DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

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Bernard A. Schwetz, D.V.M., Ph.D.
Acting Principal Deputy Commissioner
Office of the Commissioner
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Dear Dr. Schwetz:

The National Institutes of Health (NIH) reviewed the Food and Drug Administration's (FDA's) interim final rule on additional safeguards for children in clinical investigations of FDA-regulated products (21 CFR Parts 50 and 56). The NIH undertook this review of the interim final rule in response to the FDA's request for public comments that was published in the Federal Register on April 24, 2001. The NIH endorses the FDA's interim rule, and offers both general and specific comments on several issues related to the rule.

The NIH notes that the FDA's adoption of DHHS Subpart D of 45 CFR 46, with only those changes necessary given differences between FDA's and DHHS's regulatory authority, will facilitate the review and conduct of clinical research with children, and ensure that children receive consistent protections. However, the FDA's adoption of Subpart D also increases the need for guidance to Institutional Review Boards (IRBs) and clinical investigators concerning the interpretation and implementation of these regulations.

Several specific comments on FDA's interim rule follow:

1. Modify definition of "guardian." In DHHS Subpart D, a guardian is defined as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. FDA proposes to adopt this definition, and clarify that, for purposes of this rule, a guardian must be authorized to consent to a child's participation in research. The additional language suggested by FDA represents a significant departure from the DHHS definition. In particular, it is unclear whether state laws specifically authorize guardians to consent to children's participation in clinical research. Thus, the FDA's proposed change may, in practice, represent a serious, unintended obstacle to children's research participation. One possibility would be to define a guardian as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care and whose consenting on behalf of the child to research participation is consistent with applicable laws, if any.

2. IRBs should ensure age-appropriate explanations are provided to children. FDA solicits comments on how to ensure that age-appropriate explanations are provided to children. Ensuring that children are provided with age-appropriate explanations is both important and difficult. Such determinations must take into account the ages, maturity, and psychological states of the children involved. In addition, the environment in which the research will be conducted, the expertise of the researchers, and the risks and benefits of the specific protocol may be relevant. Since these are matters of informed judgment, we believe that assessment of the appropriateness of the explanation to children at a particular research site is best made by a duly constituted IRB that, as necessary, consults with individuals with expertise and experience in age appropriate explanations.

3. Clarify requirements for the review of research not otherwise approvable. Subpart 50.54(b) provides for the FDA Commissioner to determine, after consultation with a panel of experts, whether to conduct research not otherwise approvable. This language is similar to 45 CFR 46.407, except that the DHHS regulations call for this determination to be made by the Secretary, DHHS. In cases where a research study involving children is subject to both FDA and DHHS regulations, it is unclear which entity will make this determination. Requiring a determination by *both* entities may be unnecessarily duplicative.

In addition, Subpart 50.54(b) requires an opportunity for public review and comment on the Commissioner's pending decision. However, the preamble states that the FDA may not be able to provide public review and comment if the sponsor is unwilling to publicly disclose necessary information. The regulation text should state explicitly that public review and comment may not be possible in all cases given the FDA regulations relevant to sponsor confidentiality.

4. Permit IRBs to waive the requirement for parental permission. Waiver of the requirement for parental permission [46.408 (c)] is appropriate in certain, unusual circumstances. Possible examples include the development of a new test kit for sexually transmitted diseases, or studies involving children who have been the victims of sexual abuse. NIH suggests that FDA adopt the DHHS policy that allows IRBs to waive the requirement for parental permission in limited, appropriate circumstances.

5. Clarify that the option to waive informed consent in emergency settings applies to pediatric research. NIH suggests that the FDA state explicitly that the possible exceptions from obtaining informed consent for emergency research, identified in 21 CFR 50.24, apply to children as well.

6. Clarify when wards of the state can be included in clinical investigations. The DHHS regulations state that the IRB must require the appointment of an advocate. The FDA regulations suggest that the IRB itself must appoint the advocate. NIH recommends that the FDA adopt the DHHS policy. The IRB does not need to appoint the advocate itself, as long as it ensures an appropriate advocate is in place.

7. Uniform guidance needed on criteria IRBs should use to determine when clinical investigations involve no more than minimal risk to children, and when clinical investigations involve greater than minimal risk. The FDA and DHHS should develop uniform guidance on how to interpret the regulatory definition of minimal risk, as well as how to determine when risks of harm are more than minimal. Such guidance should include a process of risk assessment, not identification of specific examples thought to present no more than minimal risk. The attempt to develop specific examples fails to acknowledge that risk assessment is multi-factorial. A procedure deemed minimal risk, for instance, a blood draw, may pose greater than minimal risk in the hands of an inexperienced person, or in a setting that includes the possibility of contaminated needles. Moreover, a procedure previously thought to pose greater than minimal risks may become less risky as the result of technological changes. To ensure that all the relevant factors are taken into account, the determination of risk should be made on a case-by-case basis by a duly constituted IRB.

8. Clarify that FDA regulations apply to research on biologics. It may be helpful to state explicitly that the FDA regulations apply to biologics, as well as drugs.

9. Clarify what benefits should be taken into account when determining whether a protocol offers the prospect of direct benefit. The NIH agrees with the FDA that placebo-controlled trials in children may be conducted as long as they are in accord with risk/benefit categories 50.51 or 50.52. However, IRBs' determination of a prospect of direct benefit should be based primarily on the potential benefit of the research intervention. The NIH recommends that the FDA and DHHS develop guidance as to what benefits should be taken into account when determining whether a protocol, placebo controlled or not, offers the prospect of direct benefit.

I hope these comments from NIH are helpful to the FDA as the Agency considers whether to amend this interim final rule. I would be pleased to discuss any of these issues with you further. Please feel free to call me at (301) 496-2122 or Julie Kaneshiro at (301) 496-0786, if you have any questions or would like additional information.

Sincerely,

Lana R. Skirboll, Ph.D.
Director
Office of Science Policy, NIH

cc:
Dr. Ruth Kirschstein
Dr. Greg Koski