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PART 50 - PROTECTION OF HUMAN SUBJECTS

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SUBCHAPTER A - GENERAL

50.1 Scope

- a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 530(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including **foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas,** food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards for conduct for, persons who sponsor or

monitor investigations involving particular test articles may also be found in other parts (e.g., 21 CFR parts 312 and 9812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections **403**, 406, 409, **412**, **413**, 502, 506, 507, 510, 513-516, 518, 520, 706 and 801 of the Federal Food, Drug and Cosmetic Act and Sections 351 and 354-360F of the public Health Services Act.

50.3 Definitions

- a) **"ACT"** means the Federal Food, Drug and Cosmetic Act, as amended §§ 201-902 52 Stat 1040 et seq. as amended (21 U.S.C. 321-392)).
- b) Application for research or marketing permit includes:

- (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.**
- c) **"Clinical Investigation"** means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505 (i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of Part 58 of this chapter regarding non-clinical laboratory studies.
- d) **"Investigator"** means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving , a subject, or in the event of an investigation conducted by a team of individuals, is responsible leader of that team.
- d) **"Sponsor"** means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator) and the employees are considered to be investigators.
- f) **"Sponsor-Investigator"** means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving , a subject. The term does not include any person other than an individual, (e.g., corporation or agency).
- g) **"Human subject"** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.
- h) **"Institution"** means any public or private entity or agency (including Federal, State, and other agencies). The word "facility" as used in section 520(g) of the act is deemed to be synonymous with the term "institution" for purposes of this part.
- i) **"Institutional Review Board" (IRB)** means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase "institutional review committee" as used in section 520(b) of the act.
- j) **"Prisoner"** means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and arraignment, trial or sentencing.
- k) **"Test Article"** means any drug (including a biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-n).
- l) **"Minimal risk"** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- m) **"Legally Authorized Representative"** means an individual or juridical or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research.
- n) **Family member** means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

- (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.**

SUBPART B - Informed Consent of Human Subjects

§50.20 General Requirements for Informed Consent

Except as provided in § 50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or

appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

§ 50.21 Effective date

The requirements for informed consent set out in this part apply to all human subjects entering a clinical investigation that commences on or after July 27, 1981.

§ 50.23 Exception from general requirements

- (a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:
 1. The human subject is confronted by a life-threatening situation necessitating the use of the test article.
 2. Informed consent cannot be obtained from the subject because of an inability to communicate with or obtain legally effective consent from the subject.
 3. Time is not sufficient to obtain consent from the subject's legal representative
 4. There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.
- (b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.
- (c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

§ 50.24 Exception from informed consent requirements for emergency research (Final 11/1/96)

- a) The IRB responsible for the review, approval, and continuing review of the clinical

investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

- 1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- 2) Obtaining informed consent is not feasible because:
 - (i) The subjects will not be able to give their informed consent as a result of their medical condition;
 - ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
 - iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
- 3) Participation in the research holds out the prospect of direct benefit to the subjects because:
 - i) Subjects are facing a life-threatening situation that necessitates intervention;
 - ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- 4) The clinical investigation could not practicably be carried out without the waiver.
- 5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
- 6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with §50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.
- 7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:
 - i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
 - ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
 - iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
 - iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
 - v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's

participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

- b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.
- c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.
- d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §12.30 or 812.35 of this chapter.
- e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or

because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

§ 50.25 Elements of informed consent

- (a) Basic required elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:
1. A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental,
 2. A description of any reasonably foreseeable risks or discomforts to the subject,
 3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
 4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subjects.
 5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records,
 6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
 7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research related injury to the subject.
 8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subjects may discontinue participation at

- any time without penalty or loss of benefits to which the subject is otherwise entitled.
- (b) Additional optional elements of consent: When appropriate, one or more of the following elements of information shall also be provided to each subject:
1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
 2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
 3. Any additional costs to the subject that may result from participation in this study,
 4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
 5. A statement that significant new findings developed during the course of the research which may relate to the subjects willingness to continue participation will be provided to the subject,
 6. The approximate number of subjects involved in the study.
- (c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.
- (d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

§50.27 Documentation of informed consent

- (a) Except as provided in § 56.109 (C) informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.
- (b) Except as provided in 56.109(c) the consent form may be either of the following
1. A written consent document that embodies the elements of informed consent required by § 50.25. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or

the representative adequate opportunity to read it before it is signed.

2. A "short form" written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the total presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

NEW FROM HERE TO END

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:

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 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.

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

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 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.