b. *Presentation of evidence.* Much of the language used throughout the various discussions in the OGC memorandum has centered on the term "documentary evidence." This is highly unfortunate since under the APA, section 556, that term has an extremely limited meaning. As stated in the Attorney General's Manual (p. 77):

> As here used "documentary evidence" does not mean affidavits and written evidence of any kind. Such a construction would flood agency proceedings with hearsay evidence. In the last sentence of the subsection, there appears the phrase "evidence in written form," thus indicating that the Congress distinguished between "written evidence" and "documentary evidence." See also section 203(c) of the Emergency Price Control Act. Again, the subsection expressly states the right to adequate cross-examination. Against this background, it is clear that the "right to present his case or defense by oral or documentary evidence" does not extend to presenting evidence in affidavit or other written form so as to deprive the agency or opposing parties of opportunity for cross-examination, nor so as to force them to assume that expense of calling the affiants for cross-examination. See *Powhatan Mining Co.* v. *Ickes,* 118 F. 2d 105, 109 C.C.A.6,1941).

Great care clearly must be used in the terminology so as to avoid confusing the written evidence of parties, which are entitled to cross examination, with the use of "documentary evidence" as a word of art under the Administrative Procedure Act.

c. *Responsible employees.* While the issuance of recommendations to the Board by "responsible employees" is no longer central to the proposed rules as suggested in the General Counsel's memorandum, some consideration must be given as to who would be the responsible officer in the event that the agency chooses to issue a tentative decision or a recommendation. An earlier proposal by the General Counsel, now apparently abandoned, was to employ the phrase "due and timely execution of its functions imperatively and unavoidably (so) requires" to allow the omission of any intermediate decision. (See, e.g., General Counsel memorandum of March 20.)[14] While this has not been developed at length in this memorandum, several of the suggestions previously made, if they should re-emerge, would require a detailed analysis of this aspect of decision making.

Many of the problems here would not require fine-tuned resolution if the matters to be resolved by the agency were limited to those types of non-oral hearings used by other agencies and already approved by the courts. There would be little controversy and therefore little risk of court review. It is principally the determination to create what amounts to an amendment to the APA which requires seminal thinking in order to overcome previously poorly worked out arrangements. As the risk goes up of significant court review, the need also goes up to make sure that the procedures are precise and lawful. The procedures set forth in Appendix B to the present memorandum avoid these problems. They should be adopted because they are consistent with (1) existing law and other agency practice; and (2) are more than adequate to handle the existing or anticipated caseload.

[14] If consideration is given in the future of going to a procedure where responsible employees make recommendations to the Board, it should be kept in mind that the APA would not permit junior and inexperience staff members to perform this function.

[FR Doc. 78–12359 Filed 5–4–78; 8:45 am]

[4810–22]

DEPARTMENT OF THE TREASURY

Customs Service

[19 CFR Part 4]

VESSELS IN FOREIGN AND DOMESTIC TRADES

Extension of Time for Comments Concerning Proposed Amendments Relating to Foreign Repairs to, and Equipment Purchased for, American Vessels

AGENCY: U.S. Customs Service, Department of the Treasury.

ACTION: Notice of extension of the for comments.

SUMMARY: This notice extends the period of time permitted for the submission of comments in response to the recent proposal by the Customs Service to modify its substantive and procedural requirements relating to entries for foreign repairs and equipment purchases by American vessels. This extension will permit the preparation and submission of more detailed comments by interested members of the public.

DATES: Comments must be received on or before June 2,1978.

ADDRESS: Comments should be addressed to the Commissioner of Customs, Attention: Regulations and Legal Publications Division, U.S. Customs Service, 1301 Constitution Avenue NW., Washington, D.C. 20229.

FOR FURTHER INFORMATION CONTACT:

Jerry C. Laderberg, Carriers Rulings Branch, Carriers, Drawback and Bonds Division, U.S. Customs Service, Washington, D.C. 20229, 202–566–5706.

SUPPLEMENTARY INFORMATION:

BACKGROUND

On April 4, 1978, the Customs Service published in the FEDERAL REGISTER (43 FR 14060) notice of proposed amendments to §§ 4.7(d)(1) and 4.14 of the Customs Regulations (19 CFR 4.7(d)(1) and 4.14) to modify its substantive and procedural requirements relating to entries for foreign repairs and equipment purchases by American vessels. The proposed amendments would establish procedures for handling each aspect of a vessel repair entry and are intended to reduce the amount of time needed to process the entry.

Comments concerning the proposed amendments were to have been received on or before May 4, 1978. A request on behalf of a number of American-flag vessel operators has been received to extend the period of time for the submission of comments. Therefore, Customs is extending the period of time to comment to June 2, 1978.

LEONARD LEHMAN,
Assistant Commissioner, Regulations and Rulings.

[FR Doc. 78–12431 Filed 5–4–78; 8:45 am]

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 50]

[Docket No. 78N–0049]

PROTECTION OF HUMAN SUBJECTS

Proposed Establishment of Regulations

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing a regulation to provide protection for prisoners involved in those research activities which fall within the jurisdiction of FDA. This proposal is issued in compliance with the directive of the Secretary of the Department of Health, Education, and Welfare (DHEW), is in line with the regulations proposed by DHEW, and implements the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research on research involving prisoners. This proposal is intended to assure adequate protection of the rights and safety of prisoners who are subjects in clinical investigations subject to requirements for prior submission to FDA, or conducted in support of applications for permission to conduct further research or to market regulated products.

DATES: Written comments by July 5, 1978. The proposed effective date of the final rule is 12 months after the date of its publication in the FEDERAL REGISTER.

ADDRESS: Written comments to the Hearing Clerk (HFC–20), Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Roger W. Barnes, Office of Medical Affairs (HFM–1), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fish-

ers Lane, Rockville, Md. 20857, 301–443–1177.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of January 5, 1978 (43 FR 1050), DHEW proposed regulations governing research conducted or supported by DHEW which involves prisoners. The proposed DHEW regulations implement the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research on research involving prisoners and provide additional protection for prisoners involved in such research activities. As noted in the proposal:

> The proposed regulations set forth below cover only research conducted or supported by DHEW. They do not cover the non-DHEW supported research which is submitted to the Food and Drug Administration to satisfy its regulatory requirements. The Secretary's rulemaking authority with respect to FDA activities has been delegated to the Commissioner of FDA. The Secretary has directed the Commissioner to issue, as soon as possible, regulations that apply the standards set out in these regulations to research that the FDA accepts to satisfy its regulatory requirements. (43 FR 1051)

In order to comply with the Secretary's directive, and in order to set forth a uniform Departmental policy regarding research involving prisoners, the Commissioner of Food and Drugs is proposing regulations which will apply the principles set forth in the proposed DHEW regulations to all prisoner research that is subject to FDA jurisdiction. The Commissioner adopts the findings of both the Commission and the Secretary regarding the inherently coercive nature of the prison environment and the need for special protections for prisoners involved as subjects in clinical research. The Commissioner also believes that, wherever possible, FDA's regulations should be compatible with, if not identical to, those of the Department. A multiplicity of dissimilar and inconsistent Federal requirements is burdensome to institutions. Institutional Review Boards (IRB's), and the process of clinical investigation. The proposed Part 50, "Protection of Human Subjects," will contain regulations which apply to all clinical investigations which are subject to requirements for prior submission under section 505(i), 507(d), or 520(g) (21 U.S.C. 355(i), 357(d), or 360j(g) of the Federal Food, Drug, and Cosmetic Act, or which support or are intended to support an application for a research or marketing permit for a product regulated by the agency. While only Subparts A and C of Part 50 are being proposed at this time, the Commissioner intends, in the near future, to revise and update existing agency regulations to incorporate appropriate Departmental standards and other relevant materials on informed consent. Regulations regarding informed consent will be proposed as Subpart B of part 50. This proposal is part of a major effort of FDA to improve its regulations on clinical investigations. Applying the principles set forth in this proposal to research that is subject to FDA jurisdiction will result in nonacceptance of research not conducted in conformity with this proposal.

CLINICAL INVESTIGATIONS INVOLVING PRISONERS

The proposed regulation conforms to the requirements proposed by the Department insofar as they involve biomedical research and extends those requirements to research submitted to the agency to satisfy its regulatory requirements. The Commissioner has considered the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (published in the FEDERAL REGISTER of January 14, 1977 (42 FR 3076), as well as the comments set forth in the preamble to the January 5, 1978 DHEW proposal, and incorporates those documents as part of the discussion presented here. The Commissioner emphasizes that proposed Subpart C prohibits the use of prisoners as subjects in research subject to FDA jurisdiction if the research is not intended to improve the health of the individual prisoners. This means that no prisoner may serve as a placebo control

DEFINITIONS

Proposed § 50.3 defines a number of terms used in proposed Part 50. Many of the proposed definitions pertain to terms that can be variably or imprecisely interpreted by persons affected by the proposed regulation. These definitions are to provide a common basis of understanding for the agency, the regulated industry, and the general public regarding the terms used in part 50. In proposed § 50.3(a), the term "act" is limited to the Federal Food, Drug, and Cosmetic Act, as amended. This is consistent with definitions appearing elsewhere in the agency's regulations. Other statutes, when used, will be mentioned by name, e.g., the Public Health Service Act.

The decision to make this proposal agency-wide in scope required a term that would include all the various requirements for submission of scientific data and information to the agency under its regulatory jurisdiction, even though in certain cases no permission is technically required from FDA for the conduct of a proposed activity with a particular product, i.e., carrying out research or continuing marketing of a product. The term chosen, "application for research or marketing permit," is intended solely as a shorthand way of referring to at least 21 separate categories of data and information that are now, or in the near future will become, subject to requirements for submission to the agency; the term is defined in proposed §50.3(b).

Other proposed definitions include terms to describe the persons who initiate and carry out clinical investigations: "sponsor," "investigator," and "sponsor-investigator." The term "sponsor" is currently defined in §§ 310.3(j) and 510.3(k) (21 CFR 310.3(j) and 510.3(k), but the Commissioner believes this definition is unsatisfactory because it fails to distinguish the other commonly used term "investigator," which is not defined. Although these terms are widely understood, their precise meanings are difficult to express. The key distinctions seem to lie in who initiates the project (the sponsor) and who actually conducts the study (the investigator). These distinctions have been incorporated in the definitions proposed in § 50.3 (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 an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit thereof, and any other legal entity.) The Commissioner believes that these distinctions will clarify the participants' respective roles and duties.

Many studies (approximately 45 percent of the investigational new drug applications in the Bureau of Drugs for example) are initiated and actually conducted by the same individual; this investigator may carry out the study alone or with other investigators responsible to the initiator. 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 § 50.3(g); unlike the term "sponsor," the "sponsor-investigator" is limited to individuals.

Proposed § 50.3(h) defines "subject" as a human who is or becomes a participant in a clinical investigation, either as the recipient of the test article or as a control. The term may also, where appropriate, include either a person in normal health or a patient to whom the test article might offer a therapeutic benefit or provide diagnostic information.

The terms "institution" and "institutional review board" are defined in proposed § 50.3(i) and (j), respectively. Although since 1971 FDA has had a requirement that clinical drug investigations involving institutionalized subjects be reviewed and monitored by an institutional review committee or

board, no guidelines defining the outer limits of these concepts have been issued. The Commissioner proposes that the definition of "institution" include any corporation, scientific or academic establishment, or government agency that engages in the conduct of research on human subjects or in the delivery of medical services to individuals: a hospital, a university that performs research with students, a retirement home that primarily provides housing and personal care to the elderly but also cares for health needs of residents, a manufacturer that uses its employees as subjects in the course of product development, or a prison. Although this proposal deals only with prisoners, Part 50, when completed, will deal with the broader subject of protection of all subjects of biomedical research subject to FDA jurisdiction.

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

An "institutionalized subject," as defined in proposed § 50.3(k), includes two categories: First, any individual who is voluntarily confined on the premises of, and in the care of, an institution for more than 1 day; outpatients are excluded from the definition in keeping with existing FDA policy. Second, any individual involuntarily confined for any period of time in an institution such as a penal facility or a hospital by civil commitment.

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

The Commissioner is proposing that the final rule take effect 12 months after its date of publication in the FEDERAL REGISTER. Ongoing clinical investigations involving prisoners as subjects shall be completed by the effective date, discontinued, or brought into conformity with the requirements of the regulation. In those cases in which all phases of a clinical investigation except statistical evaluations are completed by the effective date, statistical evaluations completed after the effective date will be accepted.

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, or a medical device for human use. Even where a license is not required or already has been issued, such data may be relied upon to demonstrate the bioavailability of a marketed drug, the general recognition of safety of a product, or the absence of any need for premarket approval or a product standard for a device. In evaluating the enormous volume of clinical investigations filed with FDA, many types of scientific and regulatory review must be devoted to these studies apart from determining their ethical and scientific acceptability and their basic validity, e.g., to interpret the results and to evaluate the status of the affected products in light of the results. Given the limited resources within the agency, the Commissioner believes that FDA must have standards to screen out those clinical investigations that are likely to be unacceptable and thus should not be authorized by FDA or warrant little further evaluation in support of a product application. The promulgation of this regulation provides one process for making this judgment. Moreover, the regulation reflects principles recognized by the scientific community as essential to sound research involving human subjects. Thus, this regulation 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 (21 CFR 314.111(a)(5)) for determining whether a clinical investigation of a drug intended for human use, among other things, was scientifically reliable and valid, in the words of the act: "adequate and well-controlled," to support approval of a new drug. These regulations were issued under sections 505 and 701(a) of the act and have been upheld by the Supreme Court (see *Weinberger* v. *Hynson, Westcott & Dunning, Inc.,* 412 U.S. 609 (1973); see also *Upjohn Co.* v. *Finch,* 422 F.2d 944 (6th Cir. 1970) and *Pharmaceutical Manufacturers Association* v. *Richardson,* 318 F. Supp. 301 (D. Del. 1970)).

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

The Commissioner concludes that legal authority to promulgate this regulation exists under sections 505(i), 507(d), 520(g), and 701(a) of the act, as essential to protection of the public health and safety and to enforcement of the agency's responsibilities under sections 406, 409, 502, 503, 505, 506, 507, 510, 513, 514, 515, 516, 518, 519, 520, 601, 706, and 801 of the act, as well as the responsibilities of FDA under sections 351 and 354 to 360F of the Public Health Service Act.

The Commissioner will promulgate conforming amendments in other FDA regulations if appropriate to execute the policy set forth in this regulation.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (Secs. 406, 409, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 601, 701(a), 706, and 801, 52 Stat. 1049–1054 as amended, 1055,1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794–795 as amended, 90 Stat. 540–560, 562–574 (21 U.S.C. 346, 348, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–3603, 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 by adding new Part 50 to read as follows:

PART 50—PROTECTION OF HUMAN SUBJECTS

Subpart A—General Provisions

Subpart B—[Reserved]

Subpart C—Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects

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

Subpart A—General Provisions

§ 50.1 Scope.

This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, cosmetics, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor and/or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., Parts 312 and 812) of this chapter. Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the FDA pursuant to sections 406, 409, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 601, 706, and 801 of the act and sections 351 and 354–360F of the Public Health Service Act.

§ 50.3 Definitions.

As used in this part:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(e) "Person" includes an individual partnership, corporation, association, scientific or academic establishment, government agency or organizational

unit thereof, and any other legal entity.

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

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

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

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

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

(k) "Institutionalized subject" means:

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

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

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

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

Subpart B—[Reserved]

Subpart C—Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects

§ 50.40 Applicability.

(a) The regulations in this subpart are applicable to all clinical investigations involving prisoners as subjects, subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or conducted in support of an application for a research or marketing permit for a product regulated by the agency.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

§ 50.42 Purpose

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§ 50.44 Permitted clinical investigations involving prisoners.

(a) Clinical investigations conducted by the Food and Drug Administration, subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or conducted in support of an application for a research or marketing permit for a product regulated by the FDA may involve prisoners as subjects only if:

(1) The institution responsible for the conduct of the clinical investigation has certified to the Commissioner that the Institutional Review Board has approved the clinical investigation under § 50.48 of this subpart; and

(2) In the judgment of the Commissioner, the proposed clinical investigation involves solely research on practices both innovative and accepted, which is intended to improve, or which has a reasonable probability of improving, the health and well-being of the subjects.

(b) Except as provided in paragraph (a) of this section, clinical investigations conducted by or subject to requirements for prior submission to the agency or conducted in support of a research or marketing permit for a product regulated by the agency shall not involve prisoners as subjects.

§ 50.46 Composition of institutional review boards where prisoners are involved.

In addition to satisfying any other requirements governing Institutional Review Boards set forth in this chapter, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner advocate with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

§ 50.48 Additional duties of the institutional review boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this chapter, the Board shall review clinical investigations covered by this subpart and approve such clinical investigations only if it finds that:

(1) Any possible advantages accruing to the prisoner through his or her participation in the clinical investigation, when compared to the general living conditions, medical care, quality of food, amenities, and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to

weigh the risks of the clinical investigation against the value of such advantages in the limited choice environment of the prison is impaired;

(2) The risks involved in the clinical investigation are commensurate with risks that would be accepted by nonprisoner volunteers;

(3) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners;

(4) The information is presented in language which is appropriate for the subject population;

(5) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the clinical investigation in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the clinical investigation will have no effect on his or her parole; and

(6) Where the Board finds there may be need for followup examination or care of participants after the end of their participation, adquate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Commissioner.

(c) The institution shall certify to the Commissioner, in such form and manner as the Commissioner may require, that the duties of the Board under this section have been fulfilled.

Interested persons may, on or before July 5, 1978 submit to the Hearing Clerk (HFC–20), 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 proposal will not have a major economic impact as defined by Executive Order 11821 (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: April 22, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc. 78–11994 Filed 5–4–78; 8:45 am]

[4110–03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 184]

[Docket No. 78N–0106]

PROPYL GALLATE

Proposed Modification of GRAS Usage as a Direct Human Food Ingredient

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This is a proposal to modify the conditions of use for propyl gallate as a generally recognized as safe (GRAS) direct human food ingredient. The safety of propyl gallate was evaluated during the comprehensive safety review being conducted by the agency. and the ingredient was affirmed as GRAS. But the adopted conditions of use conflict with good manufacturing practice. This proposal would modify the regulation for the use of propyl gallate to include current good manufacturing provisions for its GRAS use in food.

DATE: Comments by July 5, 1978.

ADDRESS: Written comments (preferably four copies) to the Hearing Clerk (HFC–20), Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Corbin I. Miles, Bureau of Foods (HFF–335), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C Street SW., Washington, D.C. 20204, 202–472–4750.

SUPPLEMENTARY INFORMATION: A comprehensive study of human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction is being conducted by FDA. Pursuant to this review, the Commissioner of Food and Drug issued a proposed regulation in the FEDERAL REGISTER of September 23, 1974 (39 FR 34199) for the use of propyl gallate as an antioxidant in food. This proposal summarized the available information regarding the identity, manufacture, and safety of this food ingredient. It was proposed that propyl gallate be affirmed as GRAS as a direct human food ingredient for use as an antioxidant, under conditions of good manufacturing practice. Good manufacturing practice was defined as a maximum level of 0.015 percent in food. No comments were received on this proposal, and in the FEDERAL REGISTER of December 7, 1976 (41 FR 53613) it was adopted without change.

A manufacturer of propyl gallate recently requested clarification of the labeling requirements for this ingredient because of the changes in its permitted levels and conditions of use resulting from the GRAS affirmation regulation published on December 7, 1976. Before this regulation, the GRAS use of propyl gallate was restricted to a level where the total content of antioxidants did not exceed 0.02 percent of the fat or oil content of food (including essential (volatile) oil content of the food). The present GRAS regulation limits the use of propyl gallate to 0.015 percent of the food irrespective of the fat or oil content of the food or the content of other antioxidants. The December 7, 1976 regulation could be interpreted as authorizing increased levels of use of propyl gallate in food, and this would appear to conflict with good manufacturing practice (21 CFR 184.1(b)(1).

But the current regulation was not intended to alter the levels of use of propyl gallate in food. This condition developed because of two errors. The first error was the failure to include the restrictions that base the level of addition of the ingredient on the fat or oil content of the food and on the presence of other antioxidants. The second error resulted from adoption of the maximum weighted mean use level of 0.015 percent, rather than the maximum use level of 0.02 percent as reported in the National Academy of Sciences/National Research Council's survey of food manufacturers. Affirming the former level as GRAS is unfair to those manufacturers that are using the ingredient at the maximum level reported in the survey. Both of these errors were in the proposed regulation for propyl gallate published on September 23, 1974, and, through an oversight, were not corrected in the final regulation, which was published on December 7, 1976. The Commissioner therefore concludes that it is in the public interest to amend the existing regulation and restore the previous good manufacturing practice use of propyl gallate. He is therefore proposing that propyl gallate be affirmed as GRAS as an antioxidant at a maximum use level of 0.02 percent of the fat or oil content of the food, This maximum use level, consisting of propyl gallate alone or in combination with other antioxidants, shall represent the total content of antioxidant in food.

The proposed action does not affect the present uses of propyl gallate for pet food or animal feed.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact state-