individuals. For purposes of this proposal, the sponsor-investigator has the obligations of both a sponsor and an investigator.

In § 56.3(l) the Commissioner proposes to define the term "test article" to describe those items being studied that are subject to FDA's jurisdiction and to these regulations. The term includes those new drugs, biologics for human use and medical devices for human use, studies of which require prior review by FDA under an IND or IDE. In addition, the term includes food-additives, color additives, cosmetics, drug products and biological products for human use, electronic products, and medical devices for human use. The broad definition of "test article" is intended to include substances for which clinical investigations are submitted to FDA in support of an application for permission to market a product, but which investigations need not be conducted under an IND or IDE, e.g., studies on food additives or cosmetics, certain drug bioavailability studies described in 21 CFR 320.31, and studies on medical devices for human use not required to be submitted to FDA for prior review under proposed 21 CFR part 812. As noted earli-

er, however, a test article is covered by these regulations only if it is used in a clinical investigation involving human subjects.

REVIEW BY INSTITUTION

The agency has consistently held that review and approval of a proposed clinical investigation by an IRB does not preclude a subsequent decision by the institution itself to reject the investigation. The Commissioner recognizes that factors in addition to scientific validity and ethical acceptability must be taken into account by officials of the institution in deciding whether to authorize a particular investigation. At the same time, agency policy has been that a clinical investigation rejected by an IRB cannot be authorized later by the institution unless the IRB itself rescinds the rejection. In the absence of such a prohibition, the board would become purely advisory and its responsibilities eliminated. These principles are restated in proposed § 56.8. Comments received on the IDE proposal suggested that an institution be allowed to create a "super-IRB" or an "appellate IRB" which could reverse or overrule decisions of more particularized IRB's, i.e., those decisions dealing with a particular type of test article. The Commissioner advises that the agency has no objection to an arrangement for a full committee and specialized subcommittees if both the parent IRB and the particularized "sub-IRB's" meet the requirements of part 56. Appeals of adverse IRB determinations to other institutional bodies that do not meet the requirements of part 56, however, would not be allowed under the proposed regulation. (See also the discussion of proposed § 56.34 below.) The National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, created by mandate of the National Research Act of 1975, has received many comments relating to an IRB appeal mechanism. The Commissioner advises that FDA will carefully review the recommendations of the National Commission in this area once they are published and propose any appropriate changes in FDA regulations.

ORGANIZATION AND PERSONNEL

Proposed subpart B establishes general requirements for the organization and composition of an IRB. Most of these proposed requirements follow existing FDA and HEW requirements. The board must be composed of at least five persons with varying backgrounds. To assure sufficient diversity to evaluate the proposed clinical investigation in terms of science, law, professional ethics, and community attitudes, no IRB shall be composed entirely of members of a single profes-

sional group, or of only one sex. In addition, diversity in the racial and cultural composition of the IRB is required. Ideally, the membership would reflect both general competence in scientific matters and sensitivity to ethical concerns. Proposed § 56.21(a) describes the types of individuals who would contribute to this goal: Physicians, lawyers, clergy ethicists, consumers, social scientists, other scientists and nonscientists. This listing should not, however, be interpreted as requiring one individual from each category. The IDE proposal referred to scientific expertise to evaluate each particular proposed investigation. Comments objected that this would necessitate a large number of medical or other scientific specialists as members to assure such expertise. The Commissioner has revised this language to follow more closely current HEW regulations, so that the section requires "professional competence necessary to comprehend the scientific nature of the investigation." This revision should alleviate many of the concerns expressed by the comments.

Proposed § 56.21(b) requires that the records of an IRB identify each member by name, earned degrees, occupation and title, and other information sufficient to describe each member's chief anticipated contribution to the boards deliberations.

Proposed §§ 56.25 and 56.26 adopt from existing HEW regulations two types of requirements to protect the independence and objectivity of an IRB. Section 56.25 that a board may not consist entirely of officials or employees of the institution in which the clinical investigation is to be performed. Section 56.26 excludes any member of the board who is involved in the investigation itself from participating in the IRB's deliberations, except to respond to requests for information. In addition, no investigator or sponsor shall participate in the selection of members for an IRB to review the sponsor's or sponsor-investigator's proposed investigations, unless expressly permitted by FDA upon a showing that such participation is essential. Other conflicting interests are also forbidden, and responsibility is left to the IRB to determine whether a member has a conflicting interest. Both sections provide that the records of an IRB identify any relationships between members and institutions, sponsors, and investigators and the extent to which a member participated in reviewing an investigation in which he or she had a conflicting interest.

Comments on the IDE proposal questioned whether compensation by a sponsor for the administrative expenses of an IRB and/or the services of the members of an IRB would be

considered to violate the section analogous to proposed § 56.26(a). The Commissioner believes that reimbursement for IRB expenses probably should be permitted. Extension of an IRB concept to areas where it has not been primarily used will necessitate more IRB activity and consequently more administrative expenses for documenting activities, recordkeeping, liability insurance, and similar overhead expenditures. It is not reasonable to expect that these new costs will always be borne by the institutions or bodies that create and operate the IRBs. The Commissioner is more concerned about payment by a sponsor, directly or indirectly, for the services of IRB members. The difficulties of locating individuals willing to serve on IRB's, especially persons not affiliated with the institution, may be increased by requiring more clinical investigations to be reviewed by IRB's. At the same time, the potential problem of allowing reasonable compensation appear serious. The Commissioner does not propose, in this notice, any specific resolution of either the question of administrative expenses or the matter of member compensation; comments are especially invited to address these points, describing whether a need exists for financial assistance for sponsors and, if a need exists, ways to permit it while minimizing any conflicts of interests.

The Commissioner recognizes that an IRB may not be large enough or adequately composed to consider the scientific and safety issues of every complex and specialized clinical investigation. In such cases, the committee may wish to use a subcommittee or consultants to assist its review, provided the members of the subcommittee or the consultants also do not have any conflict of interest. The Commissioner intends to allow for such flexibility, and proposed § 56.34 explicitly authorizes use of nonvoting consultants.

PROCEDURES FOR REVIEW OF CLINICAL INVESTIGATIONS BY AN IRB

Subpart E sets forth the general and specific procedures to be followed by an IRB in its review of proposed and ongoing clinical investigations. Maximum flexibility in the operations of the board is intended. Thus, the board may have its own procedures for conducting reviews and for reporting actions to the investigator, to the parent institution, and, where appropriate, to the sponsor. Most of the proposed requirements reflect existing FDA or HEW regulations, or only modest extensions of these guidelines.

The first requirement, contained in proposed § 56.80, states the obligation of the board to put its procedures in writing, and to follow those proce-

dures. Comments on the IDE proposal suggested that discretion be left to the institution to decide whether it, or its IRB, should promulgate the board's procedures. The Commissioner has adopted this suggestion.

Proposed § 56.82 describes requirements for a quorum by which an IRB is to do business. First, all significant business, such as approval or suspension of an investigation, must be done by a quorum, as described in the regulations. Second, a quorum must consist of a majority of the members, unless the board has 20 or more members, in which case 10 members shall constitute a quorum. Third, at least one licensed physician, one scientist, and one nonscientist, e.g., lawyer, clergy, or consumer, must be present for a quorum. Finally, a quorum shall be determined by the members present at a meeting; proxy votes, telephone conferences, and votes by mail are not acceptable methods of carrying out important IRB activities. Responses to similar sections in the IDE proposal expressed concern that requiring certain types of individuals to be present for a quorum could produce a veto power on behalf of one person. Often cited was the lay representative, who, by staying away, could prevent IRB action. No specific examples of such incidents were provided. The Commissioner doubts that board members would be that irresponsible and believes that any pattern of such conduct might justify removal of the offending member from the board. The Commissioner therefore concludes that the presumed problem can be dealt with and that the general goal of balanced participation in IRB decisions justifies the quorum requirement. Other comments on the IDE proposal expressed concern that the quorum requirement could prevent IRB action in emergency situations, because of the possible unavailability of members who are not employed by the institution, e.g., lay members. The Commissioner does not believe that this problem is great. If unexpected toxicity appears with use of the test substance, emergency action to suspend the study to protect subjects can be taken by officials of an institution, upon advice of the available IRB members, without formal IRB action. Emergency action to deviate from a protocol in order to reduce or eliminate a risk to subjects will not require prior IRB review and formal board action under FDA regulations governing IRB's; these regulations (21 CFR 312.1(a)(2) FD-1571 item 10.c) appear to provide sufficient flexibility to deal with emergencies. The Commissioner believes other actions should be taken by a balance quorum. Further comments are invited on these issues, however.

As described in proposed § 56.85, the IRB shall base its evaluation of a clinical investigation upon a review of the investigational plan or protocol agreed upon by the investigator and the sponsor, reports of pertinent past investigations involving the test article, the materials to be used in obtaining consent of subjects, and any other information that the board considers necessary to a thorough evaluation of the investigation. Upon receipt of a submission, the IRB shall notify the investigator or sponsor, as appropriate, of the date of receipt and shall inform him or her that the investigation may not begin until the board has approved it and until the investigation otherwise meets FDA requirements, e.g., an IND or IDE has been filed and no objections have been received from FDA. The board may ask for additional information and may recommend modifications or conditions to the investigator before deciding to approve or reject the investigation.

The IRB should review the protocol and supporting information and decide, as soon as possible after receipt of the information, whether to approve or disapprove a proposed clinical investigation. The IRB shall notify, in writing, the investigator, the institution, and, if appropriate, the sponsor of the board's decisions. If the board disapproves the investigation, its written notification shall include a statement of the reasons therefor, as provided in proposed § 56.85(e).

A current requirement, reiterated in § 56.87(a) of this proposal, mandates the IRB to review each ongoing clinical investigation at intervals appropriate to the degree of risk, but in no case less often than once a year. The board may, as part of its continuing review of approved investigations, decide that its approval of a particular investigation should be withdrawn and the investigation be suspended or terminated; this is provided for in proposed § 56.87(b). This decision may be made at any time during the investigation and should occur as soon as possible after discovery of the grounds for such action. If an IRB decides to suspend or terminate an investigation, it shall notify in writing the investigator responsible for the conduct of the investigation and the institution of its decision, including a statement of the reasons for withdrawing its approval. It may also, if appropriate, notify the sponsor of the investigation.

CRITERIA FOR REVIEW

An institutional review board must evaluate a clinical investigation not only in terms of its scientific validity and medical soundness, but also in terms of institutional commitments and regulations, applicable law, standards of professional conduct and prac-

tice, and community attitudes. Because of the many factors a board must consider in determining to approve or disapprove a study, FDA has not in the past attempted to provide criteria for IRB approval or disapproval of investigations. The enactment of the Medical Device Amendments of 1976, however, established a new role for IRBs in the regulatory scheme and specifically provided that FDA require prior submission of IDE studies to a board unless "the process of review by [an IRB] is inadequate * * *" (section 520(g)(3)(A)(ii)(II) of the act (21 U.S.C. 360j(g)(3)(A)(ii)(II))). It has therefore become necessary for FDA to provide some guidance in defining what an IRB review must consist of to be adequate under this section of the act. This was originally contained in § 812.66 (e) and (f) of the IDE proposal and was the subject of many comments. The Commissioner believes that it is appropriate to extend IRB review standards, as modified, based on the comments, to all IRB's participating in clinical investigations subject to proposed part 56. Proposed § 56.90 does not attempt to include all the grounds on which a board might base such decisions: proposed § 56.90(a) authorizes an IRB to disapprove a study on any of the grounds within the scope of review conferred on the board by the institution that created it. The Commissioner recognizes that situations may arise where matters that would be of great concern to an IRB might be insufficient for action by FDA, e.g., where the study is at odds with local ethical and moral standards or where the board's responsibility extends into areas such as allocating financial or other resources among research programs in the institution.

In contrast, proposed § 56.90(b) outlines those factors that mandate disapproval in every situation, because they directly affect the validity of the clinical investigation or the rights and safety of the subjects. The Commissioner proposes to set forth the following criteria as specific grounds necessitating disapproval of a proposed clinical investigation by the board:

A board shall disapprove, and may suspend or terminate, a clinical investigation if it finds that:

(1) The information on the basis of which the board is evaluating the study is found to contain any untrue statement or omission of a fact material to the board's evaluation. Clearly, a reliable determination of the safety of the test article for purposes of initiating human studies cannot be made if the data on which such determination is to be made are either false or incomplete.

(2) The reports of prior investigations with the test article are found in-

adequate to support a conclusion that clinical trials are reasonably safe.

(3) The investigator responsible for the conduct of the investigation does not possess the scientific training and experience needed to conduct an investigation of the safety, and, where appropriate, effectiveness of the test article.

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

(5) The clinical investigation exposes the human subjects to undue risks. In assessing whether the risks to the subjects are undue, the board shall consider, among other factors, whether the sum of the benefits to the subjects and the importance of the knowledge to be gained justify allowing the subjects to participate, whether the subjects will be adequately protected, whether informed consent will be obtained, and whether the investigation will be subjected to continuing review by the IRB. This provision parallels HEW regulations in 45 CFR 46.102(b).

(6) The investigation does not conform to, or is not being conducted in accordance with, the understandings of the board and the requirements of FDA (e.g., IND and IDE regulations and informed consent standards).

The Commissioner recognizes that, in certain cases, the facts which would require the IRB to disapprove an investigation might not come to the board's attention until after it had already approved the investigation. In these cases, proposed § 56.90(b) provides that the board may suspend or terminate approval of that investigation, but does not mandate such action because of the complexities relating to the ongoing care of subjects, particularly patients, in the study. The decision to suspend or terminate an investigation involves additional factors such as risks to subjects from the action, the need for availability of continuing medical care for subjects in the event of suspension or termination, and the right of subjects to participate in the decision. The board is directed in proposed § 56.92 to consider these matters in determining whether to suspend or terminate a clinical investigation and what should be done regarding continuing observation of subjects.

RECORDS AND REPORTS

An IRB is required to prepare and maintain records on its activities with regard to individual clinical investigations. This obligation, which is current FDA policy, is proposed to be set forth in § 56.185. Among the records that must be kept are the materials submitted to the board by the investigator or sponsor, the information regarding

board members required by subpart B of proposed part 56, minutes and other records of meetings, including a written summary of every discussion and decision on a substantive issue, recommendations and actions of the board, and dated reports of successive reviews.

Current FDA regulations require that IRB records be retained 3 years after the completion or discontinuance of an IND study. This is not consistent with the record retention requirements applicable to the IND investigators. The Commissioner proposes in § 56.195 to eliminate this discrepancy, and to clarify other minor ambiguities in the existing regulations. As proposed, all data and information required by these IRB regulations shall be retained for one of the following three alternative periods, whichever is shortest:

(1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the clinical investigation were submitted, is approved by FDA;

(2) A period of at least 5 years following the date on which the results of the clinical investigation are submitted to FDA in support of an application for a research or marketing permit; or

(3) In other situations (e.g., where the clinical investigation does not result in the submission of data in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.

COMPLIANCE AND ENFORCEMENT

Defining the role that IRB's play in reviewing proposals for and the performance of studies involving human subjects, to protect the rights and safety of subjects and to help assure that the data produced are valid and useful for the scientific and regulatory decisions made by FDA, constitutes a major clarification of FDA policy. It does, however, raise the question of how to assure that IRB's fulfill the standards found to be necessary or desirable by FDA, and what to do if a board fails to meet these standards. Several options are available, and each has an appropriate place in FDA's compliance program. The regulatory sanctions available for use in cases of noncompliance include:

(1) Notifying the IRB of deficiencies observed during an inspection. It will be the practice of an FDA investigator to do this before leaving the premises upon concluding an inspection.

(2) Issuing more formal warnings that important discrepancies between the conditions observed and regulatory standards must be corrected for

the IRB to avoid more serious regulatory action. This step generally will be accomplished through formal regulatory correspondence.

(3) Determining that data from one or more specific clinical investigations will not be considered by FDA in support of an application for a research or marketing permit. This determination would not mean that the data from completed studies need not be submitted to FDA. The usual rule that all data and information relevant to a particular article, e.g., a proposed or marketed product, must be submitted remains in effect. A finding that a clinical investigation is not acceptable in support of an application for a research or marketing permit means that the agency will not authorize further research or future marketing if the claim of safety or effectiveness of the product, or other condition necessary for such research or marketing, is based upon that investigation. Rejection of a particular investigation from consideration in support of an application is provided for by statute in the procedures and criteria for determining whether the application is approvable under the act or the Public Health Service Act. For example, a determination that a faulty study precludes a finding that a new drug is safe would be made in accordance with the procedures set forth in section 505(d) of the act and 21 CFR Part 314. Accordingly, no special procedures need be prescribed. The standards for IRB organization and operation thus represent amplification of the legal requirements regarding evidence of safety and, where applicable, effectiveness, necessary to approve an application for a research or marketing permit.

(4) Disqualifying an IRB as an acceptable reviewer of clinical investigations. Disqualification which the Commissioner believes should be uncommon, would mean that no new clinical investigation subject to prior submission to FDA, i.e., via an IND or IDE, would be authorized if it were to be conducted under review of the board. Further, it would mean that similar ongoing investigations under its review could be terminated or suspended until transferred to another board for review. It would also mean that data and information from any clinical investigation reviewed by the board might not be considered in support of an application for a research or marketing permit. In this case, the determination that data generated under the review of the board are not acceptable in support of an application is not limited to a particular study but may extend to all investigations reviewed by the board that may have been affected by the substandard acts or omissions. This sanction would be uti-

lized when the deficiencies found with an IRB are of such a widespread or fundamental nature that the rights and safety of subjects in, or the quality and integrity of, a number of investigations reviewed by the board have probably been compromised, or when the IRB has failed to comply with FDA's standards after previous warnings from FDA.

A similar concept on the sanctions available to deal with noncomplying IRB's in the IDE proposal evoked probably more comment, and more intense objection, than any other aspect of that proposal. The Commissioner believes that this was due, at least in part, to an inadequate explanation of the agency's need for such a sanction and to a misapprehension of the frequency with which disqualification might be used. The Commissioner believes disqualification is an important alternative to rejection of specific investigations and legal prosecution (discussed below) because it can reduce by consolidation the number of FDA investigations and administrative proceedings that might be required if FDA acted only on a study-by-study basis. This mechanism also can permit the agency to accept the results of an investigation that it might otherwise have to reject for lack of any alternative sanctions; this would result in repetition of the study with an unnecessary risk to human subjects. Disqualification obviates using judicial proceedings except for the most deliberate or flagrant offenses. Unlike rejection of a specific investigation and legal prosecution, disqualification is not explicitly provided for by statute, although it is implicit in section 520(g) of the act with respect to IRB review of device investigations. This necessitates promulgation of regulations describing the procedures for and consequences of imposing this sanction; much of the remainder of this preamble is devoted to this matter. This extensive discussion should not, however, be read as implying that disqualification is the exclusive or even the primary administrative action for non-compliance with these regulations. Disqualification will be used only when the Commissioner concludes that lesser sanctions have not been or probably will not be effective in achieving compliance.

(5) Obtaining a court injunction against further violations of the act and implementing regulations. This form of judicial action has not previously been utilized by FDA to enforce the regulations regarding clinical investigations such as standards regarding IRB's, but may be considered in the future if appropriate.

(6) Recommending prosecution of a board, its institution, the investigator and/or the sponsor of a clinical inves-

tigation for violations of Federal criminal laws, including violations of the act and/or the United States Criminal Code (e.g., 18 U.S.C. 1001). Because in most instances the board is not under a direct statutory obligation to FDA, the circumstances in which this sanction might be utilized are few in number and extraordinary in nature.

The Commissioner is aware of the wide range of severity in these sanctions. He has directed the preparation of a compliance program identifying the administrative and legal sanctions which FDA may invoke upon findings of various types of noncompliance. These sanctions and the internal procedures by which they will be applied will be contained in an FDA compliance program guide to be made publicly available upon its completion, now projected for late this year. An understanding of this document should assuage fears that boards not in compliance with the IRB standards will be subject to unreasonable penalties.

DISQUALIFICATION OF AN IRB

Food and Drug Administration experience in enforcing regulations pertaining to the conduct of persons carrying out clinical investigations subject to the agency's jurisdiction has indicated a need for administrative sanctions in addition to court enforcement proceedings and rejection of data on a study-by-study basis. Criminal prosecutions are serious, demand significant resources, and may be inappropriate when the noncompliance does not reflect criminal intent, bad faith, or gross negligence. Study-by-study audits and proceedings to reject data also cost much in time and resources; they may be redundant if the violations are pervasive, or inappropriate if the data are scientifically valid. For these reasons, FDA has in the past used another sanction, termed the "disqualification process," to obtain compliance with the requirements regarding clinical investigators (see 21 CFR 312.1(c) and 511.1(c)).

Disqualification, in the case of clinical investigators, has simply meant that an investigator is no longer eligible to receive investigational drugs under the investigator's own or someone else's IND. It imposes no fine; it attaches no financial liability, except to the extent that an investigator may be unable to fulfill a research contract; it does not revoke a medical license or institutional privileges. The disqualification of an investigator is intended to achieve two objectives: First, it precludes a disqualified investigator from access to any test article until the investigator can demonstrate his or her ability and willingness to conform to the standards for conducting clinical investigations essential to

assure scientifically sound and ethical research; second, disqualification provides a mechanism for refusing to accept data prepared by the investigator in support of an application for a research or marketing permit. Disqualification has not been used with great frequency by FDA.

After reassessing FDA's experience with disqualification, evaluating the available alternatives for enforcement of these regulations, reviewing and the comments received on the IDE proposal, and considering the factors just discussed, the Commissioner has tentatively decided that the disqualification mechanism should continue to be used by FDA in all areas of clinical investigation and for all involved parties, including IRB's. In addition to these factors cited in favor of this sanction, many participants in the development and marketing of products regulated by FDA, including sponsors, investigators, and agency officials, are familiar with this process because of its use in the IND process; as IRB's gain experience with FDA, the Commissioner expects that they will better understand the disqualification mechanism and be less anxious that it may be used capriciously.

The proposed regulations governing disqualification of IRB's are set forth in subpart K of part 56. Proposed § 56.200 codifies the purposes of disqualification to state clearly the meaning of this administration action.

Comments received on the IDE proposed disqualification regulations, and statements made at a public hearing before the Commissioner on the proposed disqualification regulations regarding nonclinical testing facilities as part of the good laboratory practice rulemaking initiated in the FEDERAL REGISTER of November 19, 1976 (41 FR 51206), objected to the way in which the grounds for disqualification were set forth in these documents. Comments and statements are on display in the office of the Hearing Clerk, Food and Drug Administration, as part of the records of those proceedings (docket No. 76N-0324 and 76N-0400, respectively). The Commissioner concurs that, as drafted, those proposals implied that disqualification could occur as the result of insignificant deficiencies in meeting regulatory standards, and suggested that FDA might in the future invoke this sanction far more frequently than indicated in the preambles to those proposals.

To clarify FDA's intent in proposing the disqualification mechanism and to minimize the possible abuse of this sanction in the future, the Commissioner proposes, in § 56.202, a more restrictive statement of the grounds for disqualification of an IRB. An IRB may be disqualified only if the Commissioner finds all three of the follow

ing: (1) That the board failed to comply with one or more of the standards set forth in part 56 or in any other FDA regulations regarding standards for IRB's, e.g., any supplemental requirements in the IND or IDE regulations; (2) that the noncompliance adversely affected the validity of the data produced in the investigation, and/or the rights and/or safety of the human subjects; and (3) that other lesser regulatory actions, such as warnings or rejection of data from individual clinical investigations, have not been or probably will not be adequate to achieve compliance by the board. These requirements assure that the sanction will not be used in trivial situations but only when the violation compromised the integrity of the investigation or the interests of the subjects. The proposed regulation further requires the Commissioner to consider the availability, and past or probable effectiveness, of lesser sanctions as alternatives to disqualification. It would not, however, preclude disqualification without a prior warning or other regulatory action where the IRB's activities evidence a deliberate violation of FDA standards or a flagrant disregard of the IRB's obligations.

The Commissioner proposes, in § 56.204, to establish a uniform procedure to be followed by the several FDA bureaus regulating or reviewing clinical investigations on articles subject to FDA jurisdiction. Each bureau will be initially responsible for administering the IRB regulations for the products and substances under its purview, as part of processing applications for research and marketing permits submitted to that bureau. In those cases where the bureau believes that rejection of specific investigations and other remedies is inadequate to achieve compliance, the Commissioner may elect to begin the disqualification proceedings by providing a notice of the proposed action to the board; there would be an opportunity for a regulatory hearing before the Commissioner or a person designated by him; and final action on the proposed disqualification would be taken only by the Commissioner or a person to whom this authority had been officially delegated.

The written notice provided to the IRB upon commencement of a disqualification proceeding shall contain the following items of information, in accordance with 21 CFR 16.22(a). (1) The notice shall specify the facts that are believed to justify disqualification. (2) The notice shall state that the board has an opportunity for a regulatory hearing on the proposed disqualification before the Commissioner, or a person designated by him, and that such hearing will be conducted in accordance with the provisions of 21

CFR part 16, the procedural regulations for regulatory hearings before FDA. (3) The notice shall state the time within which a hearing may be requested, which shall not be less than 3 working days from the receipt of the notice; except in cases where safety of subjects requires immediate action, ample time would be allowed the board to prepare for and appear at the hearing. (4) The notice shall contain the name, address, and telephone number of the FDA official who has been designated by the Commissioner as presiding officer for the regulatory hearing and to whom any request may be filed by registered mail, telegram, telex, personal delivery, or any other mode of written communication.

In the past under the disqualification regulations pertaining to clinical investigators, the Bureau of Drugs has provided an "informal" conference with the officer who issued the notice before the "formal" disqualification hearing (see 21 CFR 312.1(c)(1)). These conferences frequently had many formal trappings, such as stenographic transcripts, and were often followed by the contemplated hearing. This process doubled the time and expense of all parties involved without discernable benefit. The Commissioner has therefore decided not to provide for such an informal conference in these regulations. The procedures proposed should provide adequate flexibility and fairness to all parties.

Comments on the disqualification procedures contained in the IDE proposal objected that the regulatory hearing process denied an adversary hearing, a right to counsel, transcripts, cross-examination, and an appeal mechanism. The Commissioner advises that regulatory hearings under part 16 provide all of those safeguards as well as others essential to due process. Interested persons are referred to those regulations for a complete description of the procedures proposed to be applicable to disqualification proceedings and may comment on the adequacy and appropriateness of these procedures for purposes of disqualification of IRB'S.

If, after the regulatory hearing or after the time for requesting a hearing expires without a request being made, the Commissioner upon an evaluation of the administrative record, makes the findings required for disqualification, he shall prepare and issue a final order disqualifying the IRB. Proposed § 56.206 provides that the final order shall include a statement of the basis for the disqualification. If, on the other hand, the Commissioner determines not to make these findings, he shall issue a final order terminating the disqualification proceeding and shall include a statement of the basis

for his decision to terminate the proceeding.

Once a final order has been issued, the Commissioner shall so notify the IRB and the institution that established it. If the board is disqualified, the Commissioner will also notify, to the extent possible, the sponsor of every clinical investigation subject to an IND or IRB that the IRB reviewed. Because FDA does not usually receive information about other clinical investigations before they are completed and submitted to the agency, it will not generally be possible to notify sponsors of uncompleted studies. Comments on this provision in the IDE proposal requested that the sponsors and/or the investigators of clinical investigations under review by a board be notified at the commencement, rather than the completion, of disqualification proceedings. The justification offered was that these individuals might wish to protect their interest in continuing an investigation or in knowing that the results of the investigation would be accepted by FDA later. The Commissioner is concerned that such notification might lead to excessively complicated multiparty proceedings that are unnecessary. As discussed below, after the decision to disqualify is made, questions regarding the status of ongoing investigations and the acceptability of data will be considered and any interests affected will be heard. The Commissioner is not convinced that every potentially affected sponsor and investigator should be notified every time disqualification of an IRB is proposed, but he invites further comment on this matter. The Commissioner does believe, however, that other HEW agencies dealing with IRB's should be notified of problems promptly. Therefore, proposed § 56.213(c) requires the Commissioner to provide other components of HEW with such information simultaneously with a proposal to disqualify the board.

Once an institutional review board has been disqualified, no new clinical investigation requiring prior review by FDA, as well as institutional review, will be authorized by FDA if it is to be conducted under the review of the disqualified board; this rule is proposed in § 56.210(a). Because the agency has no statutory authority to suspend or terminate clinical investigations not done under an IND or IDE, it will not be possible to deny permission to conduct these investigations when they involve a disqualified IRB.

In issuing an order disqualifying an IRB, the Commissioner must consider what, if anything, should be done regarding ongoing investigations that involve the board. Several options are available: allowing the investigations to proceed for a period of time to permit

completion or to permit corrective actions; limiting the continuation of the investigations to subjects who are already participating; requiring transfer of responsibility for the further review of the investigation to an IRB that is in compliance with FDA standards; or terminating the investigation completely. A special concern is the subject who cannot be safely withdrawn from the investigation because, for example, the subject has an implanted investigational device that must be surgically removed, or because abrupt withdrawal of the investigational drug may create a life-threatening problem. Clearly, some provision must be made for such cases if ongoing investigations are to be suspended upon disqualification of an IRB. The Commissioner does not believe it possible, much less advisable, to require that any particular option be used for ongoing investigations. This choice must be made, on a study-by-study basis, considering the nature of the investigation, the number of subjects involved, the risks to them from suspension of the study, and the need for further review by an acceptable IRB. Section § 56.210(b) of the proposed regulations authorizes, but does not require, the actions that might be taken. The Commissioner specially invites comments on these proposals and suggestions for other ways to address this sensitive problem.

Proposed § 54.210(c) provides that each application for a research or marketing permit, approved or not, that contains or relies upon a clinical investigation conducted under the review of a disqualified IRB may be examined to determine whether the study was, or would be, essential to FDA's decision to approve the application. This authority is also discretionary, and would depend on the types of problems that led to disqualification and the nature of the investigation involved. If it is determined that, without the results of the investigation in question, further clinical trials would not have been allowed or a product license would not have been approved, FDA will then determine whether data from the investigation are acceptable, notwithstanding disqualification.

To avoid FDA's having to audit every such investigation, any study reviewed by an IRB prior to or after disqualification but before reinstatement may be presumed to be unacceptable, and the person relying on the data resulting from the investigation may be required to establish that the data were not affected by the circumstances which led to disqualification. The sponsor or applicant may be required to submit validating information. If FDA determines that the clinical investigation was or would be essential, and is not acceptable, it will be eliminated from the consideration of

the application for a research or marketing permit. Elimination of such data may serve as "new information" justifying termination of an IND or IDE, initiation of the withdrawal of approval of a product license, or the revocation of a product monograph or standard.

Under proposed § 56.210(d), the FDA will not consider, in support of any application for a research or marketing permit, any clinical, investigation begun under the review of an IRB after it has been disqualified. This rule does not, however, relieve the applicant from any requirement under any other applicable statute or regulation that all data and information regarding clinical experience with the article in question be submitted to the agency.

The Commissioner advises that it is not necessary that an IRB be disqualified for the agency to reject consideration of a particular clinical investigation in support of an application for a research or marketing permit. The criteria set forth in the statute and regulations applicable to each type of application, together with the regulations regarding the conduct of clinical investigations, will still be used to evaluate the scientific validity and meaning of the results of each investigation. The agency may apply these regulations to a particular investigation and determine that it is so inadequate in terms of science or ethics that it will not or should not support a claim of safety or effectiveness for a product. If the sponsor of the product wishes to contest this finding, the opportunity to do so will be provided in the procedures for denying or withdrawing the approval of the application.

The Commissioner believes that it is contrary to the public interest to provide a two-step process whereby a particular investigation would be disqualified under procedures similar to those proposed in subpart K of part 56, and then the application itself would be denied under procedures set forth in other regulations. Efficiency and fairness suggest that these issues be resolved at the same time in one proceeding, if that is required. It may be that, although a particular investigation is not acceptable, other data and information in the application will support a product's safety or effectiveness, and therefore no proceeding is necessary to rule on the acceptability of the particular investigation. Likewise, the agency may choose to reject individual investigations without disqualifying an IRB when, for example, the investigation was performed during a period when the IRB was not in compliance with FDA standards, but the IRB has since come into compliance.

The Commissioner further advises that it is likely that the usual formal regulatory action taken for noncompliance will be rejection of individual investigations and that disqualification of an IRB will be reserved for the rare cases where the rejection of a particular investigation is an inadequate regulatory response.

The agency believes that it should affirmatively provide information regarding the disqualification of an IRB to entities having professional dealings with that board, such as other Federal, State or local government agencies supporting research studies. Many objections were received to this aspect of disqualification in the IDE proposal. The Commissioner believes, however, that because a number of Federal agencies have adopted very similar standards regarding IRBs in conjunction with human experimentation supported, by grant or contract, with the taxpayers' dollars, a Federal agency that finds an IRB out of compliance with those standards has a duty to notify its sister agencies. Moreover, the Commissioner believes that providing such information is within the purpose of section 705 of the act (21 U.S.C. 375).

Because the Commissioner recognizes that the consequences of such notice could have a serious adverse effect on the board and its members, he believes that the board and its members must be aware that such notice is one of the results of disqualification. *Cf. Wisconsin v. Constantineau*, 400 U.S. 433 (1971). Proposed § 56.213(a) expressly authorizes FDA to notify other entities when the Commissioner believes that such disclosure would further the public interest or would promote compliance with the applicable FDA standards. This determination is within the discretion of the Commissioner upon consideration of the circumstances justifying the disqualification, any mitigating conditions, and the degree to which other agencies or persons are involved with the ongoing activities of the board. If he gives any notice, the Commissioner shall provide a copy of the final disqualification order, indicate its legal meaning, and state that FDA is not advising or recommending that the person notified take any action upon the matter. A copy of each notification shall be given to the board.

Both the determination that an IRB has been disqualified and the administrative record regarding such determination are disclosable to the public under the Freedom of Information Act (5 U.S.C. 552) and under the FDA public information regulations (21 CFR part 20) as records relating to an administrative enforcement action that has been completed. This is stated in proposed § 56.213(b).

Because disqualification of an IRB may be neither a sufficient nor an appropriate sanction in every case, the Commissioner believes that disqualification must be independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by law. Proposed § 56.215 makes clear, therefore, that FDA may at any time recommend institution of any appropriate judicial proceedings, civil or criminal, and any other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification. This would, of course, include refusing to consider a particular investigation in support of a particular application, the regulatory action that probably will be most commonly used in cases of significant noncompliance with the IRB standards. The agency may also refer the matter to another Federal, State, or local governmental agency for such action as that agency determines to be appropriate.

Disqualification is principally a remedial action to prevent future violations, to assure that the rights and safety of subjects are appropriately protected and that data in support of applications are produced under circumstances that increase the likelihood of their scientific validity. Thus, the Commissioner concludes that disqualification should continue indefinitely until the agency finds that the IRB can and will fulfill the requirements imposed under these proposed standards.

Proposed § 56.219 authorizes the Commissioner to reinstate an IRB, i.e., to determine that it may again review investigations under an IND or IDE, and that data from investigations under its review may once again be considered in support of applications for research or marketing permits, if he finds that the board can provide adequate assurances that it will operate in compliance with FDA standards. An IRB that wishes to be reinstated shall explain to the Commissioner why it believes reinstatement is warranted, and shall provide a detailed description of the corrective actions the board has taken or intends to take to assure that the acts or omissions that led to its disqualification will not recur. The Commissioner may condition reinstatement upon the board's passing a subsequent FDA inspection.

In fairness to the IRB, all persons or organizations notified under proposed § 56.213(a) of the board's previous disqualification must be notified when it is later reinstated; proposed § 56.219 so provides. Once reinstated, an IRB may thereafter review additional new clinical investigations. A determination that an IRB has been reinstated is also disclosable to the public under the Freedom of Information Act and

under 21 CFR Part 20 as records relating to completed administrative enforcement actions.

LEGAL AUTHORITY

The results of literally hundreds of clinical investigations are submitted to FDA each year by persons seeking regulatory action by the agency. To obtain a marketing license, clinical research data are offered to support the safety and effectiveness or functionality of a product, e.g., a food or color additive, or a drug, biologic or medical device for human use. Even where a license is not required or already has issued, such data may be relied upon to demonstrate the bioavailability of a marketed drug, the general recognition of safety of a product, or the absence of any need for premarket approval or a product standard for a device. In evaluating the enormous volume of clinical investigations filed with FDA, many types of scientific and regulatory review must be devoted to these studies apart from determining their ethical and scientific acceptability and their basic validity, e.g., to interpret the results and to evaluate the status of the affected products in light of the results. Given the limited resources within the agency, the Commissioner believes that FDA must have standards to screen out those clinical investigations that are likely to be unacceptable and thus should not be authorized by FDA or that warrant little further evaluation in support of a product application. Promulgating these standards provides one process for making this judgment. While compliance with the requirements for IRB review does not guarantee the ethical or scientific acceptability of, or the validity of data from, a clinical investigation, failure to comply increases substantially the probability that the results will not be useful to FDA. Moreover, as noted elsewhere in this preamble, the regulations reflect principles recognized by the scientific community as essential to sound research involving human subjects. Thus, these standards will assist FDA in identifying those investigations that cannot be permitted to be carried out or considered in support of an application for a research or marketing permit.

Under section 701(a) of the Act, the Commissioner is empowered to promulgate regulations for the efficient enforcement of the Act. Previously, the Commissioner has issued regulations (21 CFR 314.111(a)(5)) for determining whether a clinical investigation of a drug intended for human use, among other things, was scientifically reliable and valid, in the words of the Act: "adequate and well-controlled," to support approval of a new drug. These regulations were issued under section

701(a) of the Act and have been upheld by the Supreme Court (see *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); see also *Upjohn Co. v. Finch*, 422 F.2d 944 (6th Cir. 1970) and *Pharmaceutical Manufacturers Association v. Richardson*, 318 F. Supp. 301 (D. Del. 1970)).

Furthermore, sections 505(i), 507(d), and 520(g) of the Act regarding clinical investigations that require prior FDA authorization, direct the Commissioner to promulgate regulations to protect the public health in the course of those investigations. For the reasons discussed at the outset of this notice, the Commissioner finds that IRB's are an essential element to safeguard the right and safety of human subjects in virtually all studies conducted under those sections of the Act. Section 520(g) of the Act further necessitates the establishment of regulations regarding the functioning of local institutional review committees to review proposed clinical testing of certain medical devices. These proposed regulations are intended to fulfill these mandates.

The Commissioner has therefore concluded that legal authority to promulgate these regulations regarding clinical investigators exists under sections 505(i), 507(d), 520(g), and 701(a) of the Act, as essential to protection of the public health and safety and to enforcement of the agency's responsibilities under sections 406, 408, 409, 502, 505, 506, 507, 510, 513, 514, 515, 516, 518, 519, 520, 601, 706, and 801 of the Act, as well as the responsibilities of FDA under sections 351 and 354 to 360F of the Public Health Service Act.

INSPECTIONS OF INSTITUTIONAL REVIEW BOARDS

It follows from the authority to promulgate these regulations that FDA also has authority to prescribe the terms on which it will accept data generated in a clinical investigation reviewed by an IRB.

Therefore, the agency will not consider data from a clinical investigation in support of an application for a research or marketing permit unless the board that reviewed the investigation consents to inspection by FDA. This rule is set forth in proposed § 56.15(b). The Commissioner believes that this requirement does not infringe on any right or obligations of an IRB or its institution that may, at any time, refuse to consent to inspection or withdraw its consent. In this event, however, FDA will not consider the results of the study in support of an application and may consider disqualifying the board. This action may adversely affect the status of an application submitted by a third person, e.g., the sponsor of a study under a grant or contract; but this is strictly a matter

between those parties. The Commissioner advises all persons who sponsor, under grant or contract, clinical investigations that may be submitted to FDA to consider including provisions regarding FDA inspections in the grant or contract. Such a provision is especially important if the board is not otherwise aware that the results of the investigation may be submitted to FDA.

Inspections of many IRB's will not necessarily be conditioned upon consent. Under section 7049(a) of the act, FDA may inspect establishments, including consulting laboratories, in which certain drugs and devices are processed or held, and may examine research data that would be subject to reporting and inspection pursuant to section 505 (i) or (j), 507 (d) or (g), 519, or 520(g) of the act. (See in this regard 21 CFR 200.10.) Thus, most sponsors and many investigators under IND's and IDE's, and those institutions in which such studies are conducted, would be subject to FDA inspection whether or not they consented.

The Commissioner wishes to point out that since 1971 FDA has exercised authority to inspect IRB's. Between 1971 and 1976, for example, approximately 75 IRB inspections were completed by the Bureau of Drugs. Language in the current regulations regarding FDA's authority has, however, been interpreted by some, e.g., the GAO in its recent report, to mandate periodic inspections. The agency intends to inspect IRB's on both a random basis and in response to particular problems. The number of IRB's inspected and the depth to which they will be audited remain a function of available FDA resources. Therefore, the Commissioner proposes in § 56.15 to restate FDA's authority and at the same time to eliminate any possible interpretation that FDA will inspect IRB's at any preestablished frequency.

The current FDA policies regarding inspection of records of clinical investigations require clarification. During FDA inspections of clinical investigators and institutions in which studies were conducted, agency officials were occasionally refused access to records containing the names of human subjects, on grounds of the confidentiality of the physician-patient relationship and the subject's right to privacy. Numerous questions and objections were also submitted regarding statements about FDA inspections of records regarding clinical investigations made in the IDE proposal. Therefore, the Commissioner finds it necessary to state clearly and publicly when FDA will request access to such records, and if such access is requested, how the agency will safeguard the privacy of subjects.

First, the agency does not need to inspect medical history records routinely. The scientific evaluation of case report forms, and of summary tables proposed from the data in these forms, is the basic mechanism by which FDA assesses the study data. However, the agency's inspections have uncovered a significant number of errors of omission and commission in information submitted to the agency. For this reason FDA has initiated an inspectional program that includes the onsite audit of certain data submitted to the agency. During this audit, access to the subject's identification is incidental to the review of such records. When such records are reviewed, as described in current regulations, "the names of the subjects need not be divulged unless the records of the particular subjects require a more detailed study of the cases, or unless there is a reason to believe that the records do not represent actual studies or do not represent actual results obtained" (see § 312.1(a) (21 CFR 312.1(a))). To assure the privacy of individually identifiable medical records, FDA has implemented clear and extraordinarily exacting guidelines for FDA personnel who conduct inspections of medical records containing the names of individual research subjects. Before an inspection, FDA personnel will generally notify the IRB of FDA's intent to inspect the IRB's records, with a view to arranging a mutually convenient inspection time. Agency personnel must invite a representative of the IRB to be present with them throughout FDA's records review, and they must inform the representative that he or she may see the records which they may wish to copy and may review any records that are copied. Agency personnel may not copy medical records containing the names of research subjects, and the representative is to be given the right to delete any information that could identify an individual subject, except when: (1) The agency has reason to believe that the consent of human subjects was not obtained; or (2) there is reason to believe that the records do not represent actual studies, or do not represent actual results obtained. The exceptions to the prohibition against the copying of individually identifiable medical records by FDA personnel rest primarily on the need to determine whether a given research subject in fact exists and whether the research subject in fact participated in the investigation. 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 (Freedom of Information and Privacy Act regulations) and the law enforcement responsibilities of the agency.

The Commissioner proposes in § 56.15(a) that an IRB permit authorized FDA personnel, at reasonable times and in a reasonable manner, and only for purposes of verification of the data and information submitted to FDA: (a) To inspect all records required by these regulations, (b) to copy such records that do not identify the names of human subjects or from which the identifying information has been deleted, and (c) to copy such records that identify the names of human subjects, without deletion of the identifying information, upon notice that FDA has reason to believe that the consent of human subjects was not obtained, that the reports submitted by the investigator to the sponsor, or to the IRB, do not represent actual cases or actual results obtained, or that such reports or other required records appear to be otherwise false or misleading.

The Commissioner recognizes the highly sensitive nature of this provision, as reflected in the many comments already received by FDA on the IDE proposal. The Commissioner welcomes reasoned discussions of the issues involved and specific proposals under which patient confidentiality could be further protected without compromising the ability of FDA to verify clinical data submitted in support of applications for research or marketing permits.

CONFORMING AMENDMENTS

The Commissioner is proposing to amend the procedural regulations (21 CFR 16.1) regarding regulatory hearings before the FDA to add a cross-reference to the procedures proposed in this notice regarding disqualification of an IRB.

The current definitions of the term "sponsor" found in 21 CFR 310.3(j) and 510.3(k) are to be superseded by the proposed definition in § 56.3(i) discussed above. Therefore, the Commissioner is proposing to eliminate the current definitions.

Because of the clarifications of the standards regarding IRB's, the Commissioner proposes to revise the IND regulations in 21 CFR 312.1(a), forms FD-1571, FD-1572, and FD-1573, to correspond with the proposed part 56. Rather than repeat these provisions in the forms in this proposal, which might confuse readers and lead to duplicative comments, the Commissioner gives notice that the forms will be revised in the final order to reiterate the standards proposed here, as modified in light of the comments received.

The Commissioner also proposes to add or revise provisions in regulations regarding food and color additives, new drug applications, bioavailability, and bioequivalence testing requirements, OTC drug products, radioactive drugs, antibiotic drugs, biological product licenses, cosmetics, and electronic products, to incorporate appropriate implementing provisions for, and cross-references to, part 56.

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-530, 601, 701(a), 706, and 801, 52 Stat. 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-518 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, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 361, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n)) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that chapter I of title 21 of the Code of Federal Regulations be amended as follows:

SUBCHAPTER A—GENERAL

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. In § 16.1, by adding new paragraph (b)(26) to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

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

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

PART 56—INSTITUTIONAL REVIEW BOARDS

Subpart A—General Provisions

- Sec.
- 56.1 Scope.
- 56.2 Circumstances in which an institutional review board is required; exemptions.
- 56.3 Definitions.
- 56.8 Review by institution.
- 56.15 Inspection of an institutional review board.

Subpart B—Organization and Personnel

- 56.21 Diversity of membership of an institutional review board.

- Sec.
- 56.25 Relationship between members and institution.
- 56.26 Relationship between members and sponsor, investigator, or investigation.
- 56.34 Consultants.

Subparts C and D—[Reserved]

Subpart E—Board Operations

- 56.80 Written procedures for review of clinical investigations by an institutional review board.
- 56.82 Quorum requirements.
- 56.85 Procedures for initial review of a clinical investigation.
- 56.87 Procedures for continuing review and suspension or termination of a clinical investigation.
- 56.90 Criteria for disapproval, suspension, or termination of a clinical investigation.
- 56.92 Order to suspend or terminate a clinical investigation.

Subparts F through I—[Reserved]

Subpart J—Records and Reports

- 56.185 Records of an institutional review board.
- 56.195 Retention of records.

Subpart K—Disqualification of an Institutional Review Board

- 56.200 Purpose.
- 56.202 Grounds for disqualification.
- 56.204 Notice of and opportunity for a hearing on proposed disqualification.
- 56.206 Final order on disqualification.
- 56.210 Actions on disqualification.
- 56.213 Public disclosure of information regarding disqualification.
- 56.215 Alternative or additional actions to disqualification.
- 56.219 Reinstatement of a disqualified institutional review board.

AUTHORITY Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 601, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-518 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 76 Stat. 794-735 as amended, 90 Stat. 540-546, 560, 562-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 361, 371(a), 376, and 381), secs. 215 351, 354-360F, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n).

Subpart A—General Provisions

§ 56.1 Scope.

This part contains the general standards for the composition, operation, and responsibility of an institutional review board that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, cosmetics, drugs for human use, medical devices for human use, biological products for human use, and electronic

products. Additional specific standards for the composition, operation, and responsibility of an institutional review board that reviews clinical investigations involving particular test articles and products may be found in other parts, e.g., parts 312 and 812, of this chapter. Compliance with these parts is intended to protect the rights and safety of human subjects involved in such investigations and to help assure the quality and integrity of the data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 601, 706, and 801 of the act and sections 351 and 354-360F of the Public Health Service Act.

§ 56.2 Circumstances in which an institutional review board is required; exemptions.

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

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

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

(2) Except as provided in this paragraph (c)(2), the Food and Drug Administration will waive the requirement on request of an applicant, if the Commissioner determines that the requirement is not necessary either for protecting the subjects involved or for assuring the validity or reliability of the scientific data (e.g., in a phase 3

investigational drug study (see § 312.1(a)(2), form FD-1571, item 10, of this chapter) on outpatient subjects). Any applicant for 2 research or marketing permit may include a request for waiver, with supporting information, in the application. In the case of applications for a research permit granted on an emergency basis, such request for waiver may be made over the telephone and be granted orally by the Food and Drug Administration at the same time the emergency application is approved on an oral basis, and may be conditioned upon subsequent review by an institutional review board. Written confirmation of any oral request for and grant of a waiver shall be included in the official application submitted subsequent to the emergency authorization of such application. The requirement will not be waived in any of the following situations:

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

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

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

§56.3 Definitions.

As used in this part:

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

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

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

(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.35 and 570.35 of this chapter.

(3) A food additive petition, described in part 171 of this chapter.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(21) Data and information regarding an electronic product submitted as

part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5 of this chapter.

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

(c) "Clinical investigation" means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research 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) "Institution" means a person (other than an individual) who engages in the conduct of research on subjects or in the delivery of medical services to individuals, as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes, for example, a hospital, retirement home, prison, academic establishment, and pharmaceutical or device manufacturer. The word "facility" as used in section 520(g) of the act is deemed to be synonymous with the term "institution" for purposes of this part.

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

(f) "Institutionalized subject" means:

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

institution is a sponsor of the clinical investigation; and

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

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

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

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

(j) "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.

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

(l) "Test article" means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, cosmetic, electronic product, or any other article subject to regulation under the Act or under sections 351 or

354-360F of the Public Health Service Act.

56.8 Review by institution.

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

56.15 Inspection of an institutional review board.

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

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

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

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

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

Subpart B—Organization and Personnel

56.21 Diversity of membership of an institutional review board.

(a) An institutional review board shall be composed of not fewer than five individuals with varying cultural backgrounds to assure complete and adequate review of the clinical investigation. The board shall be sufficiently qualified through the maturity, experience, and expertise of its members and diversity of its membership to insure respect for its advice and counsel for safeguarding the rights and safety of subjects. In addition to possessing the professional competence necessary to comprehend the scientific nature of the investigation, the board must be able to ascertain the acceptability of a study in terms of institutional commitments and regulations (where appropriate), applicable law, standards of professional conduct and practice, and community attitudes. Such board shall include at least one licensed physician, as well as individuals whose primary concerns are in nonscientific areas (e.g., lawyers, clergy, ethicists, consumers, and social scientists). No board shall consist entirely of members of only one sex, race, or professional group.

(b) The records of a board shall identify each member by name, earned degrees if any, occupation and title, and other pertinent indications of experience (such as board certification or licenses) sufficient to describe each member's chief anticipated contributions to such board's deliberations.

56.25 Relationship between members and institution.

(a) The institutional review board shall not consist entirely of individuals who are officers, employees, or agents of, or are otherwise associated with, the institution, apart from their membership on the institutional review board.

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

§ 56.26 Relationship between members and sponsor, investigator, or institution.

(a) No member of an institutional review board shall participate in the board's initial or continuing review of any clinical investigation in which the member has a conflicting interest, or of any investigation involving an investigator or sponsor who participated in his or her selection for the board, except to provide information requested by the board. The board is responsi-

ble for determining whether a member has a conflicting interest. No investigator or sponsor shall participate in the selection of members for a board that will review his or her investigation. The Food and Drug Administration may waive the requirements of this section upon a request contained in the relevant application for a research or marketing permit; the request shall contain information describing the reasons why it is necessary for the investigator or sponsor to participate in the selection of board members.

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

§ 56.34 Consultants.

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

Subparts C and D [Reserved]

Subpart E—Board Operations

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

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

§ 56.83 Quorum requirements.

(a) An institutional review board shall conduct all significant business (e.g., approval, disapproval, suspension, or termination of a clinical investigation, or approval of a consent form) by a quorum of its members present at a meeting. The quorum shall be defined in the written procedures of the board, consistent with the requirements of this section.

(b) The number of members to constitute a quorum may not be less than a majority of the members of the board, unless the board has 20 or more members, in which case 10 members shall constitute a quorum.

(c) A quorum shall consist of at least one licensed physician, one scientist, and one nonscientist (e.g., lawyer or clergy).

(d) A quorum shall be determined only by members present at a meeting. Proxy votes, telephone conferences, and votes by mail shall not constitute a meeting or presence at a meeting.

§ 56.85 Procedures for initial review of a clinical investigation.

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

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

(c) If the board has any question regarding the proposed investigation, or desires any further information, it may request the investigator or sponsor to provide the necessary information or materials as written amendments to the submission. The board may advise the investigator or sponsor, as appropriate, on modifications, conditions, or other amendments to the investigational plan or protocol and/or the material to be used to obtain consent of subjects, which might improve the acceptability of the proposed investigation to the board. Any modifications, conditions, or other amendments to the investigational plan or protocol shall be made in writing as amendments to the submission.

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

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

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

(a) An institutional review board shall continue to review a clinical investigation that it has approved until the investigation is concluded or is discontinued. Such continuing review shall be undertaken at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the investigation is being conducted in compliance with the requirements, understandings, and recommendations of the board and with the requirements of the act and implementing regulations (e.g., parts 312 and 812 of this chapter).

(b) A board may, at any time, suspend or terminate a previously approved clinical investigation. The board shall notify in writing the investigator or the sponsor, as appropriate, and the institution of its decision to take such action, including a statement of the reasons for its decision.

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

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

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

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

(2) The report of prior investigations with the test article is inadequate to support a conclusion that it is reasonably safe to initiate or continue the clinical investigation.

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

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

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

In assessing risks, the board shall consider, among other factors:

(i) Whether the risks to the subject are so outweighed by the sum of the benefits to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

(ii) Whether the rights and safety of subjects will be adequately protected;

(iii) Whether legally effective informed consent will be obtained by adequate and appropriate methods in accordance with the requirements of § 310.102 or subpart F of part 812 of this chapter; and

(iv) Whether the conduct of the clinical investigation will be or is being reviewed by the sponsor and by the board at intervals appropriate to the degree of perceived risk.

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

§ 56.92 Order to suspend or terminate a clinical investigation.

If an institutional review board decides to order the suspension or termination of a clinical investigation, it shall include in its order provisions regarding any subject who has previously been allowed to participate in the investigation and who either would (if the investigation were not suspended or terminated) continue to receive the test article or have it used involving him or her, or who would not continue to receive it or have it used involving him or her but who remains under the supervision of the investigator. Such provisions shall take into account, among other factors, the risks to the subject from the withdrawal of the test article or from its continued administration by another physician, the need for further medical supervision, the availability of qualified medical personnel, and the rights of the subject, including the right to participate in the decision as to future care.

Subparts F Through I [Reserved]

Subpart J—Records and Reports

§ 56.185 Records of an institutional review board.

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

(a) Records of information submitted to the board by an investigator and/or the sponsor;

(b) Information on board members required under subpart B of this part;

(c) Attendance at and minutes of board meetings, including a written summary of the discussion of any substantive issues and their resolution;

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

(e) Dated reports of successive reviews as they are performed.

§ 56.195 Retention of records.

An institutional review board shall retain the records required by this part regarding a particular clinical investigation for whichever of the following periods is shortest:

(a) A period of 2 years following the date on which the test article is approved by the Food and Drug Administration for marketing for the purposes which were the subject of the investigation;

(b) A period of 5 years following the date on which the results of the investigation are submitted to the Food and Drug Administration in support of or as part of an application for a research or marketing permit for the test article for the purposes that were the subject of the investigation; or

(c) In other situations (e.g., where the investigation does not result in the submission of the data from the investigation in support of an application for a research or marketing permit), a period of 2 years following the date on which the entire clinical investigation (not merely the investigator's portion of an investigation involving more than one investigator) is completed, terminated, or discontinued, or the exemption under which the investigation is being conducted is terminated or withdrawn by the Food and Drug Administration.

Subpart K—Disqualification of an Institutional Review Board

§ 56.200 Purpose.

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

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

(b) To preclude the consideration of any clinical investigations in support

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

§ 56.202 Grounds for disqualification.

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

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

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

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

§ 56.204 Notice of an opportunity for a hearing on proposed disqualification.

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

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

§ 56.206 Final order on disqualification.

(a) If the Commissioner, after the regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, makes the finding required in § 56.202, the Commissioner shall issue a final order disqualifying the institutional review board. Such order shall include a statement of the basis for

that determination and shall prescribe any actions (set forth in § 56.210(b)) to be taken with regard to ongoing clinical investigations being conducted under the review of the board. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the board of the action, as well as the institution that established the board, the sponsor of each clinical investigation subject to requirements for prior submission to the Food and Drug Administration which was under the review of the board, and the investigators of such investigations who were under the review of the board.

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

§ 56.210 Actions on disqualification.

(a) No clinical investigation subject to requirements for prior submission to the Food and Drug Administration and to requirements for institutional review board review under § 56.2 will be authorized by the Commissioner if such investigation is to be conducted under the review of a disqualified board.

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

(1) The investigation may be terminated or suspended in its entirety until the board is reinstated under § 56.219 or another board accepts responsibility for review of the investigation.

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

(3) Any subject who has previously been allowed to participate in the investigation and who remains under the supervision of an investigator, but

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

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

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

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

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

(d) No clinical investigation begun under the review of an institutional review board after the date of its disqualification shall be considered in support of any application for a research or marketing permit, unless the board has been reinstated under § 56.219. The determination that a clinical investigation may not be con-

sidered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable statute or regulation to submit the results of the investigation to the Food and Drug Administration.

§ 56.213 Public disclosure of information regarding disqualification

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

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

(c) Whenever the Commissioner has reason to believe that an institutional review board may be subject to disqualification, the Commissioner shall so notify other agencies in the Department of Health, Education, and Welfare that support research involving human subjects at the time of or after proposing disqualification of the board under § 56.204(a).

§ 56.215 Alternative or additional actions to disqualification.

Disqualification of an institutional review board under this subpart is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Commissioner may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at

the time of, or after, disqualification. The Commissioner may also refer pertinent matters to another Federal, State, or local government agency for such action as that agency determines to be appropriate.

§ 56.219 Reinstatement of a disqualified institutional review board.

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

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

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

PART 71—COLOR ADDITIVE PETITIONS

3. By amending part 71:

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

§ 71.1 Petitions.

* * * * *

(i) If clinical investigations involving human subjects are involved, petitions filed with the Commissioner under section 706(b) of the act shall include 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 § 56.22(c) 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 § 56.2(c) of this chapter.

* * * * *

SUBCHAPTER B—FOOD FOR HUMAN CONSUMPTION

PART 171—FOOD ADDITIVE PETITIONS

4. By amending part 171:

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

§ 171.1 Petitions.

* * * * *

(m) If clinical investigations involving human subjects are involved, petitions filed with the Commissioner under section 409(b) of the act shall include 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 § 56.2(c) 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 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 § 56.2(c) of this chapter.

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

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

§ 180.1 General.

* * * * *

(c) * * *

(6) If clinical investigations involving human subjects are involved, such investigations filed with the Commissioner shall include, with respect to each investigation, either a statement that the investigation has been or will be conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter; or a statement that the investigation is not subject to such requirements in accordance with § 56.2(c) of this chapter.

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 310—NEW DRUGS

§ 310.3 [Amended]

5. Part 310 is amended in § 310.3 Definitions and interpretations, by deleting and reserving paragraph (j).

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

6. Part 312 is amended in § 312.1 by redesignating paragraph (d)(11) as (d)(12) and adding a new paragraph (d)(11).

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

* * * * *

(d) * * *

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

* * * * *

PART 314—NEW DRUG APPLICATIONS

7. Part 314 is amended:

a. In § 314.1 by adding a new item 16 to form FD-356H in paragraph (c)(2) and by redesignating paragraph (f)(7) as (f)(8) and adding a new paragraph (f)(7) to read as follows:

§ 314.1 Applications.

* * * * *

(c) * * *

(2) * * *

Form FD-356H-Rev. 1974:

* * * * *

16. Conduct of clinical investigations. 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 § 56.2(c) of this chapter.

* * * * *

(f) * * *

(7) Statements regarding each clinical investigation involving human subjects contained in the application that it either was conducted in compliance with the requirements the institutional review set forth in part 56 of this chapter or was not subject to such requirements in accordance with § 56.2(c) of this chapter.

* * * * *

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

§ 314.8 Supplemental applications.

* * * * *

(n) A supplemental application that contains clinical investigations involving human subjects shall include 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 or was not subject to such requirements in accordance with § 56.2(c) 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 involvings 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 § 56.2(c) of this chapter.

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

§ 314.12 Untrue statements in application.

* * * * *

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

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

§ 314.110 Reasons for refusing to file applications.

(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 or was not subject to such requirements in accordance with § 56.2(c) of this chapter.

* * * * *

f. In § 314.111 by adding 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 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 was not conducted in compliance with such requirements.

* * * * *

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

8. Part 320 is amended:

a. In § 320.31 by adding a new paragraph (f) to read as follows:

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

* * * * *

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

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

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

* * * * *

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

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

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

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

* * * * *

(e) *Institutional review.* Information and data submitted under this section after (insert effective date of this paragraph) shall include 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 or was not subject to such requirements in accordance with § 56.2(c) of this chapter.

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

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

§ 361.1 Radioactive drugs for certain research uses.

* * * * *

(d) * * *

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

* * * * *

PART 430—ANTIBIOTIC DRUGS; GENERAL

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

§ 430.20 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 or 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 § 56.2(c) of this chapter.

PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS

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

§ 431.17 New antibiotic and antibiotic-containing products.

* * * * *

(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 § 56.2(c) of this chapter.

SUBCHAPTER F—BIOLOGICS

PART 601—LICENSING

13. Part 601 is amended:

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

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

(a) General. To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purposes and in the case of an application for a product license, shall submit data derived from laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; 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 § 56.2(c) 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 label, 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 are received from the manufacturer by the Bureau of Biologics. The applicant shall also include an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the biological product pursuant to § 25.1 of this chapter. 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)(l) and adding a new paragraph (l) to read as follows:

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

* * * * *

(h) Additional studies. (1) Within 30 days following publication of the final order, each licensee for a biological product designated as requiring further study to justify continued marketing on an interim basis, pursuant to paragraph (f)(3) of this section, shall satisfy the Commissioner of Food and Drugs in writing that studies adequate and appropriate to resolve the questions raised about the product have been undertaken, or the Federal Government may undertake these studies. Any study involving a clinical investigation that involves human subjects shall be conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter, unless it is not subject to such requirements in accordance with § 56.2(c) 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.

* * * * *

(l) Institutional review. Information and data submitted under this section after (insert effective date of this

paragraph) shall include statements regarding each clinical investigation involving human subjects that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter or was not subject to such requirements in accordance with § 56.2(c) of this chapter.

* * * * *

6. By revising § 601.30 to read as follows:

§ 601.30 Licensee 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 and product license. Unlicensed products which are not imported for sale, barter, or exchange and which are intended solely for purposes of controlled investigation involving human subjects are admissible only if the investigation is conducted in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and, if subject to them, in compliance with the requirements for institutional review set forth in part 56 of this chapter.

PART 630—ADDITIONAL STANDARDS FOR VIRAL VACCINES

14. Part 630 is amended;

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

§ 630.11 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with part 56 of this chapter, unless exempted under § 56.2. * * *

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

§ 630.31 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with part 56 of this chapter, unless exempted under § 56.2 of this chapter, by subcutaneous administration of the product. * * *

c. By revising § 630.51 to read as follows:

§ 630.51 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Mumps Virus Vaccine, Live,

shall be determined by clinical trials conducted in compliance with part 56 of this chapter, unless § 56.2 of this chapter, that follow the procedures prescribed in exempted under § 630.31 except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of mumps-susceptible individuals, each having received the parenteral administration of a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies (§ 630.50(b)) when used under comparable conditions.

d. By revising § 630.61 to read as follows:

§ 630.61 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Rubella Virus Vaccine, Live, shall be determined by clinical trials conducted in compliance with part 56 of this chapter, unless exempted under § 56.2 of this chapter, that follow the procedures prescribed in § 630.31 except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of rubella susceptible individuals, each having received the parenteral administration of a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies when used under comparable conditions.

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

§ 630.81 Clinical trials to qualify for license.

In addition to demonstrating that the measles component meets the requirements of § 630.31, the measles and smallpox antigenicity of the final product shall be determined by clinical trials of adequate statistical design conducted in compliance with part 56 of this chapter, unless exempted under § 56.2 of this chapter, and with three consecutive lots of final vaccine manufactured by the same methods

and administered its recommended by the manufacturer. * * *

PART 1003—NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY

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

§ 1003.31 Granting the exemption.

(b) Such views and evidence shall be confined to matters relevant to whether the defect in the product or its failure to comply with an applicable Federal standard is such as to create a significant risk of injury, including genetic injury, to any person and shall be presented in writing unless the Secretary determines that an oral presentation is desirable. Where such evidence includes clinical investigations involving human subjects, the data submitted shall include, with respect to each clinical investigation, either a statement that each investigation was conducted in compliance with the requirements set forth in part 56 of this chapter; or a statement that the investigation is not subject to such requirements in accordance with § 56.2(c) of this chapter.

SUBCHAPTER I—RADIOLOGICAL HEALTH

PART 1010—PERFORMANCE STANDARDS FOR ELECTRONIC PRODUCTS: GENERAL

16. Part 1010 is amended:

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

1010.4 Variances.

* * * * *

(b) * * *

(1) * * *

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

* * * * *

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

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

* * * * *

(c) * * *

(12) Such other information required by regulation or by the Director, Bureau of Radiological Health, to evaluate and act on the application. Where such information includes 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 § 56.2(c) of this chapter.

* * * * *

Interested persons may, on or before December 6, 1978, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an economic impact statement under Executive Order 11821 (as amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: August 1, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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