(iv) the estimated recoverable gas reserves in MCF at 14.73 psia made available to the applicant by means of the facilities last installed;

(v) the names of the fields connected; and

(vi) the location, including well number, of the facility attached if the attachment is for gas owned or produced by the applicant, or if the attachment is for gas purchased by the applicant, the names of the independent producers or other sellers from whom the gas is being purchased, together with the respective dates of their gas sales contracts, and FERC gas rate schedule designations, if applicable.

(4) For purposes of this paragraph, "gas-supply facilities" means those facilities, subject to the jurisdiction of the Commission under the Natural Gas Act which are:

(i) necessary to connect the facilities of an independent producer or other similar seller, with the system of the gas purchaser or the system of another natural gas company authorized to transport such gas for the account of, or for the exchange of such gas with, the gas purchaser; or

(ii) necessary to attach gas supplies in which a pipeline company has an ownership interest, whether company-developed and produced, acquired in place, or developed in conjunction with others, with the system of the pipeline company or the system of another natural gas company authorized to transport such gas for the account of, or for the exchange of such gas with, said pipeline company.

(5) Except as provided in subparagraph (b)(6) of this paragraph, applications made pursuant to this paragraph shall be filed with the Commission no later than October 1 of the year preceding the calendar year for which authorization is sought.

(6) *Transitional rules.* (i) In the event that a particular certificate granted under this paragraph prior to [date instant proposed rulemaking goes into effect] lapses during calendar year 1980, any subsequent certificate applied for prior to October 1, 1980 shall be for a period extending to December 31, 1980;

(ii) In the event that a particular certificate granted under this paragraph prior to [date instant proposed rulemaking goes into effect] lapses during calendar year 1979, any subsequent certificate applied for prior to October 1, 1980 shall be for a period extending to December 31, 1980.

(iii) Certificates granted pursuant to either subparagraphs (b)(6)(i) or (ii) of this paragraph shall be made at least 60 days before the prior certificate lapses and shall be pro-rated with regard to the applicable thresholds of subparagraph (b)(1)(i) of this paragraph to the number of months such certificate is to be in effect.

(7) *Filing.* Budget-type applications to construct and operate "gas-supply facilities" may be filed by either or both the gas-purchaser/owner and mother natural gas company authorized to transport gas for the account of, or for the exchange of gas with, the gas-purchaser/owner, depending upon which company or companies will actually construct and operate the budget-type facilities.

[Docket No. RM 79-37]

[FR Doc. 79-12718 Filed 4-23-79; 8:45 am]

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

121 CFR Part 501

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 additional safeguards for the protection of children involved in research activities that fall within FDA's jurisdiction. This proposal is issued in compliance with a 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 children. This proposal is intended to ensure adequate protection of the rights and safety of children who are subjects in clinical investigations for which prior approval by FDA is required or which are conducted in support of applications for permission to conduct further research or to market regulated products. Key sections provide that such clinical investigations can be carried out only if the methods employed are appropriate, the investigators competent, the facilities adequate, and the research procedures designed to contribute vitally to generalizable knowledge. Risks must be minimized, and the clinical investigation performed in connection with necessary diagnosis and treatment whenever possible. Adequate provisions must be made to obtain the assent of the child and the consent or permission of the parents or guardians, whenever these are necessary.

DATES: Written comments by June 25, 1979. 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 (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Roger W. Barnes, Office of Health Affairs (HFY-22), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1177.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of July 21, 1978 (43 FR 31786), DHEW proposed regulations governing research that involves children and is conducted or supported by DHEW. The proposed DHEW regulations implement the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission) on research involving children and provide additional protection for the children involved in such research activities.

The Commission's Report published in the **Federal Register** of January 13, 1978 (43 FR 2084), constitutes background material for this regulation and may be referred to for further guidance in interpreting its provisions. As noted in the proposal published by DHEW:

> These regulations (45 CFR Part 46) apply only to research conducted by the Department or to research supported by its grants and contracts. (43 FR 31791).

To set forth a uniform agency policy regarding research involving children, FDA is proposing regulations that will apply the principles set forth in the proposed DHEW regulations to all research involving children that is subject to FDA jurisdiction. The agency adopts the findings of the Commission as interpreted by the Secretary regarding the need for further rules to provide additional protection for research subjects with diminished capacity, including children. The agency also believes that, wherever possible, FDA's regulations should be compatible with, if not identical to, those of DHEW. A multiplicity of dissimilar and inconsistent Federal requirements is burdensome to institutions, Institutional Review Boards (IRB's), and the process of clinical investigation. Because the proposed Departmental regulation covers research conducted or funded by

the Department through grants and contracts, such research may involve behavioral testing of various kinds. The Departmental proposal therefore is written to accommodate both biomedical and behavioral research. FDA does not regulate behavioral research. The regulation being proposed by FDA, therefore, deals only with biomedical research that is subject to FDA jurisdiction.

This proposal is the second portion of Part 50 (21 CFR Part 50) to be proposed. On May 5, 1978 (43 FR 19417), FDA proposed regulations to provide protection for prisoners involved in research activities that fall within the jurisdiction of FDA. Comments on this proposal have been received, and a final regulation covering prisoner research will issue in the near future. The May 5, 1978 proposal included Subparts A (General Provisions) and C (Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects) of Part 50 which, when complete, will contain all of FDA's regulations on the protection of human subjects.

In this document, FDA proposes to add additional definitions to Subpart A and proposes a new Subpart D (Protections Pertaining to Clinical Investigations Involving Children). When completed, Part 50 will contain regulations applying to all clinical investigations that are subject to requirements for prior submission under section 505(i), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i), 357(d), 36O(g)), or that support or are intended to support an application for a research or marketing permit for a product regulated by the agency. FDA intends to revise and update existing agency regulations in the near future 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.

The preamble to the Departmental proposal on research involving children stated (43 FR 31791) that current FDA regulations concerning clinical investigations require IRB review only when the investigation is conducted by an institution or when the investigation is limited to institutionalized subjects. However, in a recent **Federal Register** proposal on standards for institutional review boards for clinical investigations (43 FR 35186, August 8, 1978), FDA proposed to extend the requirement for IRB review to "most investigations involving human subjects when such investigations are regulated by or submitted to FDA" (43 FR 35189). Preambles to the IRB proposal and a related proposal on the obligations of clinical investigators of regulated articles (also published in the **Federal Register** of August 8, 1978 (43 FR 35210)) discussed at length the history of IRB review and how it relates to the process of clinicial investigations submitted to FDA. Those discussions provide relevant background material to parties affected by this proposal.

The principles being set forth regarding clinical investigations involving children are to be applied to all such clinical investigations subject to FDA jurisdiction. Clinical investigations not conducted in conformity with this proposal will not be accepted by FDA.

Clinical Investigations Involving Children

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 FDA's regulatory requirements. FDA has considered the Commission's Report as well as the explanatory text set forth in the preamble to the July 21, 1978 DHEW proposal, and incorporates those documents as part of the discussion presented in this preamble. Proposed Subpart D requires that research involving children be carried out only if the conditions set forth in the proposal are met.

Definitions

Proposed §50.3 (21 CFR 50.3) defines a number of terms used in proposed Subpart D which were not proposed in the May 5, 1978 proposal on prisoner research. The definition of "children" in § 50.3(n) includes persons who have not attained the legal age of consent to general medical care as determined under the applicable law of the jurisdiction in which the research will be conducted. This provision means that the law of the site of the research shall determine the legal age of consent of the participant. Recognizing that this phrase may be ambiguous, e.g. in a multiple-investigator study conducted in several jurisdictions, the agency invites comment on the feasibility of this approach as well. Definitions are also included for "advocate" (§ 50.3(o)), "assent" (§ 50.3(p)), "permission" (50.3(q)), "parent" (50.3(r)), "guardian" (§ 50.3(s)), and "minimal risk" (§ 50.3(t)). The definitions of these terms generally follow the definitions proposed by the Department.

The proposed definitions of "assent" and "permission" include references to information specified in 45 CFR 46.103(c), which is the provision of DHEW's general regulation on protection of human subjects that defines informed consent. The section is included in the language of the regulation, as proposed, for purposes of clarity, although the reference will be changed to refer to the appropriate section of FDA regulations on informed consent after they are published.

"Informed consent" is defined in 45 CFR 46.103(c) as follows;

§ 46.103 *Definitions.*

* * * * *

(c) "Informed consent" means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

(1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;

(2) A description of any attendant discomforts and risks reasonably to be expected;

(3) A description of any benefits reasonably to be expected;

(4) A disclosure of any appropriate alternative procedures that might be advantageous for the subject;

(5) An offer to answer any inquiries concerning the procedures; and

(6) An instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

* * * * *

Proposed § 50.54(a)(5) (21 CFR 50.54(a)(5)), concerning additional IRB duties in protecting children's privacy and maintaining the confidentiality of data, corresponds to, but differs from, proposed § 46.404(a)(5) (45 CFR 46.404(a)(5)) of the Departmental regulation. The FDA may be required to verify the validity of any clinical investigation submitted to the agency. Therefore, in the August 1978 proposals concerning standards for IRB's for clinical investigations and the obligations of clinical investigators of regulated articles, FDA proposed record retention provisions for clinical investigations. Those provisions, proposed §§ 54.195 and 56.195 (21 CFR 54.195 and 56.195), would establish record retention requirements for both IRB's and clinical investigators. The policy behind the requirements that records of clinical investigations be retained, as well as the policies regarding the inspection of such records and the protection of the personal privacy of subjects of clinical

investigations, was fully discussed in both proposals.

As noted above, the discussion in the July 1978 preamble to the proposed DHEW regulation is incorporated by reference insofar as it applies to clinical studies submitted to FDA. The following portions of that preamble specifically seek advice regarding policies or provisions set out in this proposal:

> Recommendation (7) [Of the Commission's Report] concerns the solicitation of parent's or guardian's permission and of children's assent. The Department has adopted the substance of this recommendation but with some modifications. In the recommendation, the Commission leaves it to the Board as to whether, with respect to any particular project, the children are capable of assenting. However, in their comments on the recommendation, the Commission makes it clear that they believe assent should be required if the children are 7 years of age or older. Reaction to this comment was mixed. Some respondents endorsed the comment; others felt the age was set too low (with suggestions from 12 to 14 proposed as alternatives); still others recommended that the matter be left entirely to the Board for determination in the context of each particular case.
>
> The Department seeks further comment, preferably supported by studies and data, on this issue. Among the options being considered are the following:
>
> (1) Requiring assent from all children who are 12 years of age or older, if the research is not expected to be of direct benefit to the health or well being of the particular child.
>
> (2) Same as (1), but setting the age at 7.
>
> (3) In the regulation itself, leaving it to the discretion of the Board, but in the preamble to the regulation and in implementing policy statements recommending that assent normally be secured if the children are above a certain age (e.g., 12 or 7). Depending on the type of research and the types of candidates involved as subjects, the Board may wish to take a flexible approach in selecting ages at which assent may be required.
>
> (4) Leaving it to the discretion of the Board, with no guidance either in the preamble or in implementing policy statements.
>
> (5) Other alternatives. (43 FR 31786-1787).

This proposal uses the same language as the Departmental proposal used. However, FDA also seeks further comment on this issue, preferably with supporting data.

The proposed regulation, set forth below, leaves the matter to the IRB'S discretion. This should not be construed as indicating that a decision has been made as to what option will be adopted in the final regulation.

The Departmental preamble also sought advice regarding whether some specific kinds of research should be exempted from the regulations (43 FR 31792). Of the categories cited by the Department, only one ("Research involving solely the review of existing records") is of direct concern to FDA, and FDA requests comment regarding the appropriateness of narrowing the scope of Subpart D through exempting this category of research from the regulations. FDA would also be interested in suggestions concerning other categories that should be considered for exemption. Any such suggestions should include supporting data and should address the issue of whether, if a category is exempted, other protections should be developed to cover that category.

FDA is proposing that the final rule take effect 12 months after its date of publication in the **Federal Register.** Ongoing clinical investigations involving children as subjects shall be completed by the effective date, discontinued, or brought into conformity with the requirements of the regulation. Thus studies begun before, but continuing after, the effective date must comply on the effective date. However, the requirements need not be retroactively applied to children who, on the effective date, are no longer a part of a continuing study. 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.

LegalAuthority

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 has already 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 acceptability, 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, FDA must have standards to screen out those clinical investigations that are likely to be unacceptable and thus should not be authorized or that 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 priciples 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 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 (21 U.S.C. 355) and 701(a) of the act and have been upheld by the Supreme Court (see *Weinberger v. Hynson, Wescott & 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 (21 U.S.C. 355(i), 357(d), and 360j(g)), regarding clinical investigations that require prior FDA authorization, direct the agency to promulgate regulations to protect the public health in the course of those investigations. This proposal is intended to fulfill these mandates.

In sum, 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 (21 U.S.C. 346, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 361, 376, and 381), as well as the responsibilities of FDA under sections 351 and 354 to 360F of the Public Health Service Act (42 U.S.C. 262 and 263b to 263n).

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

FDA 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, 409, 502, 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-360j, 361, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 351, 354-360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-283n)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Part 50 be amended as follows:

1. In § 50.3, by adding new paragraphs (n) through (t) to read as follows:

§ 50.3 Definitions

* * * * *

(n) "Children" are persons who have not attained the legal age of consent to general medical care as determined under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

(0) "Advocate" means an individual appointed by the Institutional Review Board, or through procedures approved by the Board, to act in the best interest of the child. The advocate, although not appointed by a court, will be considered to have the fiduciary responsibilities of a guardian ad litem toward the children whose interests the advocate represents. No person may serve as an advocate if the person has any financial interest in, or other association with, the clinical investigator or the sponsor of the clinical investigation; nor, where the subject is the ward of a State or other agency, institution, or entity, may the advocate be employed by or be the recipient of grant or contract funds disbursed by, that State, agency, institution, or entity. One individual may serve as advocate for more than one child.

(p) "Assent" means a child's affirmative agreement to participate in the clinical investigation. Mere failure to object may not be construed as affirmative agreement. Assent can be given only after an explanation, based on the types of information specified in 45 CFR 46.103(c), that is appropriate to the level of understanding of the child. The procedures established by the Institutional Review Board for obtaining assent must be followed.

(q) "Permission" means the agreement of parent(s) or guardian to the participation of the child or ward in the clinical investigation. Permission can only be given following an explanation including the information specified in 45 CFR 46.103(c).

(r) "Parent" means a child's biological or adoptive parent.

(s) "Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care for the child.

(t) "Minimal risk" is the probability and magnitude of physical or psychological harm comparable to that normally encountered in the daily lives, or in the routine medical or dental examination, or in the other routine health care, of healthy children.

2. By adding new Subpart D, consisting of §§ 50.50, 50.52, 50.54, 50.56, 50.58, 50.60, 50.62, 50.64, and 50.66, to read as follows:

Subpart D—Protections Pertaining to Clinical Investigations Involving Children

Sec.

§ 50.50 Applicability.

(a) The regulations in this subpart are applicable to all clinical investigations involving children as subjects that are required to be submitted to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or that are conducted in support of an application for a research or marketing permit for a product regulated by the agency, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

(b) Compliance with these procedures will in no way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

§ 50.52 Purpose.

Children are normally legally incapable of consenting to their own participation in clinical investigations and may also be unable to comprehend fully the benefits, consequences, and risks that might be involved in such participation. This subpart provides additional safeguards for the protection of children involved in such investigations.

§ 50.54 Additional duties of an Institutional Review Board where children are involved.

(a) In addition to all other responsibilities prescribed under this chapter, each Institutional Review Board shall review clinical investigations covered by this subpart. It may approve the clinical investigation only if it is satisfied that:

(1) The research methods are appropriate to the aims of the clinical investigation;

(2) The competence of the investigator(s) and the quality of the research facility are sufficient for the conduct of the clinical investigation;

(3) Where appropriate, studies have been conducted first on animals and adult humans, and then on older children, before involving very young children;

(4) Risks are minimized by using the safest procedures consistent with a soundly designed clinical investigation. Whenever appropriate and feasible, the clinical investigation should be performed within the context of diagnosis or treatment of the particular subject;

(5) Adequate provisions are made to protect the privacy of children and their parents, and to maintain the confidentiality of data;

(6) The criteria for subject selection are appropriate for the aims of the clinical investigation and permit the selection of subjects in an equitable manner, avoiding overuse of any one group of children, including overuse due to administrative convenience or availability of a population;

(7) Where appropriate, adequate provisions are made for involving a parent, guardian, or advocate in the conduct or monitoring of the clinical investigation (e.g., in situations in which the Institutional Review Board finds the subjects to be incapable of assenting

and the clinical investigation involves more than minimal risks or more than minimal discomfort to these subjects);

(8) Adequate provisions are made for monitoring the solicitation of assent and permission, as, e.g., through participation by Institutional Review Board members or by an advocate in the actual solicitation process, either for all subjects or for a sampling of subjects: and

(9) The conditions of all applicable subsequent sections of this subpart are met.

(10) The institution sponsoring the Institutional Review Board shall certify to the Commissioner, in such manner as the Commissioner may require, that the duties of the Institutional Review Board under this subpart have been fulfilled.

§ 50.56 Clinical investigations not involving greater than minimal risk.

Any clinical investigation 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 Food and Drug Administration, that does not involve greater than minimal risk, may involve children as subjects if the Institutional Review Board finds that:

(a) The conditions of § 50.54 are met; and

(b) Adequate provisions are made for soliciting the assent of the children and the permission of their parent or guardian, as set forth in § 50.64.

§ 50.58 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

A clinical investigation 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 Food and Drug Administration, that, although involving more than minimal risk, holds out the prospect of direct benefit to the individual subject or is likely to contribute to the subject's well-being, may involve children as subjects if the Institutional Review Board finds that:

(a) The risk is justified by the anticipated benefit to the subjects:

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

(c) The conditions of § 50.54 are met; and

(d) Adequate provisions are made for soliciting the assent of the children and the permission of their parent(s) or guardian, as set forth in § 50.64.

§ 50.60 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield general knowledge about the subjects' disorder or condition.

Any clinical investigation 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 Food and Drug Administration, that involves more than minimal risk, that does not hold out the prospect of direct benefit for the individual subject, and that is not likely to contribute to the subject's well-being, may involve children as subjects if the Institutional Review Board finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The clinical investigation presents to subjects experiences that are reasonably comensurate with those inherent in the subjects' actual or expected medical, dental, or other comparable situations;

(c) The clinical investigation is likely to yield knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition;

(d) The conditions of § 50.54 are met; and

(e) Adequate provisions are made for soliciting the assent of the children and permission of their parent(s) or guardian, as set forth in § 50.64.

§ 50.62 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Any clinical investigation 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 Food and Drug Administration, that the Institutional Review Board does not believe meets the requirements of § 50.56, 50.58, or 50.60, may involve children as subjects if:

(a) The Institutional Review Board finds that the conditions of § 50.54 are met and that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law), has determined either that the clinical investigation in fact satisfies the conditions of § 50.56, 50.58, or 50.60, as applicable, or that;

(1) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children: and

(2) The clinical investigation will be conducted in accordance with basic ethical principles: and

(3) Adequate provisions are made for soliciting the assent of children and the permission of their parent(s) or guardian, as set forth in § 50.64.

§ 50.64 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the Institutional Review Board shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the Institutional Review Board the children are capable of assenting. In determining whether children are capable of assenting, the Institutional Review Board shall take into account the ages and maturity of the children involved. This judgment may be made for all children under a particular research protocol, or on a more individualized basis, as the Institutional Review Board deems appropriate. If the Institutional Review Board determines that child is so young or incapacitated that he or she cannot reasonably be consulted or that the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the clinical investigation, the assent of the child need not be obtained. If the Institutional Review Board determines that a child is so young or incapacitated, and the child is not under the guardianship of a parent, then permission of both the guardian and a subject advocate shall be obtained.

(b) If the Institutional Review Board determines under paragraph (a) of this section that the child's assent need not be obtained, it shall also determine whether an advocate should be appointed for the child. In making that determination, the Institutional Review Board shall take into account such

factors as whether there are likely to be financial or other pressures on the parent(s) or guardian that could affect their ability to consider solely the interests of the child in deciding whether to consent to the child's participation in the clinical investigation. The role of the advocate would be to advise the Institutional Review Board, parents, and investigators of any concerns the advocate may have about the child's participation in the clinical investigation.

(c) In addition to the determinations required under other applicable sections of this subpart, the Institutional Review Board shall determine that adequate provisions are made for soliciting the permission of each child's parent(s) or guardian. Where parental permission is to be obtained, the Institutional Review Board may find that permission of one parent is sufficient for research to be conducted under § 50.56 or 50.58, but in doing so the Institutional Review Board shall consider such factors as the nature of the clinical investigation and the age, maturity, status, and condition of the subject. Where the clinical investigation is covered by § 50.60 or 50.62 and permission is to be obtained from parents, both parents shall give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or the child belongs to a singleparent family (i.e., when only one parent has legal responsibility for the care and custody of the child).

(d) If the Institutional Review Board determines that a research protocol is designed for conditions or for a subject population for which the permission of the parent(s) or guardian is not a reasonable requirement to protect the subjects (e.g., neglected or abused children), it may waive the informed consent requirements of this part and the consent requirements of paragraph (c) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the clinical investigation is substituted and provided further that the waiver is not inconsistent with State or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the subjects of the clinical investigation, and the age, maturity, status, and condition of the subjects.

(e) The Institutional Review Board shall determine how permission by parents or guardians will be documented.

(f) When the Board determines that assent is required, it shall also determine how assent shall be documented.

§50.66 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity may be included in clinical investigations approved under § 50.60 or 50.62 only if the clinical investigation is conducted in schools, camps, or similar group settings in which the majority of children involved as subjects are not wards.

(b) If the clinical investigation is approved under paragraph (a) of this section, the Institutional Review Board shall require appointment of an advocate for each child, in addition to any other individual acting as guardian or in loco parentis for the child. The advocate shall act in the best interest of the child and shall have the same opportunities to intercede that are normally provided for parents.

(c) If a child who is a ward objects to participation in the clinical investigation, but the child's assent is not required under § 50.64, the child may be included as a subject only with the approval of both the child's guardian and the advocate for the child.

Interested persons may, on or before June 25, 1979, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of 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.

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

Dated April 5, 1979

Donald Kennedy,

Commissioner of Food and Drugs.

[Docket No. 78N-0331]

FR Doc. 79-12306 Filed 4-19-79; 12:55 pm]

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[21 CFR Part 310]

Requirement for Estrogens Labeling Directed to the Patient

Correction

In FR Doc. 79-11678 appearing at page 22752 in the issue of Tuesday, April 17, 1979, on page 22755, first column, second line from the top, delete "on May 17, 1979" and insert the following in its place: "30 days after the date of publication of the final rule in the **Federal Register** ."

[Docket No. 78-0303]

BILLING CODE 1505-01-M

POSTAL SERVICE

[39 CFR Part 233]

Inspection Service Authority; Mail Covers; National Security

AGENCY: Postal Service.

ACTION: Proposed rule.

SUMMARY: The Postal Service proposes to amend its mail cover regulations so as: (1) To define more specifically when the issuance of a mail cover order is necessary to protect the national security: and, (2) to provide that the requesting authority for a national security mail cover order shall be the head of the law enforcement agency requesting the cover, and that the requesting authority for an extension of such an order shall be the head of the executive department having jurisdiction of the agency. This proposal is prompted in part by a federal district court opinion declaring the present national security mail cover regulation to be unconstitutionally vague, and by the practical consideration that it is easier and quicker to amend the regulation so as to make it more specific than to pursue available appeal procedures. The purpose of both regulatory amendments is to show generally that the "national security" mail cover program is a carefully limited and well-focused program which does significantly protect the national security, but which does not significantly affect the general privacy of the mails or impair First Amendment values. This is the first substantive amendment proposed to these regulations since their adoption in 1965.

DATE: Written comments must be received on or before May 24, 1979.

ADDRESSES: Comments should be directed to Assistant General Counsel,