federal register

TUESDAY, AUGUST 8, 1978
PART V

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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OBLIGATIONS OF CLINICAL INVESTIGATORS OF REGULATED ARTICLES

Proposed Establishment of Regulations

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 16, 54, 71, 170, 171, 180, 310, 312, 314, 320, 330, 361, 430, 431, 510, 511, 514, 570, 571, 601, 630, 1003, and 1010]

[Docket No. 77N-0278]

OBLIGATIONS OF CLINICAL INVESTIGATORS OF REGULATED ARTICLES

Proposed Establishment of Regulations

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposal would clarify existing regulations concerning persons who conduct clinical investigations on new drug products and would extend these regulations to include persons who conduct clinical investigations on other products regulated by the Food and Drug Administration (FDA). This proposal is based upon findings in inspections of clinical investigators that existing requirements are not being fully followed and may be subject to varying interpretations, upon recommendations of the General Accounting Office (GAO) regarding FDA regulation of new drug testing, and upon an evaluation of the need for such regulations to implement both the Medical Device Amendments of 1976 (Pub. L. 94-295) and the agency's bioresearch monitoring program for assuring the validity of scientific data from human and animal studies.

DATE: Written comments by November 6, 1978.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Marilyn L. Watson, Bureau of Drugs (HFD-30), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301 443-6490.

SUPPLEMENTARY INFORMATION: The proposed regulations are intended to assure adequate protection of the rights and safety of subjects involved in clinical investigations and the quality and integrity of the resulting data submitted to FDA in support of applications for permission to conduct further research or to market regulated products, while providing sufficient flexibility and latitude for innovative clinical research in the interest of the public health.

CIRCUMSTANCES CREATING A NEED FOR THIS PROPOSAL

The Commissioner of Food and Drugs believes that a complete revision of the regulations governing the conduct of clinical investigators is needed because (1) current regulations have not been comprehensively reviewed in 15 years, (2) FDA inspections have disclosed numerous deviations from current standards by investigators, (3) these discrepancies may be related, at least in part, to misunderstandings over the precise meaning of FDA requirements as currently written, (4) the General Accounting Office has recommended changes in current FDA regulations, (5) the Medical Device Amendments of 1976 mandate the FDA to develop standards for clinical investigators of devices for human use, and (6) the new FDA bioresearch monitoring program, designed to assure the validity and reliability of clinical and nonclinical data submitted to the agency, can be more efficiently and effectively conducted with uniform, agencywide regulatory standards. Each of these matters is discussed in further detail in this preamble.

For several years FDA has been planning to revise substantially the regulations governing drug research which implement sections 505(i), 507(d), and 512(j) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i), 357(d), and 360b(j)). Many of the current regulations were first issued in 1963 under the Drug Admendments of 1962, which substantially expanded FDA's responsibilities in supervising drug experimentation. Other regulations were subsequently added; and the regulations are now codified in § 310.102, part 312, and part 511 (21 CFR 310.102, Part 312, and Part 511). Until now, however, there has been no comprehensive review and updating of these regulations.

The revision of regulations regarding the obligations and standards of performance expected of clinical investigators is an important part of this review. Current statements of agency policy directly applicable to investigators are found primarily in forms FD-1572 and FD-1573 (set forth in § 312.1(a) (12) and (13) (21 CFR 312.1(a) (12) and (13))), which are the documents signed by an investigator and submitted to the sponsor of research on a new drug for human use subject to a "Notice of Claimed Investigational Exemption for a new Drug" (IND; see form 1571 set forth in § 312.1(a)(2)). Many portions of the forms describe obligations in general terms such as "adequate" and refer to other requirements in terms commonly understood but subject to misinterpretation in specific cases, e.g., whether a subject is "institutionalized" and whether a "case history" includes medical records regaring the subject's condition before entry into the study. Agency policy regarding consent for use of investigational new drugs on humans is set forth in § 310.102, although significant discrepancies exist between the regulation and the statements in forms FD-1572 and FD-1573.

The Commissioner is of the opinion that the way these requirements are stated may have contributed to misunderstandings concerning the conduct FDA expects of a clinical investigator—misunderstandings manifested by FDA findings of noncompliance or inadequate performance by a number of clinical investigators. In 1972, the Bureau of Drugs undertook a special survey of IND studies involving 15 sponsors (i.e., persons filing IND's) and 155 investigators (i.e., persons working under those IND's by filing forms FD-1572 or FD-1573 with the sponsors). The results of this survey showed varying degrees of deficiencies by 115 investigators in 1 or more of the following 6 areas: obtaining or documenting informed consent properly, maintaining records of the disposition of the investigational drug, adhering to the research protocol, maintianing accurate case records on subjects, making all records available to FDA inspectors, and understanding the role of the investigator in the research program. After the survey, the Bureau of Drugs conducted 2 further surveys, the first to study 34 persons who were both sponors and investigators (i.e., physicians who both initiate and actually conduct research upon filing an IND with FDA) and the second to study 8 persons who were conducting research under IND's sponsored either by the Department of the Army of the Department of Defense (DOD) or by the National Institutes of Health (NIH). In the sponsor-investigator survey, deficiencies were found in the conduct of every IND; and in the DOD-NIH study, problems similar to thoe found in nongovernment research were frequently encountered. The Bureau of Biologics also undertook a survey of 48 clinical investigators (including 23 sponsor-investigators) who were conducting research with biologics. Again, numerous deficiencies were discovered. Copies of these surveys have been placed on file in the office of the Hearing Clerk (HFA-305), Food and Drug Adminitration, Room 4-65, 5600 Fisher Lane, Rockville, Md. 20857.

Both bureaus concluded that most of the shortcomings constituted violations that did not present any significant hazard to the subjects or compromise the integrity of the specific studies. On the other hand, there was serious concern about certain deficiencies, such as the failure to keep an institu-

tional review committee informed of progress in the study, refusal to permit FDA inspectors to examine records containing a subject's name or prior medical history, inadequate documentation of subject consent, and use of exculpatory statements in consent forms. Although these actions and omissions are not acceptable behavior for clinical investigators, the Commissioner emphasizes that the surveys do not support a conclusion that human subjects are routinely being exposed to unnecessary or avoidable risks in the course of research on new drugs and bioligics, or that decisions to approve marketing of new drugs are being made upon data that are inaccurate or unreliable or accepted without analysis or means of verification.

Nevertheless, these surveys do indicate that a serious problem of communication exits between FDA and at least some clinical investigators. The Commissioner believes that FDA's policies regarding the conduct of clinical investigators should be viewed as objectives that are compatible with, and indeed largely based upon, the ethical codes of medicine and research and accepted standards of good science. The first step to compliance with these policies is to restate them with precision and reaffirm the goals being sought.

Another reason for the Commissioner's proposing to revise the regulations governing clinical investigators is the findings of the GAO in a report entitled "Federal Control of New Drug Testing is Not Adequately Protecting Human Test Subjects and the Public," dated July 15, 1976. A copy of this report has also been placed on display in the office of the Hearing Clerk. The GAO reviewed the data generated in the Bureau of Drugs' and Bureau of Biologics' surveys discussed above and interviewed a number of FDA employees. Although FDA does not agree with a number of the GAO analyses and conclusions, the Commissioner understands the reasons for certain GAO recommendations to improve FDA regulations; this proposal is a step to implement those recommendations.

The Commissioner has been directed by Congress to establish regulations to implement section 520(g) of the act (21 U.S.C. 360j(g)), which was added by the Medical Device Amendments of 1976 and pertains to investigational use of medical devices for human use and diagnostic products. In a notice published in the FEDERAL REGISTER of August 20, 1976 (41 FR 35282), FDA proposed such regulations; proposed Subpart E of Part 812 concerned the responsibilities of clinical investigators studying the safety or effectiveness of devices with human subjects. Comments filed on that proposal have been reviewed and utilized in preparing this proposal. In the FEDERAL REGISTER of May 12, 1978 (43 FR 20726), the Commissioner issued portions of the August 20 proposal as a tentative final regulation. Those requirements proposed in subpart E on August 20 that duplicate or overlap substantially with the requirements proposed below in this notice have been deleted from the tentative final regulation. The Commissioner intends to review comments on this notice promptly and to promulgate as final at least those regulations based on this proposal that are essential to promulgation of comprehensive final regulations governing the investigational use of medical devices for human use.

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 investigators 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 Presidental 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.

Pursuant to 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 intraagency steering committee, with specific elements being assigned to several task forces, including a Clinical Investigator/Sponsor Task Force. This task force has the responsibility for developing an agency strategy to define the responsibilities of sponsors and clinical investigators in studies regulated FDA or involving products regulated by FDA, and to insure that these duties are adequately and reliably performed. To meet these goals, the task force proposed the following:

1. Promulgation of agencywide regulations—based upon existing FDA regulations for investigational new drug studies, proposed regulations for investigational use of medical devices for human use and comments received on them, and FDA experience—that would set forth the responsibilities of sponsors, monitors, and investigators in clinical investigations and procedures for enforcing these requirements.

2. Establishment of an agencywide compliance program that would include enforcement policies, regular inspections of sponsors, monitors, and clinical investigators, and special inspection is initiated by FDA to audit particular studies.

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.

UNIFORM FDA STANDARDS FOR ALL CLINICAL INVESTIGATIONS

The Commissioner proposes to make a single set of standards applicable to all clinical investigators involved in investigational studies that either require prior FDA review or are subsequently submitted to FDA in support of an application for a research or marketing permit. These regulations, if adopted, may not eliminate the need for additional requirements relevant to a particular article under study, but will reduce the potential for duplicative and inconsistent regulations or interpretations of policy. The Commissioner recognizes that one clinical investigator may, at any one time, be conducting studies on products that are regulated by several of the separate bureaus of FDA, e.g., Drugs, Biologics, and Medical Devices. A uniform standard will thus ease the burdens on these investigators in complying with the applicable regulations.

To achieve this objective, the Commissioner proposes a new Part 54 in Chapter I of Title 21 of the Code of Federal Regulations to be entitled "Clinical Investigators." The proposed new part, under Subchapter A (General) of the regulations, will be applicable to all regulated products. This proposal extends current FDA standards to all clinical investigations regulated by or submitted to the agency, lists definitions applicable to the part, presents the obligations and commitments of clinical investigators, clarifies many of the existing requirements, and improves the procedures for imposing administrative sanctions on investigators who violate these regulations. Additionally, this proposal contains specific amendments needed for conformance in other existing FDA regulations.

In order to assure uniform standards, any clinical investigation would be within the scope of this part, whether the investigation required the

prior review of any FDA bureau (i.e., Drugs, Biologics, Medical Devices and Diagnostic Products, or Veterinary Medicine) 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 four bureaus or to the Bureau of Foods or Radiological Health (proposed § 54.1 (21 CFR 54.1)).

EXEMPTIONS

The Commissioner is proposing to permit exemptions from all or part of the requirements set forth in part 54 (21 CFR Part 54) in appropriate cases. These regulations have been drafted to make them applicable to all clinical investigations regulated by or submitted to FDA, and the Commissioner maintains that the principles are reasonably applicable to all such investigations. However, FDA has not been able to review every type of clinical investigation to guarantee that these standards are totally appropriate to each particular study. Therefore, the Commissioner invites comments to identify any unique category of clinical investigation that should be exempted from any specific requirements of this proposal and to provide an adequate rationale to demonstrate why such requirements are not necessary to protect the rights and safety of subjects or to help assure the quality and integrity of the data produced. In addition, the Commissioner proposes § 54.2 (21 CFR 54.2) under which individual investigators or their sponsors may request FDA for a waiver of any particular requirements for purposes of a specific study or group of studies. In emergency situations, such a request may be granted by telephone; otherwise, such requests shall be in writing as part of the application for a research permit.

DEFINITIONS

Proposed § 54.3 (21 CFR 54.3) contains definitions for all of the special terms used in the part. Many technical terms can be variably or inaccurately 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 § 54.3(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 regulations. Other statutes when used will be mentioned by name, e.g., the Public Health Service Act.

A new definition required by the decision to make these proposed regulations agency-wide in scope is the term "application for research or marketing permit" in § 54.3(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 25 separate categories of data and information that are now, or will in the near future become, subject to requirements for submission ot 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, proposed § 54.3(c) would describe each such study as a "clinical investigation," defined to mean any experiment involving a test article (defined below), which experiment either (1) is subject to requirements under sections 505(i), 507(d), 512(j) or 520(g) of the act for prior submission to the FDA for review and in some cases approval before it can be commenced, or (2) is not subject to prior submission to FDA under an IND, or "Notice of Claimed Investigational Exemption for a New Animal Drug" (INAD), or an "Investigational Device Exemption" (IDE), but the results of which are intended to be submitted later to (or held for inspection by) FDA as part of an application for a research or marketing permit. The term thus includes, for example, human investigations performed as part of the evaluation of a test article and animal investigations conducted to determine the clinical or therapeutic effect of a drug in treating a disease in animals. There is another category of clinical research that is not included in the definition of "clinical investigation" because such studies are not regulated by or intended to be submitted to FDA; these would include studies that do not use any test articles, or do not use them in a manner requiring prior FDA approval or subsequent FDA review. The definition also excludes nonclinical studies in animals which fall within the scope of the regulations proposed under part 3e to establish good laboratory practices for nonclinical laboratory studies published in the FEDERAL REGISTER of November 19, 1976.

Other proposed definitions include terms to describe the persons who initiate and carry out clinical investigations: "sponsor," "investigator," and "sponsor-investigator." The word "sponsor" is currently defined in §§ 310.3(j) and 510.3(k) (21 CFR 310.3(j) and 510.3(k)), but the Commissioner believes this definition is unsatisfactory because it fails to distinguish the other commonly used word "investigator," which is not defined. Although 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 definitions proposed in § 54.3 (d) and (f), together with a further distinction: investigators must be individuals, while sponsors can be individuals, corporations, institutions, or other legal entities. (The term "person" is defined in paragraph (e) to include in 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 carry out the study by himself or herself or with other investigators responsible to him or her. The Commissioner considers it important to identify the hybrid role of the "sponsor-investigator" and, where appropriate, to allow special provisions for that role. Thus, this term is defined in proposed § 54.3(g). Unlike the term "sponsor," the term "sponsor-investigator" is limited to individuals.

The term "subject" is defined in proposed § 54.3(h) to mean 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 volunteers and patients, and both human beings and animals. The text of the regulation indicates when only human beings are intended as subjects. The definition of "subject" provides that, in the case of nonhuman subjects, the term may apply to either an individual or a group, depending on whether an individual or group response is being measured.

In § 54.3(i) the Commissioner proposes to define the term "test article" to describe those items being studied that are under FDA jurisdiction and these regulations. The term includes new drugs, biologics for human use, new animal drugs, and medical devices for human use, studies of which require prior review by FDA under an IND, INAD, or IDE. In addition, the term covers any other article that is subject to FDA jurisdiction; this in-

cludes food additives, color additives, cosmetics, drugs for human and animal use, biological products for human use, electronic products, and medical devices for human use. The broad definition of "test article" is intended to include substances, studies of which are submitted to FDA in support of an application for permission to market a product, but which studies need not be conducted under an IND, INAD or IDE, e.g., studies on food additives, certain drug bioavailability studies described in § 320.31 (21 CFR 320.31), and studies on medical devices for human use not subject to part 812 (21 CFR Part 812).

TEST ARTICLES

The thalidomide disaster of the early 1960's highlighted the need for strict controls over the distribution of investigational drugs. After the NDA for thalidomide was withdrawn by the manufacturer from consideration in March 1962, FDA learned that, instead of the 40 to 50 doctors believe to be involved in research on the drug, about 1,250 physician had received over 2.5 million tablets and had in turn provided the drug to almost 20,000 patients. The looseness of control over the supply of thalidomide greatly hindered effective protection of research subjects after, as well as before, the risk of phocomelia (birth deformities of the extremities) was discovered. Repetition of this problem can be prevented if test articles are distributed only to qualified and responible investigators who are kept informed of all new developments and who control the availability of the articles.

Thus, sections 505(i)(2) and 507(d)(2) of the act seek to assure that subjects to whom an investigational drug is administered are under the personal supervision of a designated investigator or under the supervision of investigators responible to him or her, and bar an investigator from supplying an investigational drug to any investigator not responsible to him or her, or to clinics, for administration to human beings (item 6.f. of form FD-1572 and item 4.f. of form FD-1573). In the FDA surveys compliance with this requirement was found to be erratic, in that a drug was provided in some instances to a physician who was not listed as an investigator in the IND. The Commissioner now proposes to restate this requirement in § 54.102 (21 CFR 54.102).

Invstigators must also maintain adequate and accurate records of all receipts and uses of test articles (item 6.b. of form FD-1572 and item 4.b. of form FD-1573). These records serve as a check to prevent unauthorized distribution, either to subjects or to other persons who might use the article in humans or animals, and to verify the case histories, to detect possible lot-to-lot variations in the article, and, if recovery of the unused stocks of the article is necessary to minimize health risks to subjects, to provide the most readily usable mechanism to identify which subjects have recently received the article and the quantities they are likely still to have. In FDA surveys of investigatores, deficiencies in drug accountability were found in approximately one-half of the studies; such noncompliance, even though it may indicate only a misunderstanding as to the form and method of recordkeeping, is not acceptable. The Commissioner is proposing to codify this requirement in § 54.108 (21 CFR 54.108). Under the proposed regulation, dispensing records for individual subjects would not by themselves be satisfactory to fulfill this requirement; a separate record indicating each dispensing of the test article, the name of the subject receiving it, and the date would provide an essential cross-index to the dispensing records and a method of accountability for each batch and for any period of time.

The ability to remove a test article from subjects and investigators is essential in the event that its continued availability poses serious risks to the public health, as the thalidomide episode illustrated. Since 1963, investigators have committed themselves to return to the sponsor any unused supply of an investigational drug if the study is terminated, supended, discontinued or completed (item 6.b. of form FD-1572 and item 4.b. of form FD-1573). The Commissioner porposes in § 54.114 (21 CFR 54.114) to restate this obligation; he is, however, broadening the current requirement in three ways: First, he is allowing for alternative disposition of test articles where the sponsor so authorizes in writing; this might permit either onsite destruction, rendering a device inoperable (as suggested by comments on a similar provision in the proposed IDE regulations published in the FEDERAL REGISTER of August 20, 1976), or use in other experiments that are being conducted on the article, or other reasonable actions to prevent further exposure of humans to experimental risks while otherwise benefiting science and the public. Second, the Commissioner proposes that return of the article be authorized whenever the sponsor deems it proper, even though the study itself is not completed, terminated, or discontinued; this could allow for substitution of one batch of the drug for another, return of a particular formulation, or withdrawal from certain investigators only, e.g., in the case of a cutback in the scope of the study from phase 2 to phase 1. Third, the Commissioner proposes to apply the requirement to all test articles, not merely investigational drugs; the inclusion of investigational devices is indicated by reference to "reusable" test articles.

The Commissioner is also proposing to codify requirements for storage of test articles that are controlled under any schedule of the Controlled Substances Act (21 U.S.C. 801 note). Section 303(f) of that act (21 U.S.C. 823(f)) provides that the Secretary of Health, Education, and Welfare shall consult with the Attorney General "as to effective procedures to adequately safeguard against diversion of such controlled substances from legitimate medical or scientific use." As a result of this consultation, FDA issued regulations in 1971 providing for storage of any controlled investigational drug in a securely locked, substantially constructed cabinet or enclosure (item 6.b. of the Form FD-1572 and item 4.b. of the Form FD-1573). These regulations were based upon similar Department of Justice regulations under 21 CFR 1301.75(a). In proposing § 54.116 (21 CFR 54.116), the Commissioner is including this requirement in the FDA regulations for clinical investigators and extending it to all test articles that are controlled substances.

In § 54.118 (21 CFR 54.118), the Commissioner proposes to prohibit clinical investigators from promoting an unmarketed test article as safe and effective for the purposes for which it is under study. Such a requirement is currently applicable only to sponsors of investigational drug studies (see § 312.1(a) (10) and (11)). Recently, FDA has encountered isolated cases where an investigator has used his or her unique access to an investigational drug as an opportunity to monopolize treatment of patients in the investigator's area—promoting the drug through professional contacts and even the lay media and using the drug more as a means of enhancing his or her clinical practice than of conducting a research-oriented investigation. This regulation would expressly allow dissemination of scientific findings, and would not apply to test articles that are lawfully marketed at the time of the investigation, e.g., marketed drugs undergoing bioavailability or bioequivalency testing or marketed devices for human use being tested to comply with the Medical Device Amendments of 1976.

PROTOCOL FOR AND CONDUCT OF A CLINICAL INVESTIGATION

The agency views a protocol defining the research objectives and outlining how they are to be attained as a critical prerequisite to a clinical investigation, but the agency also recognizes that research on living animals and humans requires flexibility. On the one hand, modifications of an investi-

gational plan may be necessary to take into account new information indicating avoidable safety risks; on the other hand, a hypothesis may be confirmed earlier than anticipated, e.g., overwhelming evidence of effectiveness or lack of effectiveness may be seen in initial trials. Therefore, FDA has permitted modification of a protocol without prior approval of the sponsor based on information gained during the study (e.g., item 5 of the form FD-1572).

However, FDA has found that significant changes that undermine the validity of a study or expose subjects to different risks of inappropriately affect their rights have sometimes been made in a protocol without notice to or approval of a sponsor. The agency is committed to encouraging research and to providing wide latitude to clinical investigators. The Commissioner believes, however, that the sponsor and, where required, the institutional review board must be consulted in the event that certain types of changes are considered. Of course, if the change is made to eliminate or reduce the risk to human subjects in the study, immediate action is always justified. Changes that may increase the risk to human subjects in the study or may adversely affect either the validity of the study or the rights of the subjects must be reviewed and approved in advance by the sponsor and, if approved, included in the protocol by way of amendment. The sponsor, in turn, is to file these changes with the IND itself (form FD-1571, item 10.a. and b.). Under § 54.25(b) (21 CFR 54.25(b)), if review by an institutional review board is required, the board must also approve such changes.

In FDA surveys of investigators, a failure to adhere to the protocol was found in about 30 percent of the cases, not all of which necessarily had adverse effects on the subjects or on the validity of the study. Five case studies illustrate the types of changes that warrant prior approval by the sponsor (and institutional review board if applicable).

1. *A significant increase in the dosage or frequency of administration of the test article, or a change in the method of administrtation.* In one recent drug investigation, the investigator sought to accelerate the pace of the study by moving to high-dose phase I exposure before low-dose exposure had been completed; some of the subjects developed liver toxicity and required extended medical care after exposure was discontinued.

2. *A significant increase in the number of subjects participating in the study.* A recently discontinued drug investigation had reached the stage where a few phase III investigators had begun routine use of the drug in their practice and, in effect, the drug was being promoted before approval. The primary purpose of an investigation is to study a drug's benefits and risks in order to reach a conclusion on whether it should be introduced into medical practice. The conversion of a study phase into a promotional phase does not in the long run help the public, the investigators, or the sponsor. Each protocol should have a built-in maximum number of subjects which, at least initially, seems likely to provide a data base adequate to make a judgment on whether the scientific hypothesis under examination should be accepted or rejected. Any significant increases above this maximum properly require justification.

3. *The utilization of subjects with medical conditions unrelated to, but possibly affecting, the scope or validity of the study.*

4. *The utilization of human subjects who require special consideration or protection and who are not specifically listed in the protocol.* The recent concern for special protections for particular subject populations led to the enactment of the National Research Act (Pub. L. 93-348), which in turn mandated the creation of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. One of the functions of this Commission is to review and recommend policies regarding research involving special populations such as children, prisoners, and the mentally disabled. The Commissioner forsees specific proposals for FDA regulations to implement appropriate recommendations of the Commission. In the interim, the Commissioner believes that at a minimum the investigators should consult in advance with sponsors and, when required, institutional review boards about utilization of such populations in clinical investigations.

5. *The administration of concomitant or concurrent thereapy under conditions which confound interpretation of results.* A recurring problem in investigational drug studies is the use of more than one pharmaceutical agent in the subject, often to treat the condition under study. The Commissioner recognizes the medical necessity to provide quality medical care to subjects who participate in research. This means that drugs or therapies other than the one undergoing evaluation bust be given to research subjects on occasion. Such concomitant medication can sometimes be anticipated and its use described in the protocol, and sometimes it cannot. The principle to be maintained is that concomitant medication is to be avoided whenever possible, introduced in such a way as not to confound the study whenever such medication is necessary, and in any event reported accurately so that the data can be interpreted correctly. If confounding concomitant medication is introduced with any frequency in a study, the validity of the study is seriously undermined, and such investigation raises a separate ethical issue of whether the subject should have received the test article in the first place.

It should be emphasized that none of these alterations of the protocol is being forbidden or even subjected to prior FDA approval, except in the case of investigational devices in proposed § 812.105 (21 CFR 812.105) published in the FEDERAL REGISTER of August 20, 1976 (41 FR 35282). In §§ 54.120 and 54.130 (21 CFR 54.120 and 54.130), the Commissioner proposes, that each protocol be in writing; that any change in a protocol be documented and dated; and that significant modifications of an investigation, if not contemplated in the original protocol of the investigator, not be undertaken without prior consultation and agreement with the sponsor and, where appropriate, the institutional review board. If the change is made to reduce the risk to subjects, it may be implemented without prior notice or approval, but the investigator must notify the sponsor and board within 10 working days. (In the IDE proposal of August 20, 1976, the Commissioner had suggested a 5-day period in this requirement; comments received have persuaded the Commissioner to modify the period to 10 days.)

Proposed § 54.132 (21 CFR 54.132) would codify a requirement applicable to the use of edible products from food-producing animals which are the subjects of a clinical investigation. It mandates that the investigator obtain authorization from FDA or the U.S. Department of Agriculture, and observe the withdrawal period following administration of the test article, before using edible products.

SUBJECTS IN CLINCIAL INVESTIGATIONS

The requirement that human subjects be informed that a test article is experimental, and that they consent to becoming participants in the experiment, first appeared in American statutory law in the final paragraph of section 505(i) of the Act, which was added by the Drug Amendments of 1962. These additions were in reaction to the thalidomide investigation, in which a significant number of patients were neither told of the experimental nature of the drug nor asked to become research subjects. A paragraph containing the verification required by section 505(i) was included in item 6.g. of form FD-1572 and item 4.g. of form FD-1573 soon after enact-

ment of the 1962 amendments. In 1966 and 1967, FDA promulgated detailed regulations defining concepts contained in section 505(i), as well as setting forth the elements of consent and the circumstances when consent must be obtained in writing or may be obtained orally (§ 310.102). When the FDA surveys were completed in the early 1970's, a significant number of deficiences were found in the performance of investigators; consequently, the Commissioner believes it important to affirm the FDA's commitment to the precepts of fully informed voluntary consent.

In a final rule published in the FEDERAL REGISTER of May 30, 1974 (39 FR 18914), the Department of Health, Education, and Welfare promulgated 45 CFR Part 46 governing informed consent in research funded or supported by the Department (revised March 13, 1975 (40 FR 11854)). There are several important differences between 45 CFR Part 46 and those currently set forth in 21 CFR 310.102. The Commissioner intends to revise and update § 310.102 in the near future in a separate rule making proposal to incorporate the appropriate departmental standards as well as other relevant materials.

In the August 20, 1976 notice, the Commissioner proposed to establish standards in subpart F of part 812 defining the requirements of informed consent for investigational use of devices, which is governed by section 520(g)(3)(D) of the Act. This section differs from section 505(i) in several important respects, both in the text and in the legislative history; certain differences therefore appear between the proposed subpart F of part 812 and the current § 310.102. These will be reviewed and reconciled in the planned revision of § 310.102.

At this time, therefore, the Commissioner proposes only to codify the current obligations under § 310.102 and proposed Subpart F of Part 812 in the standards for clinical investigators, and proposed § 54.142 (21 CFR 54.142) so provides.

The Commissioner would add a new requirement in proposed § 54.143 (21 CFR 54.143), regarding consent by owners of animals used for research purposes in a clinical investigation. Because of the risks to the animals themselves, and, in the case of food-producing animals, to humans from residues of the test article, it is important that the owner of the animal be aware of and consent to the clinical investigation.

The Commissioner concludes that the following types of records are relevant to a clinical study:

Record type	Record contents	Record location
A. "Prior Medical History" (covering the period prior to the subject's involvement in the clinical study).	Basic I.D. information Physicals Therapy Lab results, X-rays Progress notes Consultations Correspondence	Physician files. Hospital files. Other facility files (e.g., out-patient clinics and nursing homes).
B. "Clinical Study Medical History".	Same as above covering the period of the subject's involvement in the clinical study.	Same as above and an integral part of the above.
C. Case report form D. Followup report form	Clinical study and followup data abstracted from prior and clinical study medical history records.	Sponsor and FDA files, copy usually retained by the clinical investigator.

Section 54.155 proposes that the types of records described in A and B in the table above be maintained by an investigator as backup data to what is submitted in the case report. Some investigators surveyed suggested that no records regarding a subject's health before his entry into an investigation can be required. Clearly, certain portions of such records can be highly relevant, and other portions immaterial; only the pertinent parts need be included in the case report form of a specific investigation. As discussed further below, however, in certain cases, FDA's attempt to verify data will require that the inspection go beyond the case report form to corroborating information. Additionally, the data regarding administration or dispensing of test articles (as well as any control article) shall be maintained in the subject's records, as well as in the records required for control of the article in proposed § 54.108. The proposed regulation also emphasizes that the scope of observations made during the study includes the appearance of factors that might alter the effects of the test article, even though such factors are not considered to be caused by or associated with the article under investigation.

Certain comments on a similar provision contained in the IDE proposal objected that these requirements concerning the content of patient records would be an unlawful intrusion into the practice of medicine. Others proposed allowing patient data sheets to be substituted for clinical case reports in appropriate situations. The Commissioner believes that the requirements proposed in § 54.155(a) comport with sound scientific investigation and reflect the minimum amount of information necessary to be maintained as backup data for case reports to enable FDA to assure compliance with the standards governing clinical investigators, to review the progress and conduct of the investigation, and ultimately to evaluate the safety and, where applicable, the effectiveness of the test article. The Commissioner is explicitly authorized to require such records under sections 505(i)(3), 507(d)(3), 512(j), and 520(g)(2)(B)(ii) of the act; and such records are implicit in the other statutory sections under which these proposals are issued, as essential to establish the validity and completeness of reports of clinical investigations submitted to FDA in support of applications for research or marketing permits.

The Commissioner advises that proposed § 544.155(a) addresses the totality of records that must be kept regarding a clinical investigation, rather than the form and content of clinical case report forms. The latter vary from investigation to investigation and are currently governed by the protocols prepared by the sponsors and, in some cases, by FDA regulations contained in parts 312, 511, and proposed 812 or in the IND's, INAD's, and IDE's granted under those regulations. Patient data sheets are an appropriate part of the records of an investigation, but they almost certainly would be inadequate to serve as the complete records of the investigation; the acceptability of such sheets as clinical case reports would depend on the type and status of the particular investigation.

In research studies conducted in animals, proposed § 54.155 also allows records of specific measurements to be maintained on each group rather than on each individual subject in those studies where a group response rather than an individual response is an appropriate measurement.

REVIEW BY INSTITUTIONAL REVIEW BOARD

Since 1971, FDA has required initial and ongoing peer group review of clinical new drug investigations with institutionalized human subjects. Such review reinforces the protection of the rights and safety of subjects who, if

they are institutionalized, may be legally or practically less capable of making a free and informed choice to participate in the research. As a separate aspect of the FDA bioresearch monitoring program, a task force has been created to evaluate existing regulations regarding institutional review requirements, prepare recommendations to the Commissioner for improvements, and develop an agency-wide compliance program to enforce these regulations. The Commissioner anticipates publishing in the FEDERAL REGISTER in the near future a comprehensive proposal regarding institutional review boards; consequently, those matters are not the subject of this document. The Commissioner does believe, however, that this proposal should include several specific obligations of clinical investigators regarding institutional review, which reflect existing rules (item 10.c. of form FD-1571, item 3. of form FD-1572, and item 2.a. and b. of form FD-1573).

First, proposed § 54.25(a) provides that the investigator shall submit, or make certain that the sponsor submits, the proposed clinical investigation for the board's review, and that the board must approve the investigation before human subjects are allowed to participate in, or requested to consent formally to participate in, the investigation. Comments on a similar provision as part of the IDE proposal questioned whether this requirement would preclude a prestudy survey to determine whether potential subjects would be interested in participating in a contemplated study; such surveys, it was said, are useful in determining whether the investigation would be feasible if approved. The Commissioner advises that such surveys are not precluded by this regulation, so long as formal consent of each subject is obtained after the investigation is approved. Under proposed § 54.25(c), the investigator also may not use a consent form that has not been approved by the board.

Another obligation of investigators, set forth in proposed § 54.25(b) and § 54.130(a), is to submit, or make certain that the sponsor submits, all proposed changes in the investigation to the board for approval before implementation, unless the change is made to reduce or eliminate risk to the subjects. This point is discussed above in this preamble.

The investigator must report to the board any unanticipated serious adverse reactions, deaths, or any other life-threatening medical problems within 10 working days of detection by the investigator or of the investigator's being informed of them by the sponsor. The investigator must also report periodically on the progress of the investigation and within 3 months after completion, termination, or discontinuation of the entire study or of his or her protocol (whichever is sooner); such reports will guarantee that the board is aware of developments in the cessation of the investigation. These requirements are set forth in proposed §§ 54.25(d) and 54.185 (b) and (c) (21 CFR 54.25(d) and 54.185 (b) and (c)).

Finally, § 54.25 provides that the investigator shall respond to requests of the board for information and retain records of all contacts with the institutional review board as part of the records of the investigation.

RECORDS AND REPORTS OF A CLINICAL INVESTIGATION

Periodic reports to the sponsor on the progress of an investigation enable the sponsor to collate and review data to obtain an overall view of the study and provide useful information back to the investigator, as well as to FDA; FDA has required annual progress reports to be submitted by the sponsors to the agency (§ 312.1(a)(5)). The current drug investigator forms refer to this requirement, but do not indicate whether investigators are similarly obligated to report annually to sponsors (item 6.d. of form FD-1572 and item 4.d. of form FD-1573). The Commissioner proposes to resolve any ambiguity by establishing such a rule in proposed § 54.185(a).

There is currently a requirement for a final report from an investigator at the end of an investigation only in form FD-1573, item 4.d., although it is common practice to submit such a document. Occasionally, however, FDA inspectors have discovered that an investigator has stopped his research, for any of a variety of reasons, without notifying the sponsor. This failure to notify the sponsor unnecessarily delays a definitive analysis of investigation results and prevents making meaningful decisions. In proposed § 54.185(b), the Commissioner proposes to require that an investigator submit a final report within 3 months of the completion, termination, or discontinuation of the entire clinical investigation or of his or her protocol, whichever occurs first.

To warn other investigators of possible hazards and permit reassessment of the benefit-to-risk ratio justifying a clinical investigation, timely reports of adverse reactions are currently required (item 6.d. of form FD-1572 and item 4.d. of form FD-1573; compare § 312.1(a)(6)). To specify more precisely when reports are required and how quickly they must be submitted, the Commissioner proposes in § 54.185(c) that a special report be required for any serious adverse effect, death, or life-threatening problem that may reasonably be regarded as caused by or associated with the test article and that was not previously anticipated (in nature, severity, or degree of incidence) in the written information given to the investigator by the sponsor (item 6.a. of form FD-1572, item 4.a. of form FD-1573, and § 312.1(a)(6)). This requirement should eliminate any repeated reports of routine and minor side effects (nausea, dizziness, drowsiness) once these are inserted in the sponsor's brochure for investigators, but would require reports of unusual, serious, or unanticipated reaction.

Another change in special reporting obligations is the replacement of current nonspecific deadlines ("promptly" and "immediately") with a simple standard: As soon as possible but in no event later than 10 working days after discovery.

Numerous comments were recieved on a provision similar to proposed § 54.185(c) in the IDE proposal of August 20, 1976, except that that provision required reporting of all known deaths and all life-threatening medical problems occurring in the study, regardless of cause; and required reports to be filed within 5 working days. Many objected to reporting a serious incident when it could be and in fact was foreseen, for example, when an extremely serious or terminal medical condition for which no accepted therapy exists is being treated with the test article. The Commissioner agrees that special reports under such circumstances would be unnecessarily burdensome, and has revised this proposal accordingly. The comments on the 5-day reporting period argued that it was too brief to permit an adequate review of the case by the investigator to determine whether the incident could reasonably be regarded as caused by or associated with the test article. The Commissioner is now proposing a period of 10 working days, which he believes is clearly adequate for the type of determination being requested. Absolute proof of causality is not necessary; a reasonable belief that an association may exist between the test article and the adverse phenomenon is sufficient to justify notification to the sponsor and the institutional review board.

These changes are intended to keep special reports as an important means to communicate important safety information. The Commissioner also proposes to require expressly that all reports be accurate and adequate in content, a standard now only implicit in the regulations.

The clinical investigation records that would be required to be prepared by an investigator under this proposal include: Communications with an institutional review board, if any (§ 54.25(f)); receipts and disposition of

the test article (§ 54.108); the protocol and any changes in it (§ 54.120); records on individual subjects (§ 54.155); and reports on the investigation (§ 54.185(d)).

The current investigational drug regulations require an investigator to retain copies of these records either for 2 years following approval of a marketing permit (e.g., NDA or NADA) for the drug, or 2 years after discontinuation of the IND (or INDA) if an NDA (or NADA) is not approved (item 6.e. of form FD-1572 and item 4.e. of form FD-1573). This second provision seems unnecessarily burdensome. The agency needs an adequate opportunity to take steps to verify the study if it desires, while an investigator should have a reasonable and finite period of responsibility. A distinction should also be drawn between the purposes for which the investigator studied the article and other purposes; experience shows that products may be approved for marketing for one use while still being investigated for other uses. The Commissioner therefore proposes in § 54.195(a) (21 CFR 54.195(a)) to require records to be kept for one of three alternate 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.

Existing FDA regulations do not provide any mechanism for an investigator to transfer his or her records to another party, should he or she decide to move or retrire, or be otherwise unable to continue his or her obligations. The proposed § 54.195(b) allows such a transfer for the first time.

Compliance and Enforcement

Defining the obligations of investigators in conducting clinical investigations constitutes a major restatement and clarification of FDA policy. It does, however, raise the question of what to do if an investigator fails to carry out these requirements. Several options are available, and each has an appropriate place in the FDA compliance program. The regulatory sanctions available for use in cases of noncompliance include:

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

2. Issuing more formal warnings that important discrepancies between the conditions observed and regulatory requirements must be corrected if the investigator is to avoid more severe 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 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 look upon that study as providing evidence of safety or effectiveness of the product or for any other condition required by law for a research or marketing permit. 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 conduct of clinical investigators 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 investigator as an acceptable researcher to conduct clinical investigations regulated by or submitted to FDA. This would mean that no new clinical investigation subject to prior submission to FDA (i.e., via an IND, INAD, or IDE) would be authorized if it were to be conducted by the investigator. Second, similar ongoing clinical investigations conducted by the investigator would be terminated immediately or phased out if transfer of patients to another investigator was necessary. Third, data and information from any clinical investigation previously performed by the investigator might not be considered in support of any application for a research or marketing permit. This might lead to termination of a previously granted permit if, without the investigator's studies, the safety or effectiveness of the article could no longer be demonstrated. In the case of disqualification, the determination that data generated by the investigator are not acceptable in support of an application is not limited to a particular study but may extend to all investigations carried out by the investigator which may have been affected by the violative behavior. This sanction would be utilized when the deficiencies found in an investigator's work are of such a widespread or fundamental nature that the safety of subjects in, or the rights of human subjects in, or the quality and integrity of a number of studies conducted by the investigator have probably been compromised, or when the investigator has failed to comply with FDA regulations after previous warnings from the agency. The Commissioner deems disqualification an important alternative to rejection of specific investigations and prosecution (discussed below) because it can reduce by consolidation the number of investigations and proceedings that might be required for a study-by-study review, it can permit the agency to accept a study that might otherwise have to be rejected and repeated with an unnecessary risk to human subjects, and it obviates using judicial proceedings except for deliberate or flagrant offenses. Unlike rejection of a specific investigation and prosecution, disqualification is not explicitly provided for by statute and thus necessitates the 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 noncompliance with these regulations. It 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 obligations of clinical investigations, but will be considered in appropriate circumstances.

6. Recommending prosecution of an investigator and/or the sponsor of a clinical investigation for violations of Federal criminal laws, including violations of the Act and/or the U.S. Criminal Code (e.g., 18 U.S.C. 1001). Even where the investigator is not under a direct statutory obligation to comply with FDA investigational require-

ments or to submit information to FDA, and in fact does not send data to the agency but merely transmits them to the sponsor, the investigator is likely to be aware that FDA will be the ultimate recipient. In such cases, the investigator could be liable for aiding and abetting in a violation (18 U.S.C. 2) or for causing a violation to be made by a third party. Nevertheless, the circumstances in which criminal penalties might be sought represent the rare and extraordinary cases, such as deliberate fraud or willful and harmful violations of individual rights or safety.

The Commissioner is aware of the wide range of severity in these sanctions. He has directed the preparation of a compliance program that will identify the administrative and legal sanctions 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. An understanding of this document should assuage fears that individuals not in compliance with the clinical investigator regulations will be unduly subject to extreme penalties.

DISQUALIFICATION OF A CLINICAL INVESTIGATOR

The experience of FDA in enforcing regulations pertaining to the conduct of persons carrying out studies 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 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 (§§ 312.1(c) and 511.1(c) (21 CFR 312.1(c) and 511.1(c))).

Disqualification 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 or INAD. 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 such investigator can demonstrate his or her ability and willingness to conform to the standards for conducting clinial investigations essential to insure 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.

In 15 years, the Food and Drug Administration has disqualified only 24 investigators. The Bureau of Drugs has disqualified 22; and the Bureau of Biologics (and its predecesor, the Division of Biologics Standards), 2. Although the results of FDA surveys discussed above are of concern, the Commissioner does not believe that they indicate that the majority of investigators are not performing acceptably or that large numbers of disqualifications are necessary, and he is hopeful that a reaffirmation and more precise statement of FDA rules will significantly improve compliance.

After reassessment of agency experience with disqualification and the available alternatives for enforcement of these regulations, and for the reasons just discussed, the Commissioner has determined that disqualification should continue to be used by FDA in all areas of clinical investigation, not simply investigational new drug studies. In addition, the disqualification process, unlike rejection of a study, provides the individual alleged to have violated these regulations an opportunity to be heard before the agency in his or her own behalf. The Commissioner is aware that in some instances, the sponsor of a clinical investigation has little or no interest in defending the quality of the study or the actions of the investigator because such sponsor may benefit most by acquiescing in the agency's challenge to the study. Disqualification creates a forum for the individual whose work is being questioned to explain or justify the activities that are in doubt. Finally, 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.

The regulations governing disqualification of clinical investigators are proposed to be set forth in subpart K of part 54. Proposed § 54.200 (21 CFR 54.200) codifies the purposes of disqualification and states clearly the meaning of this administrative action.

Comments received on the proposed disqualification regulations regarding clinical investigators of investigational devices published in the FEDERAL REGISTER of August 20, 1976, and statements made at a hearing before FDA on the proposed disqualification regulations regarding nonclinical testing facilities as part of the good laboratory practice rule making published in the FEDERAL REGISTER of November 19, 1976, objected to the way in which the grounds for disqualification were set forth in those documents. Comments and statements are on display in the office of the Hearing Clerk as part of the records of those proceedings. The Commissioner concurs that, as drafted, those proposals implied that disqualification could occur as the result of insignificant deficiencies in investigator conduct, 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 intent in proposing the disqualification mechanism and to minimize the possible abuse of this sanction in the future, the Commissioner proposes in § 54.202 (21 CFR 53.202) a more restrictive statement of the grounds for disqualification of a clinical investigator. A clinical investigator may be disqualified only if the Commissioner finds all three of the following: (1) That the investigator failed to comply with one or more of the obligations set forth in part 54 or in any other FDA regulation governing the conduct of clinical investigators, e.g., the IND, INAD, or IDE regulations; (2) that the noncompliance adversely affected (a) the validity of the data produced in the investigation, and/or (b) the rights of human subjects, and/or (c) the safety of human or animal subjects; and (3) that other lesser regulatory actions, such as warnings or rejection of individual studies, have not been or probably will not be adequate to achieve compliance by the investigator. These requirements assure that the sanction will not be used in trivial situations, but only when the violation has compromised the integrity of the study or the rights or safety 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 investigator's conduct evidences a deliberate violation of the regulations or a flagrant disregard of his or her obligations.

The Commissioner proposes, in § 54.204 (21 CFR 54.204), 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 clinical investigator 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 studies and other remedies are inadequate to achieve compliance, the Commissioner or his designate, on recommendation from the Bureau Director, may elect to commence the proceeding by providing a notice of the proposed action to the investigator; 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 clinical investigator upon commencement of a disqualification proceeding shall contain the following items of information, in accordance with § 16.22(a) (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 investigator 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 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 investigator 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 (§ 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 discernible 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 regarding clinical investigators of investigational medical devices, contained in the August 20, 1976, 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 these safeguards as well as others essential to due process. Interested persons are referred to those regulations for a complete description of the procedures referred to in proposed § 54.204 as applicable to disqualification proceedings.

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 investigator. Proposed § 54.206 (21 CFR 54.206) provides that the final order shall include a statement of the basis for the disqualification. If, on the other hand, the Commissioner does not 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 investigator. If the investigator is disqualified, the Commissioner will also notify, to the extent possible, the sponsor of every clinical investigations subject to an IND, INAD, or IDE in which the investigator is participating or has participated. 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 sponsor be notified at the commencement, rather than the completion, of disqualification proceedings. In certain cases, it may be both appropriate and advisable for the sponsor of an investigation to be made aware of the allegedly violative conduct of one of its investigators; such information ought not necessarily be withheld from the sponsor until after FDA has disqualified the investigator. Therefore, proposed § 54.213(c) allows, but does not require, the Commissioner to provide the sponsor with such information simultaneously with a proposal to disqualify the investigator unless there are overriding safety considerations that warrant earlier notification. The Commissioner is not convinced that every sponsor needs to be notified every time disqualification of an investigator is proposed, but he invites further comment on this matter.

Once a clinical investigator has been disqualified, no new clinical investigation requiring prior review by FDA will be authorized by the agency if it is to include the investigator. This rule is proposed in § 54.210(a) (21 CFR 54.210(a)). Since the agency has no statutory authority to suspend or terminate clinical investigations not done under an IND, INAD, or IDE, it will not be possible to deny permission to conduct these investigations when they involve the disqualified investigator.

In issuing an order disqualifying a clinical investigator, the Commissioner must consider what, if anything, should be done regarding ongoing investigations that involve the investigator. 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 actual conduct of the investigation to an investigator who is in compliance with FDA requirements; 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 which 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 investigator. The Commissioner does not believe it possible, much less advisable, to require that any particular option be used for all 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 involvement of an acceptable investigator. Proposed § 54.210(b) authorizes, but does not require, the actions that might be taken. The Commissioner especially invites comments on these proposals and suggestions for other ways to address this sensitive problem.

Proposed § 54.10(c) provides that each application for a research or marketing permit, approved or not, that contains or relies upon a clinical investigation conducted by a disqualified investigator 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 disqulification 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 appoved, FDA will then determine whether data from the investigation are acceptable, notwithstanding disqualification.

To avoid FDA's auditing every such investigation, any study performed by an investigator before or after disqualification, but before reinstatement, may be presumed to be unacceptable; and the person relying on the data resulting from the investigation may have to establish that the data were not affected by the kind of circumstances that 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 not be considered in support of the application for a research or marketing permit. Elimination of such data may serve as "new information" justifying termination of an IND, INAD, or IDE, initiation of the withdrawal of approval of an authorizing regulation or of a product license, or the revocation of a product monograph or standard.

Under proposed § 54.210(d), after an investigator has been disqualified, FDA will not consider any clinical investigation begun by that investigator in support of any application for a research or marketing permit. However, the applicant is not relieved 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 investigator be disqualified in order 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 judge 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 a product or an investigator who conducted the clinical investigation 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 not in 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 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 finding that a product is safe or effective, 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 the investigator when, for example, the investigation was performed during a period when the investigator was not in compliance with FDA regulations but 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 a clinical investigator will be reserved for cases where the rejection of a particular investigation is an inadequate regulatory response.

The agency maintains that it should affirmatively provide information regarding the disqualification of a clinical investigator to entities having professional dealings with that investigator, such as other Federal, State, or local government agencies supporting research studies, State and local licensing agencies by whom the investigator is licensed, and institutions and universities in which the investigator practices or teaches. Many objections were received to this aspect of disqualification in the IDE proposal of August 20, 1976. The Commissioner notes, however, that in the past, officials of such entities have in fact complained to FDA that it failed to notify them about a disqualification and that this failure deprived them of an opportunity to consider the liability of the institution for which they were responsible or the value of continuing to fund research by the investigator after the disqualification. Moreover, the Commissioner deems the providing of such information within the purpose of section 705 of the act (21 U.S.C. 375).

Because he recognizes that the consequences of such notice could have a serious adverse effect on the reputation and career of the individual, the Commissioner believes that the investigator must be aware that such notice is one of the results of disqualification (*Wisconsin* v. *Constantineau*, 400 U.S. 433 (1971)). Proposed § 54.213(a) (21 CFR 54.213(a)) would expressly authorize FDA to notify such entities when the Commissioner believes that such disclosure would further the public interest or would promote compliance with applicable FDA regulations. 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 institutions or persons have an involvement in the ongoing activities of the investigator. 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 such notification shall be given to the investigator.

Under proposed § 54.213(b), a determination that a clinical investigator 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 FDA public information regulations under part 20 (21 CFR Part 20) as records relating to an administrative enforcement action that has been completed.

Since disqualification of a clinical investigator 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 § 54.215 (21 CFR 54.215) makes clear, therefore, that FDA may at any time recommend institution of any appropriate judicial proceedings (civil or criminal) and may take any other appropriate regulatory action, in addition to or in lieu of, and before, at the same time as, or after, disqualification. This would, of course, include refusing to consider a particular study in support of a particular application—the regulatory action that probably will be most commonly used in cases of significant noncompliance with the clinical investigator regulations. The agency may also refer the matter to another Federal, State, or local law enforcement, regulatory, research-supportive or other governmental agency for such action as that agency determines to be appropriate.

In accordance with § 312.1(a)(8), the sponsor of a clinical investigation must remove an investigator from further participation in the investigation at any time the investigator fails to keep the required records. Proposed § 54.217 (21 CFR 54.217) makes clear that the sponsor has authority to suspend or terminate a noncomplying investigator whether or not FDA has commenced

any action to disqualify that investigator. Furthermore, in removing an investigator, the sponsor is not required to utilize either the grounds or the procedures for disqualification set forth in this proposed regulation. The sponsor is required, however, to advise the appropriate bureau within FDA of this action and to supply the reasons for it within 15 working days. This principle follows the decision of the Federal district court in *Froning* v. *Travenol Laboratories, Inc.* (N.D. Calif., Civil Action C75-0767, 1975, a copy of which has been placed on file with the FDA hearing clerk), in which an investigator was denied injunctive relief to compel the sponsor to continue shipping investigational drugs after the sponsor had determined to suspend the investigator for what the sponsor concluded were violations of the protocol.

Disqualification is principally a remedial action to prevent future violations and 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 investigator can and will fulfill the requirements imposed under these proposed regulations.

Proposed § 54.219 (21 CFR 54.219) authorizes the Commissioner to reinstate a clinical investigator (i.e., to determine that he or she may again conduct investigations under an IND, INAD, or IDE, and that data from investigations performed by him or her may once again be considered in support of applications for research or marketing permits), if the Commissioner finds that the investigator can provide adequate assurances that he or she will operate in compliance with the requirements of FDA regulations. An investigator who wishes to be reinstated shall explain to the Commissioner why he or she believes reinstatement is warranted, and shall provide a detailed description of the corrective actions the investigator has taken or intends to take to assure that the acts or omissions which led to the disqualification will not recur. The Commissioner may condition reinstatement upon commitments from other persons (e.g., sponsor, parent institutions, institutional review boards, or other investigators) to monitor in detail the investigator's activities, and/or upon the submission of a specific protocol providing for additional steps that the Commissioner determines are necessary to assure compliance. Reinstatement may also be contingent upon the investigator's passing a subsequent FDA inspection.

In fairness to the investigator, all persons notified under proposed § 54.213(a) of the investigator's previous disqualification must be notified when he or she is later reinstated; proposed § 54.219 so provides. Once reinstated, a clinical investigator may thereafter conduct additional new investigational studies without again going through the reinstatement process. A determination that an investigator has been reinstated is disclosable to the public under the Freedom of Information Act (5 U.S.C. 552) and under 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, a drug or biologic for human use, a drug for animal use, or a 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 of 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. The promulgation of these regulations provides one process for making this judgment. While compliance with the regulations does not guarantee the ethical or scientific acceptability of, or the validity of data from, a clinical investigation, failure to comply substantially increases 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 and animal subjects. Thus, these regulations 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 (21 U.S.C. 371(a)), the Commissioner is empowered to promulgate regulations for the efficient enforcement of the act. Previously, the Commissioner has issued regulations under § 314.111 (a)(5) (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 statute, "adequate and well-controlled") to support approval of a new drug. These regulations were issued under section 701(a) and have been upheld by the Supreme Court (*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), 512(j) 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. These proposed regulations are intended to fulfill this mandate.

The Commissioner has therefore concluded that legal authority to promulgate these regulations regarding clinical investigators exists under sections 505(i), 507(d), 512(j), 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, 503, 505, 506, 507, 510, 512, 513, 514, 515, 516, 518, 519, 520, 601, 706, and 801 of the act (21 U.S.C. 346, 348, 349, 352, 353, 355, 356, 357, 360, 360b, 360c, 360d, 360e, 360f, 360g, 360h, 360i, 361, 376 and 381), as well as the responsibilities of FDA under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

Inspections of Clinical Investigators

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 performed by an investigator. Therefore, the proposed regulations under § 54.15(c) provide that the agency will not consider data from a clinical investigation in support of an application for a research or marketing permit unless the investigator who conducted the investigation consents to inspection by FDA. The Commissioner believes that this requirement does not infringe on any rights or obligations of an investigator who may, at any time, refuse to consent to inspection or

withdraw his or her consent. In this event, however, FDA will not consider the results of the study and may consider disqualifying the investigator. Such 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 or perform under grant or contract clinical investigations that may be submitted to FDA to consider including in the grant or contract provisions regarding FDA inspections. Such a provision is especially important if the investigator is not otherwise aware that the results of the investigation may be submitted to FDA.

Inspections of many, perhaps most, clinical investigators will not be conditioned upon consent. Under section 704(a) of the act (21 U.S.C. 374(a)), 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 sections 505 (i) or (j), 507 (d) or (g), 519, or 520(g) of the act. (See in this regard § 200.10 (21 CFR 200.10).) In addition, any establishment registered under section 510 of the act is subject to inspection under section 704. Thus, most sponsors and many investigators under IND's, INAD's, IDE's, and those institutions in which such studies are conducted would be subject to FDA inspection whether or not they consented.

Current FDA policies regarding inspection of clinical investigators (item 6.e. of form FD-1572 and item 4.e. of form FD-1573) require clarification. During the FDA surveys discussed above, 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 FDA inspections of clinical investigators under the IDE proposal of August 20, 1976. 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 reason to believe that the records do not represent actual studies or do not represent actual results obtained" (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 investigator of FDA's intent to inspect the investigator's records, with a view to arranging a mutually convenient inspection time. Agency personnel must invite the investigator to be present with them throughout FDA's records review, and they must inform the investigator 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 investigator is to be given the right to delete any information that could identify an individual subject, except when: (1) A more detailed study of the records regarding particular subjects is indicated; 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 § 54.15(a) that an investigator permit authorized FDA personnel, at reasonable times and in a reasonable manner: (1) To inspect the facilities used by the investigator for the clinical investigation, and (2) 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 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.

The Commissioner recognizes the highly sensitive nature of this provision, as reflected in the many comments already received by FDA on the IDE proposal. He 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 regarding regulatory hearings before the agency set forth in § 16.1 (21 CFR 16.1), to delete cross-references to the current regulations regarding disqualification of investigators, and to include a cross-reference to the procedures proposed in this notice.

The current definitions of the term "sponsor" found in §§ 310.3(j) and 510.3(k) (21 CFR 310.3(j) and 510.3(k)) are to be superseded by the proposed definition in § 54.3(f) discussed above. Therefore, the Commissioner is proposing to eliminate the current definitions.

Because of the clarification of the obligations of clinical investigators, the Commissioner intends to revise the current investigator forms FD-1572 and FD-1573 to correspond with the proposed part 54. Rather than repeat these provisions in the forms in this proposal, which might confuse readers and lead to duplicative comments, the Commissioner will propose, in a separate FEDERAL REGISTER issuance, the changes in the forms to reiterate the regulations proposed here, as modified in light of the comments received.

With the revision of the obligations of clinical investigators, the Commissioner also deems it appropriate to revise the substantive provisions governing the use of new animal drugs in clinical investigations set forth in

§ 511.1(b) (21 CFR 511.1(b)). The revision clarifies and incorporates all of the requirements under section 512(j) of the act.

The proposed procedures regarding disqualification of clinical investigators will supersede existing regulations in §§ 312.1(c) and 511.1(c). Therefore, the Commissioner is proposing to revoke these sections.

The Commissioner also proposes to add or revise regulations regarding food and color additives, new drug applications, bioavailability and bioequivalence testing requirements, OTC drug products, radioactive drugs, antibiotic drugs, new animal drug applications, biological product licenses, cosmetics, and electronic products, to incorporate appropriate implementing provisions for, and cross-references to, part 54.

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, 512-516, 518-520, 601, 701(a), 706, and 801, 52 Stat. 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-403 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b-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:

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. In § 16.1 by revising paragraph (b)(8) and by revoking and reserving paragraph (b)(11) as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(8) Section 54.204(b) of this chapter, relating to disqualifying a clinical investigator.

* * * * *

(11) [Reserved]

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2. By adopting new Part 54 to read as follows:

PART 54—CLINICAL INVESTIGATIONS

Subpart A—General Provisions

Secs.
54.1 Scope.
54.2 Exemptions.
54.3 Definitions.
54.15 Inspection of facilities and records.

Subpart B—Organization and Personnel

54.25 Institutional review board.

Subparts C-E [Reserved]

Subpart F—Test Articles

54.102 Use of test article by unauthorized persons.
54.108 Records of receipt and disposition of test articles.
54.114 Disposition of unused test articles.
54.116 Handling of controlled substances.
54.118 Promotion of test articles.

Subpart G—Protocol for Conduct of a Clinical Investigation

54.120 Protocol.
54.130 Conduct of a clinical investigation.
54.132 Withdrawal, withholding and discard periods for clinical investigations in food-producing animals.

Subpart H—Subjects in Clinical Investigations

54.142 Consent of human subjects.
54.143 Owner consent regarding animal subjects.
54.155 Records regarding subjects.

Subpart I [Reserved]

Subpart J—Records and Reports

54.185 Reporting of results of a clinical investigation.
54.195 Retention of records.

Subpart K—Disqualification of a Clinical Investigator

54.200 Purpose.
54.202 Grounds for disqualification.
54.204 Notice of and opportunity for hearing on proposed disqualification.
54.206 Final order on disqualification.
54.210 Actions upon disqualification.
54.213 Public disclosure of information regarding disqualification.
54.215 Alternative or additional actions to disqualification.
54.217 Suspension or termination of an investigator by a sponsor.
54.219 Reinstatement of a disqualified clinical investigator.

AUTHORITY: Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 601, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 68 Stat. 511-517 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-403 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 357, 360, 360b-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

§ 54.1 Scope.

This part contains the general obligations and commitments of, and regulations governing conduct of, persons who conduct clinical investigations regulated by the Food and Drug Administration under section 505(i), 507(d), 512(j), 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, human and animal drugs, animal food additives, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and regulations governing conduct of, persons who conduct clinical investigations involving particular test articles and products may also be found in other parts of this chapter, e.g., parts 312, 511, and 812. Compliance with these parts is intended to protect the rights and safety of 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, 512, 513-516, 518-520, 601, 706, and 801 of the Act and sections 351 and 354-360F of the Public Health Service Act.

§ 54.2 Exemptions.

Any investigator subject to the requirements of this part, or the sponsor of such investigator, may request the Food and Drug Administration for a waiver of any specific requirements. Such a request shall be submitted in writing as part of an application for a research permit in accordance with §§ 312.1, 511.1, or part 812 of this chapter, and shall set forth the basis for the applicant's belief that compliance with a particular requirement is not necessary either to protect the rights and safety of subjects involved in the particular clinical investigation or to help assure the quality and integrity of the data produced in the investigation. The Commissioner may, in the Commissioner's discretion, grant in writing a request for a waiver of certain requirements if it agrees with the applicant that compliance with those requirements in the course of the particular clinical investigation is not necessary. 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 agency at the same time the emergency application is appoved on an oral basis. Written confirmation shall be included in the official application submitted subsequent to this emergency authorization of such application.

§ 54.3 Defintitions.

As used in this part, the following terms shall have the meanings specified:

(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 parts 171 and 571 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 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) A "Notice of Claimed Investigational Exemption for a New Animal Drug," described in part 511 of this chapter.

(13) A new animal drug application, described in part 514 of this chapter.

(14) Data and information regarding a drug for animal 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.

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

(16) 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.

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

(18) 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.

(19) 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.

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

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

(22) 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.

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

(24) 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.

(25) 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 that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), 512(j), or 520(g) of the act, or is not subject to requirements for prior submission of 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) "Investigator" means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject.

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

(f) "Sponsor" means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of anther 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.

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

(h) "Subject" means an individual 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 healthy human being or a healthy or unhealthy animal or a patient to whom the test article might offer a therapeutic benefit or provide diagnostic information. The test "subject" applies both to human beings and to other animals; whenever only human subjects are referred to, the adjective "human" shall be used. The term "subject," when applied to animals other than man, may apply to individuals and/or groups based upon whether an individual or group response is being measured.

(i) "Test article" means any drug (including a biological product for human use), medical device for human use,

human or animal food additive, color additive, cosmetic, electronic, product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Act.

§ 54.15 Inspection of facilities and records.

(a) An investigator shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner:

(1) To inspect the facilities utilized by the investigator for the clinical investigation;

(2) For purposes of verification of case reports and other information prepared for the sponsor as part of the data and information to be submitted by the sponsor to the Food and Drug Administration:

(i) To inspect records required to be made or kept by the investigator as part of or relevant to the investigation;

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

(iii) 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) An investigator shall permit an authorized representative of the sponsor (e.g., the monitor selected under § 52.28 of this chapter), at reasonable times and in a reasonable manner, to inspect the facilities utilized by the investigator for the clinical investigation and to inspect, for purposes of verification of case reports and other information prepared for the sponsor, the records required to be made of kept by the investigator as part of the investigation.

(c) The Food and Drug Administration will not accept a clinical investigation as evidence in support of an application for a research or marketing permit if the investigator who conducted the investigation refuses to permit an inspection under this section. The determination that a clinical investigation may not be accepted 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

§ 54.25 Institutional review board.

If the clinical investigation is subject to an institutional review requirement under either parts 312 or 812 of this chapter or any other applicable regulation in this chapter:

(a) An investigator shall submit the proposed clinical investigation (including the protocol of the investigation, a report of prior investigations if a medical device for human use, and the materials to be used in obtaining the consent of human subjects, described in § 54.142(b)) for review by the board, and shall obtain the approval of the board, before any human subjects are allowed to participate in, or requested formally (i.e., in accordance with § 310.102 or subpart F of part 812 of this chapter, whichever is applicable) to consent to participate in, the investigation.

(b) An investigator shall submit any proposed change in or deviation from the protocol of the clinical investigation for review by the board if the change or deviation may increase the risk to human subjects in the study or may adversely affect the validity of the investigation or the rights of the human subjects, and shall obtain the approval of the board before such change or deviation is implemented. When the change or deviation is done to eliminate or reduce the risk to human subjects, it may be implemented before review or approval by the board; the investigator shall notify the board of the change or deviation in writing within 10 working days after implementation.

(c) In obtaining the consent of subjects, an investigator shall not use a form that has not been approved by the board.

(d) An investigator shall submit to the board the progress report required in § 54.185(a). An investigator shall submit to the board the final report required in § 54.185(b). An investigator shall submit to the board any special report relating to adverse effects required by § 54.185(c), or any information regarding similar reports received from the sponsor, as soon as possible and in no event later than 10 working days after the investigator discovers the information or is notified of it by the sponsor, e.g., when uncovered by another investigator or in a nonclinical laboratory study.

(e) An investigator shall provide accurate and adequate information regarding the clinical investigation to the board in response to its request.

(f) An investigator shall maintain records of all submissions to, and all actions by, the board regarding the clinical investigation.

Subparts C-E—[Reserved]

Subpart F—Test Articles

§ 54.102 Use of test article by unauthorized persons.

An investigator shall only permit a test article to be administered or dispensed to or used involving subjects who are under his or her personal supervision or under the supervision of another investigator who is responsible to him or her and, if it is a test article intended for use in humans, who is named by the investigator in his or her signed statement undertaking the obligations of an investigator or sponsor-investigator, e.g., forms FD-1571, FD-1572, or FD-1573 in § 312.1 of this chapter. An investigator shall not supply a test article to any other person for administration to or use upon subjects or for any other purpose, without the prior authorization of the sponsor.

§ 54.108 Records of receipt and disposition of test articles.

An investigator shall maintain adequate and accurate records showing the receipt and disposition of all supplies of a test article shipped to such investigator by the sponsor, including the dates, serial, lot, or other identification numbers (if any), quantities received, each quantity dispensed, administered, or used, with the identification of the subject who received it or involving whom it was used, and each quantity otherwise disposed of, including identification of the person who disposed of it, the person (if any) who received it, and the purpose or reason for its disposal, e.g., contamination or return to the sponsor. The records required in this section are separate from and in addition to the records required for individual subjects in § 54.155.

§ 54.114 Disposition of unused test articles.

An investigator shall return to the sponsor any unused or reusable supply of a test article, or otherwise dispose of the article as authorized in writing by the sponsor, upon request of the sponsor, upon completion, suspension, termination, or discontinuance of the clinical investigation, or upon termination or withdrawal by the Food and Drug Administration of the exemption under which the investigation is being conducted.

§ 54.116 Handling of controlled substances.

If a test article is a substance listed in any schedule of the Controlled Substance Act (21 U.S.C. 801 note; 21 CFR

Part 1308), the investigator shall take reasonable precautions to prevent theft or diversion of the article into illicit channels, including storage of the substance in a cabinet or other enclosure, which is substantially constructed and securely locked and to which access is restricted by the investigator.

§ 54.118 Promotion of test articles.

An investigator shall not represent in a promotional context that an unmarked test article is safe or effective for the purposes for which it is under investigation or otherwise promote or commercialize the article. This requirement is not intended to restrict the full exchange of scientific information concerning the article, including dissemination of scientific findings in scientific or lay communications media; its intent is to restrict promotional claims of safety or effectiveness for the article while the article is under investigation to establish its safety or effectiveness and to preclude commercial use or test-marketing of the article before authorization for marketing by the Food and Drug Administration.

Subpart G—Protocol for and Conduct of a Clinical Investigation

§ 54.120 Protocol.

(a) Each clinical investigation shall have a written protocol.

(b) All changes or revisions to a protocol, and reasons therefor, shall be documented by the investigator, dated, and maintained with the protocol.

§ 54.130 Conduct of a clinical investigation.

A clinical investigation shall be conducted in accordance with the protocol. An investigator shall not implement a change in the protocol, or otherwise deviate from such protocol, if the change or deviation may increase the risk to subjects in the study or may adversely affect the validity of the investigation or the rights of the human subjects, without the prior review and written approval of the sponsor of the investigation and, when such review is required under either § 312.1 or Part 812 or any other applicable regulation in this chapter, by an institutional review board. When the change is made to eliminate or reduce the risk to human subjects, it may be implemented before review or approval by the sponsor and the board; the investigator shall notify the sponsor and the board of the change or deviation in writing within 10 working days after implementation.

§ 54.132 Withdrawal, withholding, and discard periods for clinical investigations in food-producing animals.

An investigator in a clinical investigation that includes food-producing animals as subjects shall not offer the animals for slaughter for food purposes, or otherwise offer for food purposes edible products from the animals, without prior authorization from the Food and Drug Administration or the U.S. Department of Agriculture, and shall observe the authorized withdrawal, withholding, or discard time periods.

Subpart H—Subjects in Clinical Investigations

§ 54.142 Consent of human subjects.

(a) An investigator shall inform each human subject (or, where appropriate, the legal representative of the human subject), including any human subject used as a control, that the test article is being used for research purposes, provide the other information required by § 310.102(h) or subpart F of part 812 of this chapter, whichever is applicable, and obtain and properly document the consent of such subject (or the subject's legal representative), except in exceptional cases as defined in § 310.102(d) or subpart F of part 812 of this chapter, whichever is applicable.

(b) An investigator shall provide to the sponsor, and to the institutional review board, if any, a copy of any written materials to be given or read to the human subject, or the subject's legal representative, regarding the information required to be given by § 310.102(h) or subpart F of part 812 of this chapter (whichever is applicable), and a copy of any form to be used to document the consent of such subject or the subject's legal representative.

§ 54.143 Owner consent regarding animal subjects.

An investigator shall inform the owner or owners of each animal subject that the test article is being used for research purposes in a clinical investigation, and shall obtain and properly document the consent of such owner or owners.

§ 54.155 Records regarding subjects.

(a) An investigator shall maintain adequate and accurate records on which case reports on each subject (including a subject used as a control) are based, which shall include the following:

(1) Detailed medical history records which contain: (i) Medical history before the subject's involvement in the clinical investigation which includes basic identifying information linking the subject's record to the subject's case report forms submitted to the Food and Drug Administration, results of all diagnostic tests performed, diagnoses made, therapy provided, and other data on the condition of the subject.

(ii) Medical history during the subject's involvement in the clinical investigation, which includes all data described in paragraph (a)(1)(i) of this section as it relates to the exposure of the subject to the test or control article, and to any concomitantly or concurrently administered therapy, including the date (and time, if relevant) of each dispensing or administration and the quantity dispensed or administered; and, all relevant observations and data on the condition of the subject throughout the subject's participation in the investigation, including the appearance of factors that might alter the effects of the test article (e.g., development of an apparently unrelated intercurrent illness).

(2) Any documentation regarding the consent of the human subject required under § 310.102 or subpart F of part 812 of this chapter, whichever is applicable.

(b) In research in animals other than man, where a group response (rather than an individual response) is an appropriate measurement, the records required in this section may be maintained on each group for the specific measurement rather than on each individual subject in the group.

Subpart I—[Reserved]

Subpart J—Records and Reports

§ 54.185 Reporting of results of a clinical investigation.

(a) An investigator shall make accurate and adequate reports to the sponsor, and to any institutional review board that has reviewed and is continuing to review the investigation, on the progress of the clinical investigation at appropriate intervals not exceeding 1 year.

(b) An investigator shall make an accurate and adequate final report to the sponsor, and to any institutional review board that has reviewed and is continuing to review the investigation, within 3 months after the completion, termination or discontinuation of the entire clinical investigation or of such investigator's participation in it, whichever is sooner. This report shall include all case reports not provided to the sponsor in periodic or special reports.

(c) An investigator shall make an accurate and adequate special report to the sponsor, and to any institutional review board that has reviewed and is continuing to review the investigation, on any serious adverse effect, death, or life-threatening problems that may reasonably be regarded as caused by or associated with the test article and

which was not previously anticipated (in nature, severity or degree of incidence) in the written information on the article provided to the investigator by the sponsor. Such reports shall be made as soon as possible and in no event later than 10 working days after the investigator discovers the serious adverse effect, death, or medical problem.

(d) An investigator shall retain a copy of each report he or she submits to the sponsor and to an institutional review board under this section.

§ 54.195 Retention of records.

(a) An investigator shall retain the records required by this part or by any other regulations in this chapter regarding clinical investigations (e.g., parts 312, 511, and 812) for whichever of the following periods is shortest:

(1) 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 that were the subject of the investigation;

(2) 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

(3) In other situations (e.g., where the investigation does not result in the submission of the data from the investigation in support of or as part 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.

(b) In the event the investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to any other person who will accept responsibility for the records, e.g., the sponsor, an institutional review board, or another investigator. Notice of such transfer shall be given in writing to the sponsor.

Subpart K—Disqualification of a Clinical Investigator

§ 54.200 Purpose.

The purposes of disqualification of an investigator who has failed to comply with any of the regulations set forth in this part, or other regulations governing the conduct of investigators in this chapter, may be one or both of the following:

(a) To preclude him or her from conducting clinical investigations subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), 512(j), or 520(g) of the act until such time as it becomes likely that he or she will abide by such regulations or that such violations will not recur. The determination to disqualify an investigator does not constitute a finding or recommendation that the investigator is not qualified to practice or teach medicine or should be subject to other sanctions by other persons such as licensing boards or employers.

(b) To preclude the consideration of any clinical investigations in support of applications for a research or marketing permit from the Food and Drug Administration, which investigations have been conducted by the investigator, until such time that it becomes likely that he or she will abide by such regulations or that such violations will not recur 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.

§ 54.202 Grounds for disqualification.

The Commissioner may disqualify an investigator upon finding all of the following:

(a) The investigator failed to comply with any of the regulations set forth in this part or other regulations regarding the conduct of investigators in this chapter;

(b) The noncompliance adversely affected the validity of the clinical investigation or the rights of the human subjects, 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 investigator will comply with such regulations in the future.

§ 54.204 Notice of and opportunity for hearing on proposed disqualification.

(a) Whenever the Commissioner has information indicating that grounds exist under § 54.202 which in the Commissioner's opinion may justify disqualification of an investigator, the Commissioner may issue to the investigator a written notice proposing the investigator be disqualified.

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

§ 54.206 Final order on disqualification.

(a) If the Commissioner, after the regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, makes the findings required in § 54.202, the Commissioner shall issue a final order disqualifying the investigator. Such order shall include a statement of the basis for that determination and shall prescribe any actions (set forth in § 54.210(b)) to be taken with regard to ongoing clinical investigations being conducted by the investigator. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the investigator of the action, as well as the sponsor of each clinical investigation subject to requirements for prior submission to the Food and Drug Administration that was being conducted by the investigator and has not been terminated or discontinued or as to which the exemption under which it is being conducted has not been terminated or withdrawn by the Food and Drug Administration.

(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 § 54.202, 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 investigator and provide a copy of the order.

§ 54.210 Actions on disqualification.

(a) No clinical investigation subject to requirements for prior submission to the Food and Drug Administration will be authorized by the Commissioner if such investigation is to be conducted, in whole or part, by a disqualified investigator.

(b) The Commissioner, after considering the nature of each ongoing clinical investigation subject to requirements for prior submission to the Food and Drug Administration that is being performed by the investigator, the number of subjects involved, the risks to them from suspension of the investigation, and the need for involvement of an acceptable investigator, may direct, in the final order dis-

qualifying an investigator under § 54.206(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 investigator is reinstated under § 54.219 or another investigator accepts responsibility for the investigation.

(2) No new subject shall be allowed to participate or be requested to participate in the investigation until the investigator is reinstated under § 54.219 or another investigator accepts responsibility for the investigation.

(3) Any human subject who has previously been allowed to participate in the investigation and who remains under the supervision of the 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 investigator or one acting as a control, shall 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 investigator is reinstated under § 54.219 or another investigator accepts responsibility for the investigation.

(4) Any human 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 investigator accepts responsibility for the investigation; or

(ii) The disqualified investigator determines in writing that it is contrary to the health of the subject to defer further use of the test article until another investigator can assume responsibility for 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 subjects.

(c) Once an investigator has been disqualified, each application for a research or marketing permit, whether approved or not, containing or relying upon any clinical investigation performed by the investigator 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 investigator. Any investigation done by an investigator before or after 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 investigator, 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 by an investigator after the date of his or her disqualification shall be considered in support of any application for a research or marketing permit, unless the investigator has been reinstated under § 54.219. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable statute or regulation to submit the results of the investigation to the Food and Drug Administration.

§ 54.213 Public disclosure of information regarding disqualification.

(a) Upon issuance of a final order disqualifying an investigator, 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 notice 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 § 54.206(a) and shall state that the disqualification constitutes a determination by the Commissioner that the investigator is not eligible to conduct clinical investigations subject to requirements for prior submission to the Food and Drug Administration and that the results of any clinical investigations conducted by the investigator 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 investigator 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 investigator 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 investigator may be subject to disqualification, the Commissioner may, in the Commissioner's discretion, so notify the sponsor of any ongoing clinical investigation in which that investigator is participating simultaneously with or subsequent to proposing disqualification of the investigator under § 54.204(a), unless there are overriding safety considerations that warrant earlier notification of the sponsor.

§ 54.215 Alternative or additional actions to disqualification.

Disqualification of an investigator 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 proceeding (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.

§ 54.217 Suspension or termination of an investigator by a sponsor.

The sponsor of a clinical investigation may at any time remove an investigator from further participation in the investigation, whether or not the Commissioner has commenced any action to disqualify the investigator. The sponsor need not utilize either the grounds or the procedures for disqualification set forth in this subpart. If a sponsor removes an investigator from a clinical investigation, the sponsor shall notify the appropriate Bureau within the Food and Drug Administration in writing of the reasons for such removal as soon as possible, but in no event later than 15 working days after such removal.

§ 54.219 Reinstatement of a disqualified investigator.

(a) An investigator who has been disqualified may be reinstated as eligible to conduct clinical investigations subject to requirements for prior submission to the Food and Drug Administration, or as acceptable to be the source 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 investigator, that the investigator can adequately assure that he or she will conduct such studies in compliance with the requirements set forth in this part and other applicable regulations in this chapter, e.g., parts 312, 511, or 812.

(b) A disqualified investigator who wishes to be so reinstated shall present in writing to the Commissioner reasons why he or she believes he or she should be reinstated and a detailed description of the corrective ac-

tions the investigator 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 submission of an acceptable protocol for a specific clinical investigation providing for additional corrective actions, and/or the submission or special undertakings by a sponsor, an institution, an institutional review board, or another investigator to review in detail the investigator's compliance with agency requirements, and/or the investigator's being found in compliance with the applicable regulations upon an inspection.

(c) If an investigator is reinstated, the Commissioner shall so notify the investigator and all persons who were notified under § 54.213 of the disqualification of the investigator. A determination that an investigator has been reinstated is disclosable to the public under part 20 of this chapter.

PART 71—COLOR ADDITIVE PETITIONS

3. By amending part 71 as follows:

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

§ 71.1 Petitions.

* * * * *

(h) If clinical investigations are involved, petitions filed with the Commissioner under section 706(b) of the act shall include, with respect to each clinical investigation contained in the petition, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to such requirement in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in the investigation and those required in the regulations.

b. In § 71.6 by revising paragraph (b) to read as follows:

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

* * * * *

(b) *Substantive amendments.* After a petition has been filed, the petitioner may submit additional information or data in support thereof. In such cases, if the Commissioner determines that the additional information or data amount to a substantive amendment, the petition as amended shall be given a new filing date, and the time limitation shall begin to run anew. If clinical investigations are involved, additional information or data submitted in support of filed petitions shall include, with respect to each clinical investigation contained in the petition, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to, but was not conducted in compliance with, such requirements, a statement that describes in detail all differences between the practices used in the investigation and those required in the regulations.

* * * * *

PART 170—FOOD ADDITIVES

4. Part 170 is amended:

a. In § 170.17 by adding a new paragraph (d) to read as follows:

§ 170.17 Exemption for investigational use and procedure for obtaining authorization to market edible products from experimental animals.

* * * * *

(d) If intended for clinical investigation in animals other than laboratory research animals, the investigation is conducted in compliance with the requirements set forth in parts 54 and 511 of this chapter.

b. In § 170.35 by adding a new paragraph (c)(1)(vi) to read as follows:

§ 170.35 Affirmation of generally recognized as safe (GRAS) status.

* * * * *

(c) * * *

(1) * * *

(vi) If clinical investigations are involved, additional information and data submitted in support of filed petitions shall include, with respect to each clinical investigation, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter. If the investigation was not conducted in compliance with such regulations, a statement shall be submitted that describes in detail all differences between the practices used in the study and those required in the regulations.

PART 171—FOOD ADDITIVE PETITIONS

5. By amending part 171 as follows:

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

§ 171.1 Petitions.

* * * * *

(l) If clinical investigations are involved, petitions filed with the Commissioner under section 409(b) of the act shall include, with respect to each clinical investigation contained in the petition, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter. If the investigation was subject to but was not conducted in compliance with such requirements, a statement shall be submitted that describes in detail all differences between the practices used in the investigation and those required in the regulations.

b. By revising § 171.6 to read as follows:

§ 170.6. Amendment of petition.

After a petition has been filed, the petitioner may submit additional information or data in support thereof. In such cases, if the Commissioner determines that the additional information or data amount to a substantive amendment, the petition as amended shall be given a new filing date, and the time limitation shall begin to run anew. Where the substantive amendment proposes a substantial change to the petition which may affect the quality of the human environment, the petitioner is required to submit an environmental impact analysis report pursuant to § 25.1 of this chapter. If clinical investigations are involved, additional information and data submitted in support of filed petitions shall include, with respect to each clinical investigation; either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in the investigation and those required in the regulations.

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

5a. Part 180 is amended in § 180.1 by adding a new paragraph (c)(5) to read as follows:

§ 180.1 General.

* * * * *

(c) * * *

(5) If clinical investigations 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 set forth in part 54 of this chapter; or a statement that the investigation is not subject to such requirements in accordance with § 54.2 of this chapter. If any such study was not conducted in compliance with such regulations, a statement shall be submitted that describes in detail all differences between the practices used in conducting the investigation and those required in the regulations.

PART 310—NEW DRUGS

§ 310.3 [Amended]

6. In § 310.3 *Definitions and interpretations,* by deleting and reserving paragraph (j).

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

7. In § 312.1 by deleting paragraph (c) and reserving it; and by amending paragraph (d)(11) by inserting "or" after the semicolon in the first sentence and by transferring the remainder of the text to a flush paragraph at the conclusion of paragraph (d), and by reserving paragraph (d)(12) and adding a new paragraph (d)(13), to read as follows:

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

* * * * *

(c) [Reserved]

(d) * * *

(11) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of newly found serious or potentially serious hazards, contraindications, side-effects, and precautions pertinent to the safety of the new drug; or

(12) [Reserved]

(13) The clinical investigations are not being conducted in compliance with the requirements set forth in this part of Part 54 of this chapter:

He shall notify the sponsor and invite his immediate correction or explanation. A conference will be arranged with the Bureau of Drugs if requested. If the Bureau of Drugs does not accept the explanation of the correction submitted by the sponsor, the sponsor shall have an opportunity for a regulatory hearing before the Food and Drug Administration pursuant to part 16 of this chapter on the question of whether his exemption should be terminated. Such hearing shall be requested within 10 days after receipt of notification that the explanation or correction is not acceptable. After evaluating all the available information including any explanation and or correction submitted by the sponsor, if the Commissioner determines that the exemption should be terminated he shall notify the sponsor of the termination of the exemption and the sponsor shall recall unused supplies of the drug. If at any time the Commissioner concludes that continuation of the investigation presents a danger to the public health, he shall terminate the exemption forthwith and notify the sponsor of the termination. The Commissioner will inform the sponsor that the exemption is subject to reinstatement on the basis of additional submissions that eliminate such danger and will afford the sponsor an opportunity for a regulatory hearing before the Food and Drug Administration pursuant to part 16 of this chapter on the question of whether the exemption should be reinstated. The sponsor shall recall the unused supplies of the drug upon notification of the termination.

* * * * *

PART 314—NEW DRUG APPLICATIONS

8. By amending part 314 as follows:

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.* With respect to each clinical investigation contained in the application, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in the investigation and those required in the regulations.

* * * * *

(f) * * *

(7) With respect to each clinical investigation contained in the application, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement describing in detail all differences between the practices used in the investigation and those required in the regulations.

(8) The signature of the applicant or responsible official or agent on a completed Form FD-356H.

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

§ 314.8 Supplemental applications.

* * * * *

(m) A supplemental application that contains clinical investigations shall include, with respect to each investigation, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement describing in detail all differences between the practices used in the investigation and those required in the regulations.

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

§ 314.9 Insufficient information in application.

* * * * *

(d) 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, with respect to each clinical investigation contained in the application, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement describing in detail all differences between the practices used in the investigation and those required in such regulations.

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

§ 314.12 Untrue statements in application.

* * * * *

(d) Any clinical investigation contained in the application was subject to but was not conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter, and differences between the practices used in conducting the investigation and those required in such regulations were not described in detail.

e. In § 314.110 by adding paragraph (a)(10) to read as follows:

§ 314.110 Reasons for refusing to file applications.

(a) * * *

(10) The applicant fails to include in the application, with respect to each clinical investigation contained in the application, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement describing in detail all differences between the practices used in the investigation and those required in such reguations.

* * * * *

f. In § 314.111 by adding paragraph (a)(10), to read as follows:

§ 314.111 Refusal to approve the application.

(a) * * *

(10) Any clinical investigation contained in the application was subject to but was not conducted in compliance with the requirement set forth in parts 54 and 312 of this chapter, and differences between the practices used in conducting the investigation and those required in such parts were not described in detail.

* * * * *

g. In § 314.115 by adding new paragraph (c)(6) to read as follows:

§ 314.115 Withdrawal of approval of an application.

* * * * *

(c) * * *

(6) That any clinical investigation contained in the application was subject to, but was not conducted in compliance with, the requirements set forth in parts 54 and 312 of this chapter, and differences between the practices used in conducting the investigation and those required in such parts were not described in detail.

* * * * *

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

9. By amending part 320 as follows:

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

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

* * * * *

(e) An in vivo bioavailability study in humans shall be conducted in compliance with the requirements set forth in part 54 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 (d) to read as follows:

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

* * * * *

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

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

10. By amending § 330.10 by adding paragraph (d) 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.

* * * * *

(d) *Clinical investigations.* Information and data submitted under this section after (insert effective date of final regulation promulgating this paragraph) shall include, with respect to each clinical investigation from which the information and data are derived, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to those requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in the investigation and those required in the regulations.

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

11. By amending § 361.1 by adding new paragraph (d)(10) to read as follows:

§ 361.1 Radioactive drugs for certain research uses.

* * * * *

(d) * * *

(10) *Clinical investigator requirements.* The investigator shall comply with the requirements set forth in part 54 of this chapter.

* * * * *

PART 430—ANTIBIOTIC DRUGS; GENERAL

12. By amending § 430.20 by adding new paragraph (f) to read as follows:

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

* * * * *

(f) No regulation providing for the certification of an antibiotic drug for human use shall be issued or amended unless each clinical investigation on which the issuance or amendment of the regulation is based was conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter; or was not subject to such requirements in accordance with § 54.2 of this chapter; or, if it was subject to but was not conducted in compliance with such requirements, differences between the practices use in conducting the investigation and those required in such regulations were described in detail.

PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS

13. By amending in § 431.17 by adding new paragraph (k) to read as follows:

§ 431.17 New antibiotic and antibiotic-containing products.

* * * * *

(k) With respect to each clinical investigation contained in the request, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the

investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in conducting the investigation and those required in such regulations.

PART 510—NEW ANIMAL DRUGS

§ 510.3 [Amended]

14. In § 510.3 *Definitions and interpretations,* by deleting and reserving paragraph (k).

PART 511—NEW ANIMAL DRUGS FOR INVESTIGATIVE USE

15. In § 511.1 by revising paragraph (b); by deleting and reserving paragraph (c); and by redesignating paragraph (d)(2) as (d)(3) and adding a new paragraph (d)(2) to read as follows:

§ 511.1 New animal drugs for investigational use exempt from section 512(a) of the act.

* * * * *

(b) *New animal drugs for clinical investigation in animals.* A shipment or other delivery of a new animal drug or an animal feed containing a new animal drug intended for clinical investigational use in animals shall be exempt from section 512 (a) and (m) of the act if all the following conditions are met:

(1) The label of such drug bears the statement:

Caution. Contains a new animal drug for use only in investigational animals in clinical trials. Not for use in humans. Edible products of investigational animals are not to be used for food unless authorization has been granted by the United States Food and Drug Administration or by the United States Department of Agriculture.

In the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear the caution statements required by paragraphs (a) or (b) of this section, the statements may be included on the carton label and other labeling on or within the package from which the new animal drug is to be dispensed.

(2) The person or firm distributing or causing the distribution of the new animal drug or animal feed containing a new animal drug shall use due diligence to assure that the new animal drug or animal feed containing a new animal drug will actually be used for tests in animals and that it is not used in humans.

(3) The persons claiming the exemption has filed with the Food and Drug Administration a completed and signed "Notice of Claimed Investigational Exemption for a New Animal Drug," three copies, including a signed statement containing the following information:

(i) The best available descriptive name of the drug, including, to the extent known, the chemical name and structure of any new drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

(ii) Complete list of components of the drug including any reasonable alternates for inactive components.

(iii) Complete statement of quantitative composition of the drug, including reasonable variations that may be expected during the investigational stage.

(iv) Description of source and preparation of any new animal drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new drug substance.

(v) A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

(vi) A statement covering all information available to the sponsor derived from preclinical investigations and in any clinical studies and experience with the drug, as follows:

(*a*) Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug. Such information shall include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Food and Drug Administration will notify the sponsors to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. Representatives of the Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

(*b*) If the drug has been marketed commercially or investigated (e.g., outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

(*c*) If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. The summary shall also include a statement of the expected pharmacological effects of the combination.

(*d*) If the drug is a radioactive drug, sufficient data shall be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed with dose upon administration to an animal subject.

(vii) A copy (one in each of the three copies of the notice) of all information material, including label and labeling, that is to be supplied to each investigator. This informational material shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe, for the information of clinical investigators, all relevant hazards, contraindications, side effects, and precautions suggested by prior investigations and experience with both the drug under investigation and related drugs.

(viii) The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

(ix) The names, addresses, and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and

effectivenes of the drug as it is received from the investigators.

(x) The protocol to be followed by the investigators in conducting the clinical investigations.

(xi) The approximate number of animals to be treated, or, if not available, the amount of new animal drug to be shipped.

(xii) If the new animal drug is given to food-producing animals, the notice shall also include:

(*a*) A commitment that the edible products from such animals shall not be used for food without prior authorization in accordance with this section.

(*b*) Approximate dates of the beginning and end of the experiment or series of experiments.

(*c*) The maximum daily dose(s) to be administered to a given species, the size and/or age of animal, maximum duration of administration, method(s) of administration, and proposed withdrawal time, if any.

(xiii) A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for the discontinuation.

(xiv) A statement that the sponsor will notify each investigator if a new animal drug application is approved or if the investigation is discontinued.

(xv) If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new animal drug for which an application is not approved.

(xvi) When requested by the agency, an environmental impact analysis report pursuant to § 25.1 of this chapter.

(xvii) An active drug control not fulfilling the requirements of § 514.111 (a)(5)(vi)(*b*) of this chapter shall be subject to the requirements for an investigational animal drug.

(4) Authorization for use of edible products derived from a treated food-producing animal may be granted under this section and when the following specified conditions are met, except that in the case of an animal administered any unlicensed experimental veterinary biological product regulated under the viruses, serums, toxins statute (21 U.S.C. 151 et seq.) the product shall be exempt from the requirements of this section when U.S. Department of Agriculture approval has been obtained as provided in 9 CFR 103.2. Conditional authorization may be granted in advance of identification of the name(s) and address(es) of the clinical investigator(s) as required by paragraph (b)(3)(ix) of this section. Information required for authorization shall include, in addition to all other requirements of this section, the following:

(i) Data to show that consumption of food derived from animals treated at the maximum levels with the minimum withdrawal periods, if any, specified in accordance with paragraph (b)(3)(xii)(*c*) of this section, will not be inconsistent with the public health; or

(ii) Data to show that food derived from animals treated at the maximum levels and with the minimum withdrawal periods, if any, specified in accordance with paragraph (b)(3)(xii)(*c*) of this section, does not contain drug residues or metabolites.

(iii) The name and location of the packing plant where the animals will be processed, except that this requirement may be waived, on request, by the terms of the authorization.

Authorizations granted under paragraph (b)(4) of this section do not exempt investigational animals and their products from compliance with other applicable inspection requirements. Any person who contests a refusal to grant such authorization shall have an opportunity for a regulatory hearing before the Food and Drug Administration pursuant to part 16 of this chapter.

(5) On written request by the Food and Drug Administration, the sponsor shall submit any additional information reported to or otherwise received by him with respect to the investigation deemed necessary to facilitate a determination whether it is grounds in the interest of public health for terminating the exemption.

(6) The clinical investigation is conducted in compliance with the requirements set forth in part 54 of this chapter.

(c) [Reserved]

(d) * * *

(2) The clinical investigations are not being conducted in compliance with the requirements set forth in this part or in part 54 of this chapter; or

(3) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is being or has been used for purposes other than bona fide scientific investigation, he shall first notify the sponsor and invite his immediate correction. If the conditions of the exemption are not immediately met, the sponsor shall have an opportunity for a regulatory hearing before the Food and Drug Administration, pursuant to part 16 of this chapter, on whether the exemption should be terminated. If the exemption is terminated, the sponsor shall recall or have destroyed the unused supplies of the new animal drug.

* * * * *

PART 514—NEW ANIMAL DRUG APPLICATIONS

16. By amending part 514 as follows:

a. In § 514.1 by adding new paragraph (b)(12)(iv) to read as follows:

§ 514.1 Applications.

* * * * *

(b) * * *

(12) * * *

(iv) With respect to each clinical investigation contained in the application, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 51 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement describing in detail all differences between the practices used in conducting the investigation and those required in such regulations.

* * * * *

b. In § 514.8 by adding paragraph (m) to read as follows:

§ 514.8 Supplemental new animal drug applications.

* * * * *

(m) A supplemental application that contains clinical investigations shall include, with respect to each investigation, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 511 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in conducting the investigation and those required in such regulations.

(c) In § 514.15 by adding paragraph (d) to read as follows:

§ 514.15 Untrue statements in applications.

* * * * *

(d) Any clinical investigation contained in the application was subject to but was not conducted in compliance with the requirements set forth in parts 54 and 511 of this chapter, and differences between the practices used in conducting the investigation and those required in such regulations were not described in detail.

d. In § 514.110 by adding paragraph (b)(9) to read as follows:

§ 514.110 Reasons for refusing to file applications.

* * * * *

(b) * * *

(9) It fails to include, with respect to each clinical investigation contained in the application, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 511 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in conducting the investigation and those required in such regulations.

* * * * *

e. In § 514.111 by adding paragraph (a)(12) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(12) Any clinical investigation contained in the application was subject to but was not conducted in compliance with the requirements set forth in parts 54 and 511 of this chapter, and differences between the practices used in conducting the investigation and those required in such parts were not described in detail.

* * * * *

f. In § 514.115 by adding paragraph (b)(5) to read as follows:

§ 514.115 Withdrawal of approval of applications.

* * * * *

(b) * * *

(5) That any clinical investigation contained in the application was subject to but was not conducted in compliance with the requirements set forth in parts 54 and 511 of this chapter, and differences between the practices used in conducting the investigation and those required in such parts were not described in detail.

* * * * *

PART 570—FOOD ADDITIVES

17. By amending part 570 as follows:

a. In § 570.17 by adding paragraph (d) to read as follows:

§ 570.17 Exemption for investigational use and procedure for obtaining authorization to market edible products from experimental animals.

* * * * *

(d) If intended for clinical investigation in animals other than laboratory research animals, the investigation is conducted in compliance with the requirements set forth in parts 54 and 511 of this chapter.

b. In § 570.35 by adding paragraph (c)(1)(vi) to read as follows:

§ 570.35 Affirmation of generally recognized as safe (GRAS) status.

(c) * * *

(1) * * *

(vi) If clinical investigations are involved, additional information and data submitted in support of filed petitions shall include, with respect to each clinical investigation, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation is not subject to such requirements in accordance with § 54.2 of this chapter. If the investigation was not conducted in compliance with such regulations, a statement shall be submitted that describes in detail all differences between the practices used in the investigation and those required in the regulations.

PART 571—FOOD ADDITIVE PETITIONS

18. By amending part 571 as follows:

a. In § 571.1 by adding paragraph (l) to read as follows:

§ 571.1 Petitions.

* * * * *

(l) If clinical investigations are involved, petitions filed with the Commissioner under section 409(b) of the act shall include, with respect to each investigation contained in the petition, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in the investigation and those required in the regulations.

b. By revising § 571.6 to add a new concluding sentence, to read as follows:

§ 571.6 Amendment of petition.

After a petition has been filed, the petitioner may submit additional information or data in support thereof. In such cases, if the Commissioner determines that the additional information or data amounts to a substantive amendment, the petition as amended will be given a new filing date, and the time limitation will begin to run anew. Where the substantive amendment proposes a substantial change to the petition which may affect the quality of the human environment, the petitioner shall submit an environmental impact analysis report pursuant to § 25.1 of this chapter. If clinical investigations are involved, additional information and data submitted in support of filed petitions shall include, with respect to each clinical investigation, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement that describes in detail all differences between the practices used in the investigation and those required in such part.

PART 601—LICENSING

19. By amending part 601 as follows:

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 purpose, 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; with respect to each clinical investigation, either a statement that the investigation was conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or, if the investigation was subject to but was not conducted in compliance with such requirements, a statement describing in detail all differences between the practices used in the investigation and those required in the regulations; 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)(1) and adding a new paragraph (k) 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 products have been undertaken, or the Federal Government may undertake these studies. Any such study involving a clinical investigation shall be conducted in compliance with the requirements set forth in parts 54 and 312 of this chapter, unless it is not subject to such requirements in accordance with § 54.2 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 license or licenses shall be revoked.

* * * * *

(k) *Clinical investigations.* Information and data submitted under this section after (insert effective date of final order promulgating this paragraph) shall include, with respect to each clinical investigation, either a statement that the investigation was conducted in compliance with the requirements set forth in part 54 of this chapter; or a statement that the investigation was not subject to such requirements in accordance with § 54.2 of this chapter; or if the investigation was subject to but was not conducted in the compliance with such requirements, a statement that describes in detail all differences between the practices used in the investigation and those required in the regulations.

c. By revising § 601.30 to read as follows:

§ 601.30 Licenses required; products for controlled investigation only.

Any biological or trivalent organic arsenical manufactured in any foreign country and intended for sale, barter, or exchange shall be refused entry by collectors of customs unless manufactured in an establishment holding an unsuspended and unrevoked establishment and product license. Unlicensed products that are not imported for sale, barter, or exchange and that are intended solely for purposes of controlled investigation are admissible only if the investigation is conducted in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and the requirements set forth in parts 54 and 312 of this chapter.

PART 630—ADDITIONAL STANDARDS FOR VIRAL VACCINES

20. By amending part 630 as follows:

a. In § 630.11 by revising the first sentence to read as follows:

§ 630.11 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with parts 54 and 312 of this chapter. * * *

* * * * *

b. In § 630.31 by revising the first sentence 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 parts 54 and 312 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 parts 54 and 312 of this chapter that follow the procedures prescribed in § 630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of mumps-susceptible individuals, each having received the parenteral administration of a virus vaccine dose that is not greater than that which was demonstrated to be safe in field studies under § 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 parts 54 and 312 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 that is not greater than that which was demonstrated to be safe in field studies when used under comparable conditions.

e. In § 630.81 by revising the first sentence to read as follows:

§ 630.81 Clinical trials to qualify for license.

In addition to demonstrating that the measles component meets the requirements of § 630.31, the measles and smallpox antigenicity of the final product shall be determined by clinical trials of adequate statistical design conducted in compliance with parts 54 and 312 of this chapter and with three consecutive lots of final vaccine manufactured by the same methods and administered as recommended by the manufacturer. * * *

* * * * *

PART 1003—NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY

21. 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, 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 54 of this chapter; or a statement that the investigation is not subject to such requirements in accordance with § 54.2 of this chapter. If the investigation was not conducted in compliance with such regulations, a statement shall be submitted that describes in detail all differences between the practices used in the investigation and those required in the regulations.

* * * * *

PART 1010—PERFORMANCE STANDARDS FOR ELECTRONIC PRODUCTS: GENERAL

22. By amending part 1010 as follows:

In § 1010.4 by adding paragraph (b)(1)(x) to read as follows:

§ 110.4 Variances.

* * * * *

(b) * * *

(1) * * *

(x) If the electronic product is used in a clinical investigation, the investigation shall be conducted in compliance with the requirements set forth in part 54 of this chapter.

* * * * *

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, 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 54 of this chapter; or a statement that the investigation is not subject to such requirements in accordance with § 54.2 of this chapter. If the investigation was not conducted in compliance with such regulations, a statement shall be submitted that describes in detail all differences between the practices used in the investigation and those required in the regulations.

* * * * *

Interested persons may, on or before Novembers 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 brackets 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.

[FR Doc. 78-21790 Filed 8-7-78; 8:45 am]