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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50 and 56

[Docket No. 00N-0074]  
RIN 0910-AC07

Additional Safeguards for Children in Clinical Investigations of  
FDA-Regulated Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Interim rule; opportunity for public comment.

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SUMMARY: The Food and Drug Administration (FDA) is issuing an interim rule to amend its regulations to provide additional safeguards for children enrolled in clinical investigations of FDA-regulated products. This interim rule is intended to bring FDA regulations into compliance with provisions of the Children's Health Act of 2000 (the Children's Health Act), which requires that within 6 months of its enactment all research involving children that is conducted, supported, or regulated by the Department of Health and Human Services (HHS) be in compliance with HHS regulations providing additional protections for children involved as subjects in research. To comply with this congressionally mandated timeframe and for other reasons described in this document, FDA is publishing this regulation as an interim rule.

FDA is requiring additional safeguards to protect children because of expected increases in the enrollment of children in clinical investigations as a result of recent pediatric initiatives. These initiatives include FDA's 1998 pediatric rule (the 1998 pediatric rule) and the pediatric provisions of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).

DATES: This interim rule is effective April 30, 2001. Submit written comments by July 23, 2001. Submit written comments on the information collection requirements by May 24, 2001.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk

Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Carol Drew, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

FDA's authority includes regulation of safety and effectiveness testing in humans of certain FDA-regulated products. FDA-regulated products include human drug and biological products, medical device products, and dietary supplements, nutritional, food additive, and foods. This rule covers safety and effectiveness testing of FDA-regulated products in children. FDA expects an increase in testing of drug and biological products in children as a result of recent initiatives in pediatric research.

A. Recent Initiatives in Pediatric Research

The 1998 pediatric rule (63 FR 66632, December 2, 1998) requires manufacturers to assess the safety and effectiveness of certain drug and biological products in pediatric patients. In the preamble to the 1998 pediatric rule, FDA stated that many drug and biological products marketed in the United States that are or could be used in children are inadequately labeled for use in pediatric patients or specific pediatric subgroups. FDA concluded that the absence of pediatric labeling information for these drug and biological products posed significant risks for children.

The 1998 pediatric rule establishes a presumption that certain drug and biological products will be studied in pediatric patients. The 1998 pediatric rule also authorizes FDA to require pediatric studies of those marketed drug and biological products that: (1) Are used in a substantial number of pediatric patients for the labeled indications, and where the absence of adequate labeling could pose significant risks to pediatric patients; or (2) would provide a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications, and the absence of adequate labeling could pose significant risks to pediatric patients.

The Modernization Act (Public Law 105-115) established economic incentives for manufacturers to conduct pediatric studies on drugs for which exclusivity or patent protection is available under the Drug Price Competition and Patent Term Restoration Act (Public Law 98-417) or the Orphan Drug Act (Public Law 97-414). These provisions attach 6 months of marketing exclusivity to any existing exclusivity or patent protection on a drug for which FDA has requested pediatric studies and the manufacturer has conducted such studies in accordance with the requirements of the Modernization Act.

As of October 1, 2000, FDA had received 194 proposed pediatric study requests under the exclusivity provisions of the Modernization Act and had issued 157 Written Requests for pediatric studies. A Written Request is

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a specific document from FDA in which the agency requests submission of

certain studies to determine if the use of a drug could have meaningful health benefits in the pediatric population. Sponsors have indicated they are conducting or planning to conduct over 80 percent of the studies for which Written Requests have been issued.

FDA expects that the combination of the pediatric exclusivity incentive of the Modernization Act and the requirements of the 1998 pediatric rule will significantly increase the number of FDA-regulated products for which pediatric studies will be conducted. This increase in studies has led to concern over the adequacy of existing safeguards for pediatric study subjects.

In addition to the Modernization Act and the 1998 pediatric rule, FDA has initiated other actions to encourage the development of adequate pediatric use information for drug and biological products. Among other actions, FDA has published several pediatric guidance documents. (See FDA's pediatric website at <http://frwebgate.access.gpo.gov/cgi-bin/leaving.cgi?from=leavingFR.html&log=linklog&to=http://www.fda.gov/cder/pediatric.>)

FDA's view that additional pediatric safeguards are necessary is underscored by title XXVII, section 2701 of the Children's Health Act (Public Law 106-310), in which Congress directs the Secretary of HHS (the Secretary) to require all research involving children that is conducted, supported, or regulated by HHS to be in compliance with 45 CFR part 46, subpart D (HHS subpart D) within 6 months of the date of enactment. The Children's Health Act was signed by the President on October 17, 2000. Clinical investigations involving FDA-regulated products, therefore, must comply with the standards of HHS subpart D by April 17, 2001. To respond to this congressionally mandated timeframe and for other reasons described in this document, FDA is publishing this regulation as an interim rule.

In addition to requiring that HHS subpart D be applied to clinical investigations involving FDA-regulated products, Congress is requiring a substantive review of HHS subpart D. Title X, section 1003 of the Children's Health Act requires the Secretary to review HHS subpart D, consider any necessary modifications to ensure the adequate and appropriate protection of children participating in research, and report the findings to Congress. If, as a result of this evaluation, HHS proposes to modify HHS subpart D, FDA will review and modify this interim rule as appropriate.

## B. Early Initiatives for Pediatric Safeguards

The National Research Act (Public Law 93-348), signed into law on July 12, 1974, created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission). One of the Commission's charges was to make recommendations pertaining to research involving children, including the purposes of such research, the steps necessary to protect children as subjects, and requirements for the informed consent of children or their parents or guardians. The Commission was required to recommend to the Secretary (of HHS or the Department)\1\ policies defining circumstances under which research with and for children might be appropriate. The recommendations of the Commission pertaining to research involving children were published in the Federal Register of January 13, 1978 (43 FR 2084). After review of the Commission's report, recommendations, and public comments, the Secretary published in the Federal Register of July 21, 1978 (43 FR 31786), a notice of proposed rulemaking on

research involving children conducted or supported by HHS. HHS reviewed the public comments received on the proposal and also considered the Basic HHS Policy for the Protection of Human Research Subjects (45 CFR part 46). On March 8, 1983, HHS published its final rule incorporating requirements for the protection of children involved as subjects in HHS-conducted or HHS-supported research (48 FR 9814). This rule is codified at 45 CFR part 46, subpart D. These regulations supplemented basic regulations governing the protection of human subjects involved in research conducted or supported by HHS (30 FR 18914, May 30, 1974).

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\\1\ At the time, HHS was named the Department of Health, Education, and Welfare. To avoid confusion, this document uses only the Department's current name, HHS.

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In the Federal Register of April 24, 1979 (44 FR 24106), FDA proposed regulations and solicited comments on applying the principles set forth in the HHS regulations to all pediatric research subject to FDA jurisdiction. This proposal was not finalized and was withdrawn on December 30, 1991 (56 FR 67440).

#### C. Current Safeguards for Pediatric Research

HHS subpart D provides protections for children involved in HHS-conducted or HHS-supported research. If an FDA-regulated clinical investigation is not conducted or supported by HHS, HHS subpart D does not impose requirements on the investigation. Nevertheless, FDA has historically relied on the HHS regulations to provide appropriate guidance for pediatric studies. In addition, as described below, there are other safeguards in place for pediatric research.

Current FDA regulations in part 56 (21 CFR part 56) governing institutional review boards (IRBs) include children as a class of vulnerable subjects, but do not specifically address the enrollment of children in clinical investigations. Portions of part 56 address pediatric issues. In Sec. 56.111(a)(3), IRBs are required to determine that the selection of subjects in research is equitable and, to do so, should be ``particularly cognizant of the special problems of research involving vulnerable populations, such as children \* \* \*.''' Section 56.111(b) states, ``When some or all of the subjects, such as children \* \* \*, are likely to be vulnerable to coercion or undue influence [,] additional safeguards have been included in the study to protect the rights and welfare of these subjects.''' Section 56.107(a) addresses IRB membership and provides that if an IRB ``regularly reviews research that involves a vulnerable category of subjects, such as children, \* \* \* consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.''

FDA's information sheets entitled ``Guidance for Institutional Review Boards and Clinical Investigators'' address issues regarding informed consent and the assent of children. This guidance states that although FDA regulations regarding informed consent do not specifically address the enrollment of children, the basic requirements of Sec. 50.20 (21 CFR 50.20) regarding informed consent apply. The information sheets also state that HHS regulations for conduct of

studies in children may be used as guidance for all pediatric studies. These information sheets are available at <http://frwebgate.access.gpo.gov/cgi-bin/leaving.cgi?from=leavingFR.html&log=linklog&to=http://www.fda.gov/oc/oha/IRB/toc.html>.

FDA also has published a guidance entitled ``E11 Clinical Investigation of Medicinal Products in the Pediatric Population'' (ICH E11). This guidance was prepared by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as part of the ICH effort to harmonize technical requirements for the registration of pharmaceutical products among the European Union, Japan, and

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the United States. ICH E11 addresses issues in pediatric drug development including ethical considerations in pediatric studies. It states that pediatric populations represent a vulnerable subgroup and special measures are needed to protect the rights of pediatric study participants. Section 2.6 of ICH E11 addresses relevant issues including: The roles and responsibilities of IRBs and independent ethics committees, recruitment of study participants, consent and assent, and minimizing risk and distress in pediatric studies.

The documents described above provide considerable information and guidance regarding the participation of children in clinical trials. Nonetheless, given the expected increase in the number of children enrolled in clinical investigations as a result of recent pediatric initiatives, additional safeguards for children enrolled in clinical investigations of FDA-regulated products are appropriate.

## II. Highlights of the Interim Rule

This interim rule will apply the safeguards described in HHS subpart D to children participating in clinical investigations of FDA-regulated products. These safeguards are also intended to ensure the adequate protection of the rights and welfare of children who participate in clinical investigations. Nothing in the regulations described in this interim rule is intended to preempt any applicable Federal, State, or local laws that require additional safeguards for children participating in clinical investigations.

FDA is adopting HHS subpart D, as directed by Congress, with only those changes necessary due to differences between FDA's and HHS's regulatory authority. The agency is aware that dissimilar or inconsistent Federal requirements governing pediatric protections could be burdensome to institutions, IRBs, and the process of clinical investigation.

FDA's regulations governing informed consent and IRBs apply to clinical investigations that are subject to FDA's jurisdiction. The scope of the regulations is described in Secs. 50.1 (21 CFR 50.1) and 56.101 and includes all clinical investigations that are subject to requirements for prior submission under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i) and 360j(g)) or that support an application for a research or marketing permit for a product regulated by the agency as defined in Secs. 50.3(b) (21 CFR 50.3(b)) and 56.102(b). This includes color additive petitions, petitions submitted to establish that a substance that may become a component of food is generally recognized as safe for use, food

additive petitions and petitions for establishing a tolerance for unavoidable contaminants in food, drug applications, biologics licenses, and medical device applications. In contrast, HHS subpart D regulations cover research involving children as subjects, conducted or supported by the Department. With minor exceptions, FDA does not conduct or support research involving human subjects. Instead, FDA regulates research conducted by outside sponsors and investigators, where the research is subject to IRB review and approval. Because of these differences, FDA is making some modifications to HHS subpart D. For example, throughout the interim rule, FDA has modified the description of the scope of the rule from applying to research conducted or supported by the Department as described in HHS subpart D, to applying to clinical investigations subject to FDA's regulatory authority. Some research involving FDA-regulated products is also conducted or supported by HHS and falls within the scope of both HHS and FDA regulations.

In addition, in its adoption of provisions of HHS subpart D, FDA has made minor editorial changes in response to the ongoing initiative regarding plain language in government writing. FDA solicits comments on all provisions in this interim rule and has identified certain points on which comments would be particularly useful.

Finally, FDA has made changes to the scope and definitions sections of part 50 (21 CFR part 50) and part 56 to reflect that studies of certain foods, dietary supplements, and infant formulas are covered by these regulations. The regulations in part 101 (21 CFR part 101) governing petitions for nutrient content claims state that clinical studies submitted in support of such a petition must be conducted in accordance with the requirements of parts 50 and 56 (Sec. 101.69(f)). The regulations governing petitions for health claims contain the same requirement (Sec. 101.70(d)). Therefore, the agency is clarifying that parts 50 and 56 govern clinical investigations, including those involving children, when such investigations may be submitted in a petition under Sec. 101.69 or Sec. 101.70. Consistent with the congressional directive that the protections of the HHS subpart D regulations be extended to all research involving children regulated by FDA, studies in children in support of infant formulas and in support of premarket notification of dietary supplements that contain new dietary ingredients are also subject to parts 50 and 56.

#### A. What Definitions Is FDA Adopting From HHS Subpart D?

FDA is adopting several terms from 45 CFR 46.402 of HHS subpart D for inclusion in the FDA definitions at Sec. 50.3. These include the terms ``assent'' (Sec. 50.3(n)), ``children'' (Sec. 50.3(o)), ``parent'' (Sec. 50.3(p)), ``permission'' (Sec. 50.3(r)), and ``guardian'' (Sec. 50.3(s)). The definitions of these terms in Sec. 50.3 generally follow the definitions in HHS subpart D, with changes as identified and discussed below. In addition, FDA is defining the term ``ward'' (Sec. 50.3(q)) in a manner that is consistent with its use in HHS subpart D.

##### 1. What is Assent?

The definition of ``assent'' at Sec. 50.3(n) is adopted from HHS subpart D with a minor change to clarify that the assent applies to participation in clinical investigations involving FDA-regulated products. FDA's regulation, like the HHS regulation, defines assent as a child's affirmative agreement to participate in research. FDA's definition also states that mere failure to object to participation in

clinical investigations should not, absent affirmative agreement, be considered assent.

2. What Does the Term ``Children'' Mean?

The definition of ``children'' at Sec. 50.3(o) includes persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations 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 will determine the legal age of consent of the participant.

3. What Does ``Parent'' Mean?

FDA did not previously have a definition for parent at Sec. 50.3 and is adopting the definition from HHS subpart D. ``Parent'' is defined as a child's biological or adoptive parent.

4. What Does the Term ``Ward'' Mean?

The term ``ward'' is used in HHS subpart D but is not defined. In Sec. 50.3(q), FDA has developed a definition for ward that is consistent with the use of the term in HHS subpart D. Under Sec. 50.3(q), a ward is a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

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5. What Does ``Permission'' Mean, and How Is It Different From Informed Consent?

The definition of ``permission'' at Sec. 50.3(r) is adopted from 45 CFR 46.402(c) of HHS subpart D with a minor change to clarify that permission applies to participation in clinical investigations involving FDA-regulated products. FDA's definition at Sec. 50.3(r) generally adopts the HHS definition and states that permission is the agreement of parent(s) or guardian to their child's or ward's participation in a clinical investigation.

FDA's regulation at Sec. 50.3(r) adds a sentence clarifying that permission must be obtained in compliance with part 50, subpart B and must include the elements of informed consent described in FDA's regulations at Sec. 50.25. This approach is consistent with HHS's interpretation of the term ``permission.'' Under the requirements for permission by parents or guardians and assent by children, 45 CFR 46.408(d) of HHS subpart D states that permission by parents or guardians shall be documented in accordance with and to the extent required by 45 CFR 46.117 of HHS subpart A (45 CFR part 46, subpart A). Section 46.117 of HHS subpart A outlines the requirements for documenting informed consent. Addressing comments made on requiring parental consent to participation in research in the preamble to its final rule (48 FR 9814), the Department stated that inserting this reference to 45 CFR 46.117 of HHS subpart A clarified that the requirements for informed consent shall apply to permission.

The agency is retaining the term permission because this term is used in HHS subpart D and is familiar to IRBs. The term permission also distinguishes children from other participants in clinical investigations. Children are defined as persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations under the applicable law of the jurisdiction in which the clinical investigation will be conducted. Because children are unable, due to age, to give consent themselves, permission is provided by a parent or guardian on their behalf. The term informed consent under Sec. 50.20 applies to other participants in clinical

investigations. FDA solicits comments on its definition of permission.  
6. What Is a ``Guardian,'' and What Is the Difference Between a Guardian and a Legally Authorized Representative?

FDA's current regulations do not have a definition for guardian in part 50. In this interim rule, FDA is adopting a modification of the term ``guardian'' as used in HHS subpart D. In HHS subpart D, a guardian is an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. FDA is adopting this definition and is adding text to clarify that authorization to consent to general medical care must include participation in research and, for purposes of this rule, a guardian is also an individual authorized to consent to a child's participation in research. FDA is adding this clarification because of concern that, in some cases, authorization to consent to general medical care may not extend to consent to participation in research. For a guardian to be able to grant permission for a child to participate in research, the guardian must either have authority to consent to a child's general medical care (where participation in clinical research falls within general medical care) or must have authority to consent to a child's participation in research.

FDA is adopting the term guardian because this term is currently used in HHS subpart D in the context of research involving children, and is familiar to IRBs. In contrast, FDA's regulations at Sec. 50.3 and HHS's regulations at 45 CFR 46.102(c) use the term ``legally authorized representative'' for an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures involved in the research. FDA's definition of the term guardian is intended to clarify that a guardian must be an individual authorized to consent to a child's participation in research. FDA seeks comments on its definition of the term guardian and any implications under State or local law.

#### B. What New Duties Do IRBs Assume Under This Interim Rule?

FDA has adopted the provisions in 45 CFR 46.403 of HHS subpart D with minor changes. The provisions are included in FDA regulations at Sec. 50.50. Section 50.50 directs that in addition to other responsibilities assigned under parts 50 and 56, IRBs must now review research covered by subpart D of part 50 and approve only research that satisfies the criteria described in Sec. 50.51, Sec. 50.52, or Sec. 50.53 and the conditions of all other applicable sections of part 50, subpart D.

FDA has also made conforming changes to part 56 of its regulations governing IRBs. Under part 56, subpart C, describing IRB functions and operations, FDA is adding new paragraph (c) to Sec. 56.111. New Sec. 56.111(c) requires that to approve research in which some or all of the subjects are children, an IRB must determine that all such research is in compliance with part 50, subpart D.

Similarly, FDA has added new paragraph (h) to Sec. 56.109 on IRB review of research to require that when some or all of the subjects of ongoing research are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D. This review of research that is ongoing on the effective date of this rule must be conducted either at the time of continuing review or, at the discretion of an IRB, at an earlier date. Under Sec. 56.109(f), IRBs conduct continuing review of research at intervals appropriate to the degree of

risk of the research, but not less than once per year. FDA expects that the degree of risk posed to children will be considered by the IRB in determining when to conduct a continuing review of an ongoing trial for compliance with part 50, subpart D.

FDA regulations set out criteria to be satisfied if an IRB is to approve research (Sec. 56.111). These criteria are the same for initial review and continuing review and include a determination by the IRB that:

- (1) Risks to subjects are minimized,
- (2) Risks to subjects are reasonable in relation to anticipated benefits,
- (3) Selection of subjects is equitable,
- (4) Informed consent is adequate and appropriately documented,
- (5) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects,
- (6) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, and
- (7) Appropriate safeguards have been included to protect vulnerable subjects.

Under new Sec. 56.109(h), at the time of continuing review, or at an earlier date if the IRB so determines, the IRB must review research involving children, with reference to the risk categories and criteria as defined in part 50, subpart D, to determine if an ongoing clinical investigation fits into one of the risk categories at Sec. 50.51, Sec. 50.52, or Sec. 50.53. If an IRB determines that the research does not fit any of these three categories, but that the research may fit under Sec. 50.54, the IRB should contact FDA for further guidance. FDA emphasizes that it expects the volume of studies that are

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candidates for classification under Sec. 50.54 to be extremely small. FDA believes it is appropriate to permit review of ongoing investigations for compliance with part 50, subpart D at the time of continuing review or at an earlier date identified by the IRB because this is the least disruptive way to ensure compliance. If an IRB determines that research in progress does not fit any of the four risk categories defined in part 50, subpart D, the IRB has authority to suspend or terminate approval of the research under Sec. 56.113. Under Sec. 56.113, the IRB must report any such action to FDA. FDA notes that many ongoing pediatric studies have been approved by IRBs based upon the standards described in HHS subpart D, so the agency anticipates that very few, if any, ongoing studies will be suspended or terminated.

#### C. When May IRBs Approve a Clinical Investigation Not Involving Greater Than Minimal Risk?

Under Sec. 50.51, an IRB may approve a clinical investigation in which no greater than minimal risk is presented only if an IRB finds and documents that adequate provisions are made for soliciting the assent of the children involved and the permission of their parents or guardians as set forth in Sec. 50.55. In adopting this provision, FDA has made minor changes to the language used in 45 CFR 46.404 of HHS subpart D. Rather than stating that HHS will ``conduct or fund research'' in which the IRB finds no greater than minimal risk to children, FDA has modified this language to state the conditions under which an IRB may approve a clinical investigation involving an FDA-

regulated product in which there is no greater than minimal risk to children. FDA believes this change is required by the scope of FDA's regulatory authority. Similar changes have been made as necessary throughout the codified section to reflect the scope of FDA's regulatory authority.

FDA previously adopted the Department's definition of minimal risk (45 CFR 46.102(g) of subpart A) without change in Sec. 50.3. FDA anticipates that among the types of procedures that might be used in a clinical investigation that would present no more than minimal risk to children would be clean-catch urinalysis, obtaining stool samples, administering electroencephalograms, requiring minimal changes in diet or daily routine, or the use of standard psychological tests. Examples of the types of clinical investigations that would present no more than minimal risk would include a taste test of an excipient or tests of devices involving temperature readings orally or in the ear. FDA anticipates that there may be circumstances under which products with an established safety profile in adults may present no more than minimal risk in children.

#### D. When May IRBs Approve Clinical Investigations Involving Greater Than Minimal Risk But Presenting the Prospect of Direct Benefit to the Individual Subjects?

Under Sec. 50.52, an IRB may approve a clinical investigation in which an IRB finds more than minimal risk to children but that presents the prospect of direct benefit to individual subjects only if the IRB finds and documents that:

- (1) The risk is justified by the anticipated benefit to the subjects,
- (2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches, and
- (3) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in Sec. 50.55.

Section 50.52 adopts the provisions of 45 CFR 46.405 of HHS subpart D with minor changes to conform to FDA's regulatory authority. FDA expects that many clinical investigations of FDA-regulated products in children will be allowed to proceed under Sec. 50.52. These clinical investigations generally are performed in children with the disease or condition for which the product is intended.

FDA recognizes that in the case of clinical investigations of FDA-regulated products conducted under an investigational new drug application (IND) or investigational device exemption (IDE), it may not always be possible to know the level of risk the subject will be exposed to ahead of time. This may create difficulties for IRBs trying to assess whether a clinical investigation involves more than minimal risk. IRBs may need to make such judgments on a case-by-case basis.

While the level of risk in a clinical investigation may change during the course of a study, appropriate strategies may be included in the study design that may mitigate risks. These might include exit strategies in the case of adverse events or a lack of efficacy, or establishing a data monitoring committee (DMC) to review ongoing data collection and recommend study changes, including stopping a trial on the basis of safety information. FDA invites comment on appropriate criteria for IRBs to use in assessing when a clinical investigation may involve more than minimal risk to children.

The agency also recognizes that the requirement for the prospect of direct benefit to individual subjects may create ambiguity about whether placebo-controlled clinical investigations may be conducted in children. FDA believes that clinical investigations involving placebos in children may be conducted in accord with Sec. 50.52. There is evidence of direct benefit to subjects from participating in placebo-controlled trials, including increased monitoring and care of subjects, even though a subject may not actually receive the test product. FDA invites comment on the issue of conducting placebo-controlled trials in children.

E. When May an IRB Approve a Clinical Investigation Involving Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, But Likely to Yield Generalizable Knowledge About the Subjects' Disorder or Condition?

Section 50.53 provides that in certain circumstances an IRB may approve a clinical investigation in which the IRB finds that more than minimal risk to children is presented: (1) By an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or (2) by a monitoring procedure that is not likely to contribute to the well-being of the subject. The clinical investigation may be approved only if the IRB finds and documents that:

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

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(4) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in Sec. 50.55.

FDA has adopted these requirements from 45 CFR 46.406 of HHS subpart D, with minor modifications to conform to FDA's regulatory authority.

FDA recognizes that Sec. 50.53 raises issues similar to those raised by Sec. 50.52 about standards for IRBs to use in assessing when a clinical investigation involves more than minimal risk. Some comments submitted previously on HHS's proposed rule (43 FR 31786, July

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21, 1978) indicated that no attempt should be made to define the concept of ``minor increase'' or to provide guidance to IRBs on evaluating whether a ``minor increase over minimal risk'' is involved. These comments stated that because of varying situations and circumstances, IRBs would need to make judgments on a case-by-case basis. FDA believes that IRBs are qualified to assess and document when a specific protocol falls under this category. However, FDA is soliciting comments on whether further definition should be provided to aid IRBs in making such determinations, including: (1) How to measure a minor increase in risk, (2) at what point a minimal risk develops into a major risk, and (3) whether IRBs have the expertise necessary to determine minor increases over minimal risk.

Section 50.53(c) contains the phrase ``likely to yield generalizable knowledge about the subjects' disorder or condition.''' The criterion in Sec. 50.53(c) raises the question whether clinical investigations of FDA-regulated products conducted to determine the safety and effectiveness of such products yield generalizable knowledge about a subject's disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition. FDA believes there are circumstances in which clinical investigations yield such information. Such circumstances may include cases where a child has been identified as at high risk for a disease and receives investigational interventions to prevent the disease or ameliorate manifestations of the disease in the future. In these situations, even in children who would not otherwise have manifested the disease, the clinical investigations may yield important information that might contribute to the understanding of a disease, disorder, or condition. FDA believes that IRBs are capable of making this assessment. Therefore, FDA is adopting this provision from HHS subpart D.

F. When May an IRB Allow a Clinical Investigation to Proceed That Is Not Otherwise Approvable But Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children?

An IRB may allow a clinical investigation that does not meet the requirements of Sec. 50.51, Sec. 50.52, or Sec. 50.53 to proceed only if the IRB finds and documents 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 the Commissioner of Food and Drugs (the Commissioner) determines that the conditions of Sec. 50.54(b) are met. After consultation with a panel of experts and following opportunity for public review and comment, the Commissioner must determine, under Sec. 50.54(b)(1), that the clinical investigation satisfies the conditions of Sec. 50.51, Sec. 50.52, or Sec. 50.53 or, under Sec. 50.54(b), that three conditions are met. The conditions in Sec. 50.54(b) are as follows:

(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,

(2) The clinical investigation will be conducted in accordance with sound ethical principles, and

(3) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

FDA's regulation in Sec. 50.54 generally follows the provisions in 45 CFR 46.407 of HHS subpart D with some modification. In Sec. 50.54(b), FDA has charged the Commissioner with determining whether such a clinical investigation can proceed. The Commissioner is to consult with a panel of experts. FDA anticipates that this panel may include an advisory committee supplemented, if needed, by appropriate experts. This provision also provides for public review and comment on the Commissioner's pending decision. However, FDA may not be able to provide for public review and comment on the Commissioner's pending decision if the sponsor is unwilling to publicly disclose necessary information. FDA's trade secret and commercial confidentiality requirements (21 CFR 20.61) protect certain types of information from public disclosure. This type of privileged information is sometimes

included in INDs and IDEs. Because FDA believes full public review and comment is critical in determining whether a clinical investigation should proceed under these circumstances, if a sponsor is unwilling to waive this privilege, FDA may not be able to satisfy the public review and comment requirement and any such clinical investigation could not proceed.

#### G. When May an IRB Waive the Assent Requirement?

FDA has adopted in Sec. 50.55 the provisions of 45 CFR 46.408 of HHS subpart D, describing when assent may be waived. Even in cases where an IRB determines waiver of assent is necessary, FDA regulations require the permission of parents or guardians to the extent informed consent is required in part 50. Documentation of permission must be consistent with the documentation required for informed consent at Sec. 50.27.

Section 50.55(a) allows an IRB to make a judgment as to whether children are capable of providing assent. Section 50.55(b) states that in making this determination, an IRB must take into account the ages, maturity, and psychological state of the children involved. An IRB may make this determination for each individual child to be involved in the clinical investigation or for all children under a particular protocol. FDA has made format changes in adopting 45 CFR 46.408 to clarify the conditions for waiving the assent requirement. Section 50.55(c) states that assent is not a necessary condition for proceeding with a clinical investigation if the IRB determines: (1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or (2) that the intervention or procedure involved in the clinical investigation presents a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation. Section 50.55(d) states that even where an IRB determines the children are capable of assenting, the IRB may still waive the assent requirement if: (1) The clinical investigation involves no more than minimal risk to the subjects, (2) the waiver will not adversely affect the rights and welfare of the subjects, (3) the clinical investigation could not practicably be carried out without the waiver, and (4) when appropriate, the children will be provided with additional pertinent information after participation. Section 50.55(g) provides that when an IRB determines that assent is required, the IRB must determine whether and how assent must be documented. FDA solicits comments on how to ensure that age-appropriate explanations are provided to children.

#### H. May an IRB Waive the Permission Requirement for Parents or Guardians?

FDA has not adopted the provisions of 45 CFR 46.408(c) that allow an IRB to waive the requirements for obtaining permission in certain circumstances. Section 46.408(c) of HHS subpart D allows an IRB to determine that a research protocol is designed for conditions or for a subject population for which the permission of parents or guardians is not a reasonable requirement to protect the subjects. This

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provision allows the IRB to substitute an appropriate mechanism to protect children who will participate as subjects in research.

Section 46.408(c) of HHS subpart D allows IRBs to waive the permission of parents or guardians in certain circumstances in which waiver of informed consent would not be permitted under FDA regulations. Therefore FDA is not adopting the exceptions described in HHS subpart D. The only exceptions to FDA's requirements for informed consent, and thus for obtaining permission, are found in part 50 of FDA's regulations.

#### I. Can Wards of the State Ever Be Included in Clinical Investigations?

FDA has adopted in Sec. 50.56 the provisions of 45 CFR 46.409 of HHS subpart D describing when children who are wards of the State or any other agency, institution, or entity may be included in research.

Under Sec. 50.3(q), a ward is defined as a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law. Under Sec. 50.56(a), wards can be included in clinical investigations only if such research is: (1) Related to their status as wards, or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. Section 50.56(a) is written to ensure that if wards of the State participate in clinical investigations, they do so not because it is administratively convenient for a clinical investigator or sponsor to include them as participants, but because they are subject to potential benefit from the clinical investigation.

If an IRB approves such research, the IRB must appoint an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as a guardian or in loco parentis. Section 50.56(b) provides that one individual may serve as advocate for more than one child. The advocate must be an individual who has the background and experience to act in the best interest of the child for the duration of the child's participation in the clinical investigation. The advocate must not be associated in any way with the clinical investigation, the investigator(s), or the guardian organization. FDA interprets the term ``guardian organization'' to refer to the State, agency, institution, or other entity in whose legal custody the child is placed.

FDA believes that wards require special protections. FDA also believes that Sec. 50.56(b) provides protection from any conflict of interest issues that may arise in the appointment of an advocate. FDA notes that any issues relating to compensation or funding for advocates or the liability of advocates are left to the IRBs and other involved institutions, agencies, or entities to resolve. FDA is soliciting comments on any difficulties such entities may have with the appointment of advocates.

#### III. Effective Date

The agency is issuing this regulation as an interim rule effective April 30, 2001. This action is being issued in accordance with title XXVII, section 2701 of the Children's Health Act. Section 2701 requires that 6 months after enactment, all research involving children conducted, supported, or regulated by HHS be in compliance with HHS subpart D. The Children's Health Act was signed by the President on October 17, 2000. FDA interprets the Children's Health Act to require FDA to adopt HHS subpart D by April 17, 2001.

FDA is issuing this interim rule to comply with the Children's

Health Act. Generally, the Administrative Procedure Act and FDA regulations require notice to the public and an opportunity for comment prior to the effective date of a rule (5 U.S.C. 553(b) through (d); 21 CFR 10.40(b)). This process may be dispensed with under 5 U.S.C. 553(b)(3)(B) and Sec. 10.40(e)(1) (21 CFR 10.40(e)(1)) if the Commissioner finds, for good cause, that notice and public procedures would be impracticable, unnecessary, or contrary to the public interest. This interim rule meets these standards.

Section 2701 of the Children's Health Act requires FDA to adopt specific existing HHS regulations within 6 months. Because of the specificity of Congress's directive and FDA's limited discretion in adopting the standards of HHS subpart D, notice and an opportunity to comment is unnecessary. As described in section I.B of this document, HHS subpart D was itself issued through notice-and-comment rulemaking. Moreover, Congress has specifically identified in section 1003 of the Children's Health Act the process, timetable, and specific considerations for review of the regulations in HHS subpart D and, by implication, the regulations adopted in this interim rule. Depending upon the outcome of the review, it is possible that HHS and relevant agencies will propose new regulations addressing the protection of children involved in research. These regulations would be adopted with notice and an opportunity for public comment. Finally, FDA believes the anticipated increase in pediatric research makes it important to the public health that the requirements described in this rule become effective as soon as possible.

In addition, for the reasons described above, the Commissioner of Food and Drugs also finds good cause under 5 U.S.C. 553(d)(3) and Sec. 10.40(c)(4)(ii) for making this interim rule effective in less than 30 days.

#### IV. Analysis of Economic Impacts

FDA has examined the impacts of this interim rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612 (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104-121))), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant economic impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 (Public Law 104-4) requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation).

This interim rule is consistent with the principles set forth in Executive Order 12866 and these two statutes. The interim rule is a ``significant regulatory action'' as defined in section (3)(f) of Executive Order 12866. However, as explained below, the rule is not an economically significant regulatory action as defined in the Executive order and does not require a Regulatory Flexibility Analysis. The

Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for the interim rule because the rule is not expected to have an effect on the economy that exceeds \$100 million adjusted for inflation in any one year. The current inflation-adjusted statutory threshold is about \$110 million.

This interim rule requires IRBs reviewing FDA-regulated clinical

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investigations involving children to apply FDA's new regulations establishing additional safeguards for children in clinical investigations, as adopted from HHS subpart D. Until now, FDA has relied primarily on its own regulations governing adult studies, in combination with HHS subpart D, as guidance for the review of clinical investigations in children. In this rule, FDA requires the IRB to review and document the risks to children participating in clinical investigations before the clinical trial may proceed. In some instances, this may be a departure from current practice and may place additional requirements on IRBs. FDA believes the burden of these added requirements to be small. Under current standards, IRBs are already required to make several determinations concerning subject risk and to document subject risks. The additional requirements of this rule state that IRBs must specifically identify which of the four risk categories applies to pediatric subjects in a clinical investigation. We expect that this determination would require some additional effort, but take at most one person-hour of additional time. To estimate costs, FDA multiplied the estimated number of clinical investigations in children subject to the rule's requirements by the estimated additional time required of the affected IRBs for each trial reviewed. Then FDA multiplied the total estimated time by a standardized cost of \$75 per man-hour.

Table 1 below presents, for several different product categories, an estimate of the number of FDA-regulated clinical investigations in children that will require review by IRBs. Estimates are provided for new drug and biological products (based on numbers of approved new molecular entities and important new biological products), medical devices (based on premarket approval applications (PMAs) and 510(k) premarketing submissions (510(k)s)), and infant formula and food additives that require premarket approval by FDA's Center for Food Safety and Applied Nutrition (CFSAN).

Under current law, manufacturers may receive additional economic incentives to conduct pediatric studies on drugs for which FDA has requested pediatric studies. For currently marketed drugs, approximately 175 pediatric studies have already been reviewed by IRBs and of these studies, about 100 have been completed. However, FDA estimates that 51 studies have yet to be reviewed by an IRB and another 75 will require an annual review by an IRB. In future years, manufacturers of many newly approved drugs will be required, as a condition of approval, to conduct pediatric studies. Assuming that 3 pediatric studies per new drug require review, FDA estimates that about 138 pediatric studies per year will be conducted for new drugs and biologics. The estimate includes pediatric clinical trials for new drug and biological products that are approved, as well as trials for investigational drugs that reach phase 3 but are not approved. Approximately one-third of investigational drugs reaching phase 3 (when pediatric trials may commence) are never approved for marketing in the United States.

Table 1.-- Estimated Number of IRB Reviews Per Year for  
Clinical Investigations in Children

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Per year 2002 through

2001	2009
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New drug and biological products

    New trials for pre-2001 drug and biological products

51

    Annual review of ongoing trials

75

    Post-1/1/2001 drug and biological products

138

138

New devices (PMAs and 510(k)s)

    Post-1/1/2001 devices

170

170

Foods and Food Additives

    Infant formula

5

5

    Food additives

1

1

Total IRB reviews per year

440

314

Total IRB costs per year

\$33,000

\$23,550

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For medical devices, FDA expects about 170 pediatric studies per year to be reviewed by IRBs. About 20 of these pediatric studies per year are for submitted PMAs and the remainder are for submitted 510(k)s. These figures reflect discussions with officials from FDA's Center for Devices and Radiological Health and a review of recent approvals, which found that only about 10 percent of PMAs and 1 percent of 510(k)s are likely to involve pediatric trials. Similar to the estimates shown for drug and biological products, FDA assumed that three pediatric trials were conducted for each submitted PMA or 510(k) involving trials with children.

CFSAN regulates infant formula and food additives. Unlike the regulation of human drugs and medical devices, which require INDs, there is no requirement for sponsors to notify FDA when they are conducting clinical investigations of infant formula and food additives. FDA learns of these trials only when applications are submitted to CFSAN for product review and premarket approval. Therefore, we are less certain of the number of pediatric clinical trials involving these kinds of products, but have based our estimate for these products on the number of pediatric trials in applications submitted to CFSAN. Over the last 5 years, CFSAN has received data from about five trials per year with applications for infant formula. Pediatric trials of food additives are highly unusual. According to one CFSAN official, only a handful of applications containing data from pediatric trials have been received by CFSAN over the last 20 years.

(One example is data received on the food additive Olestra that was tested in children because it was known to cause mild diarrhea in adults.) Therefore, we estimated that, per year, one pediatric trial studying food additives is conducted in the United States. The agency seeks particular industry comment on this figure, because of the uncertainty of this estimate.

The total annual cost of reviewing ongoing and future pediatric clinical trials, as shown in table 1 of this document, is estimated to be \$33,000 for the year 2001 and \$23,550 per year in years 2002 through 2009.

In addition to these annual costs, we assume that each IRB reviewing FDA-regulated pediatric clinical trials will have to conduct a one-time review and update of their standard operating procedure (SOP) documents to include the requirements of this rule. Experts at

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FDA estimate that up to 1,500 IRBs may review protocols for research performed under an IND or IDE. Because we believe that most IRBs currently follow procedures similar to those required by this rule, we estimate that changes to existing SOPs will require no more than 8 man-hours. Multiplying the 1,500 IRBs by 8 and applying a standardized cost of \$75 per man-hour equals a one-time cost of \$900,000. This one-time cost would occur in the year 2001, following implementation of the rule.

This rule specifies that IRBs review ongoing pediatric trials to verify compliance with the requirements of this rule. These reviews are to occur during the first periodic review following the implementation of this rule or sooner, at the discretion of the IRB. If the ongoing trial is not in compliance with the requirements of the rule, the trial, under certain circumstances, could be placed on clinical hold. FDA believes that the likelihood of this occurrence is remote, because IRBs currently reviewing pediatric research are already routinely following HHS subpart D regulations, which are essentially similar to the requirements of this rule (see FDA's information sheets, ``Guidance for Institutional Review Boards and Clinical Investigators``). Furthermore, by the time this rule becomes effective, most pediatric studies conducted in response to FDA requests for studies of marketed drugs under the pediatric exclusivity provision of the Modernization Act will be completed. We therefore have assumed no costs associated with clinical holds, but seek industry comment on this assumption.

We estimate that the costs of this rule will total \$933,000 in the year 2001 and \$23,550 per year in years 2002 through 2009.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities, unless the rule is not expected to have a significant economic impact on a substantial number of small entities. Although many IRBs are components of small entities, this rule imposes very modest new costs on any individual IRB. The estimated one-time cost of SOP review and revision for any individual IRB is only \$600. The estimated additional cost per clinical trial review amounts to only \$75. FDA expects that any given IRB will conduct no more than a few reviews of trials involving children. Therefore, under the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rule will not have a significant economic effect on a substantial number of small entities.

## V. Paperwork Reduction Act of 1995

This interim rule contains no new collections of information. The information requested for clinical investigations in children is already covered by the collection of information in IND regulations (21 CFR part 312), IDE regulations (21 CFR part 812), IRB regulations (21 CFR 56.115), food additive petition and nutrient content claim petition regulations (21 CFR 101.69 and 101.70), and infant formula regulations (21 CFR parts 106 and 107) approved by the Office of Management and Budget (OMB).

In accordance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520), OMB approved the information collection in IND regulations and assigned OMB control number 0910-0014. The approval expires on September 30, 2002. OMB approved the information collection in IDE regulations and assigned OMB control number 0910-0078. The approval expires on August 31, 2003. OMB approved the information collection in IRB regulations and assigned OMB control number 0910-0130. The approval expires on October 31, 2001. OMB approved the information collection in food additive and nutrient content claim petitions and assigned OMB control number 0910-0381. The approval expires on September 30, 2001. OMB approved the information collection in infant formula regulations and assigned OMB control number 0910-0188. The approval expires on February 29, 2004. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## VI. Environmental Impact

The agency has considered the environmental effects of this interim rule and has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VII. Federalism

FDA has analyzed this interim rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the interim rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the interim rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

## VIII. Opportunity for Public Comment

Interested persons may submit to the Dockets Management Branch (address above) written comments regarding this interim rule by July 23, 2001. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB (address above) by May 23, 2001.

List of Subjects

21 CFR Part 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

21 CFR Part 56

Human research subjects, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 50 and 56 are amended as follows:

PART 50--PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 21 CFR part 50 is revised to read as follows:

Authority: 21 U.S.C 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.

Sec. 50.1 [Amended]

2. Amend Sec. 50.1 Scope as follows:

a. In the first sentence of paragraph (a) after the word ``including'' add the phrase ``foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas,''.  
b. In the third sentence of paragraph (a) add numerically to the list of Federal Food, Drug, and Cosmetic Act sections the numbers ``403,'', ``412,'', and ``413,''.  
3. Amend Sec. 50.3 by adding paragraphs (b)(23), (b)(24), (b)(25), (n), (o), (p), (q), (r), and (s) to read as follows:

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Sec. 50.3 Definitions.

\* \* \* \* \*

(b) \* \* \*

(23) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(24) Data and information submitted in a petition for a nutrient content claim, described in Sec. 101.69 of this chapter, or for a health claim, described in Sec. 101.70 of this chapter.

(25) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in Sec. 190.6 of this chapter.

\* \* \* \* \*

(n) Assent means a child's affirmative agreement to participate in

a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

(o) Children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

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

(q) Ward means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

(r) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be obtained in compliance with subpart B of this part and must include the elements of informed consent described in Sec. 50.25.

(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 when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research.

4. Add subparts C and D to part 50 to read as follows:

Subpart C--[Reserved]

Subpart D--Additional Safeguards for Children in Clinical Investigations

Sec.

50.50 IRB duties.

50.51 Clinical investigations not involving greater than minimal risk.

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

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

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

50.55 Requirements for permission by parents or guardians and for assent by children.

50.56 Wards.

Subpart C--[Reserved]

Subpart D--Additional Safeguards for Children in Clinical Investigations

Sec. 50.50 IRB duties.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D

and approve only those clinical investigations that satisfy the criteria described in Sec. 50.51, Sec. 50.52, or Sec. 50.53 and the conditions of all other applicable sections of this subpart D.

Sec. 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in Secs. 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Sec. 50.55.

Sec. 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in Secs. 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds and documents 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; and
- (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in Sec. 50.55.

Sec. 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in Secs. 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents that:

- (a) The risk represents a minor increase over minimal risk;
- (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in Sec. 50.55.

Sec. 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in Secs. 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of Sec. 50.51, Sec. 50.52, or Sec. 50.53, the clinical investigation may proceed only if:

(a) The IRB finds and documents 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 of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

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(1) That the clinical investigation in fact satisfies the conditions of Sec. 50.51, Sec. 50.52, or Sec. 50.53, as applicable, or

(2) That the following conditions are met:

(i) 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;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Sec. 50.55.

Sec. 50.55 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 D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.

(b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in

the context of the clinical investigation.

(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

(1) The clinical investigation involves no more than minimal risk to the subjects;

(2) The waiver will not adversely affect the rights and welfare of the subjects;

(3) The clinical investigation could not practicably be carried out without the waiver; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that the permission of each child's parents or guardian is granted.

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under Sec. 50.51 or Sec. 50.52.

(2) Where clinical investigations are covered by Sec. 50.53 or Sec. 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by Sec. 50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

#### Sec. 50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under Sec. 50.53 or Sec. 50.54 only if such clinical investigations are:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar 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 IRB must require appointment of an advocate for each child who is a ward.

(1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

(2) One individual may serve as advocate for more than one child.

(3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.

(4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

5. The authority citation for 21 CFR part 56 is revised to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.

Sec. 56.101 [Amended]

6. Amend Sec. 56.101 Scope in the first sentence of paragraph (a) by adding after the word ``including'' the phrase ``foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas,''.  
7. Amend Sec. 56.102 by adding paragraphs (b)(21), (b)(22), and (b)(23) to read as follows:

Sec. 56.102 Definitions.

\* \* \* \* \*

(b) \* \* \*

(21) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(22) Data and information submitted in a petition for a nutrient content claim, described in Sec. 101.69 of this chapter, and for a health claim, described in Sec. 101.70 of this chapter.

(23) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in Sec. 190.6 of this chapter.

8. Amend Sec. 56.109 by adding paragraph (h) to read as follows:

Sec. 56.109 IRB review of research.

\* \* \* \* \*

(h) When some or all of the subjects in a study are children, an IRB must determine that the research study is in compliance with part 50, subpart D of this chapter, at the time of its initial review of the research. When some or all of the subjects in a study that is ongoing on April 30, 2001 are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D of this chapter, either at the time of continuing review or, at the discretion of the IRB, at an earlier date.

9. Amend Sec. 56.111 by adding paragraph (c) to read as follows:

Sec. 56.111 Criteria for IRB approval of research.

\* \* \* \* \*

(c) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 50, subpart D of this chapter.

Dated: February 28, 2001.

Ann M. Witt,

Acting Associate Commissioner for Policy.

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