U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Rec'd 8/17/01

AUG 13 2001

National Human Research Protections Advisory Committee

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20857

Re: **COMMENT ON:**
Docket #00N-0074 April 24, 2001
Interim Rule: "Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products"

Dear Director:

Thank you for the opportunity to comment on the interim rule published in the *Federal Register* on April 24, 2001 concerning 21 CFR Parts 50 and 56. These comments supplant the letter forwarded to you on July 20 requesting an opportunity to submit comments to you by August 17, 2001. These comments are forwarded to you on behalf of the Secretary's National Human Research Protections Advisory Committee (NHRPAC).

If you require clarification or any additional information please feel free to contact me (913/588-7105) or Kate-Louise Gottfried, Executive Director, NHRPAC, 301/402-5189.

Sincerely,

Mary Faith Marshall, Ph.D.
Chairperson, NHRPAC

Attachment

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Re: **COMMENT ON:** Docket #00N-0074
April 24, 2001 Interim Rule: "Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products"

Specific Comment on FDA's Decision to Adopt HHS 45 CFR 46 Subpart D, EXCLUDING §46.408 (c)

The National Human Research Protections Advisory Committee (NHRPAC) of the Department of Health and Human Services (HHS) requests that the Food and Drug Administration (FDA) review and reverse its recent decision not to adopt the provision of 45 CFR 46, Subpart D, §46.408(c) that allows for the waiver of parental permission in specific circumstances in research involving children. Specifically, we request that the FDA utilize an aggressive interpretation of the Food Drug and Cosmetic Act to enable mature adolescents to consent to involvement in certain types of important clinical studies without parental permission. If such an interpretation of the law is not possible or acceptable, NHRPAC believes that the FDA should seek to change the law to allow FDA and HHS regulations to be consistent in this area.

We focus here specifically on the concern that if this provision of the regulations is not adopted **vital** research involving mature adolescents for whom seeking parental permission is not in their best interests will not be conducted. We believe that in specific circumstances parental permission may be waived and that the informed consent of the adolescents is sufficient to permit research as long as there are procedural safeguards in place to protect the adolescent's welfare.

On April 24, 2001 the Food and Drug Administration (FDA) of the Department of Health and Human Services published an interim rule in the *Federal Register* (vol. 66, #79) concerning 21 CFR Parts 50 and 56: "Additional Safeguards for Children 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, which requires that all research involving children conducted, supported, or regulated by HHS be in compliance with HHS regulations providing additional protections for children involved as research subjects are in place. This rule applies to FDA's authority to regulate safety and effectiveness testing in children of such products as: human drugs and biologicals, medical devices, and dietary supplements, nutritionals, food additives, and foods. The interim rule appropriately points out the importance of the FDA adopting HHS regulations as directed by Congress. It states: "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." NHRPAC agrees.

HHS 45 CFR Part 46 Subpart D, §46.408 (c)

The interim rule states that the FDA is adopting HHS subpart D (45 CFR 46) with only those changes deemed necessary due to differences between FDA's and HHS's regulatory authority. One provision of 45 CFR 46 not adopted by the FDA is the section §46.408(c) that allows IRBs to waive the requirement for the permission of parents or guardians in specific limited research circumstances. The interim rule states that this section is not adopted because waiver of informed consent is not permitted under FDA law. Applying this rationale will potentially result in an incongruous system where the HHS regulation and the FDA regulation are in conflict. For example, NIH supported clinical research, subject to HHS regulation, which utilizes an investigational drug subject to FDA regulation could have two inharmonious sets of regulations controlling the conduct of the research protocol.

> Section 45 CFR §46.408(c) states:
>
> If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that this waiver is not inconsistent with Federal, State, or local laws. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

This section of the regulations has been invoked by IRBs to permit waiver of parental permission in research involving mature adolescents in certain circumstances in which it is not in the adolescent's interests to inform his/her parents about the specific illness or behavior that is under study.

We speak here about a specific group of adolescents assessed to be "mature" because of psychological and behavioral factors which enable them to make decisions concerning their own interests in a manner comparable to adult decision making. In general, such adolescents will be fourteen years of age or greater and have demonstrated the ability to assess the consequences of their actions and to make choices that are consistent with their best interests. Such mature minors have been recognized in virtually every state to be allowed to consent for clinical treatment related to sexually transmitted diseases, pregnancy, and serious life-threatening diseases such as HIV/AIDS. NHRPAC notes that in clinical trials involving these diseases, communicating with and involving parents in the process of consent for adolescents is the preferred circumstance, but there are instances where doing so could result in potentially volatile and dangerous situations for the adolescent. In such cases, NHRPAC supports the concept of adolescents being permitted to consent for clinical research studies related to such disorders and diseases without parental permission as long as additional procedural safeguards are invoked by the IRB to protect the interests of the adolescent.

There are specific procedural safeguards which NHRPAC believes are mandatory if an IRB chooses to invoke this section of the regulations in research studies involving FDA regulated drugs and devices. First, IRBs must evaluate each research protocol on a case by case basis to determine the vital importance of the research protocol to the adolescent subjects involved. In general, protocols will have been evaluated previously in adults and hold out the potential for direct benefit to the adolescents. Second, the IRB must evaluate the protocol to determine if some or all of the subjects will be permitted to waive parental involvement in the consent process. Third, the IRB must receive from the investigator a plan for the assessment of the capacity and maturity of each individual subject to determine that the subject is "mature". This assessment should be performed by a professional independent of the research team. Fourth, the IRB must develop appropriate procedural safeguards to protect the interests of the adolescent such as an independent counselor available to counsel the adolescent, monitor the consent process, and provide ongoing consultation to the adolescent throughout the study. And, finally, the IRB must review the progress of such studies frequently and be held accountable for investigator compliance with proposed safeguards. Fifth, any IRB that routinely reviews research protocols that may involve adolescents as potential subjects should include at least one member familiar with the medical and psycho-social characteristics of that age group, and other IRBs that review such protocols should seek the advice of consultants who have this expertise.

An Example of the Need for Adoption of a §46.408(c) Provision by the FDA

An important example of the harm that might have occurred if such a regulation were not in place is in the research studies utilizing new therapeutic modalities for HIV and AIDS in adolescents. In the midst of the growing HIV epidemic in the late 1980s and early 1990s it became evident that older teenagers, particularly boys, were contracting this disease. Research studies in this population were critically important to assure safety and efficacy of new drugs. Many of these adolescents sought treatment for HIV and requested that their diagnosis be kept confidential from their parents. Confidential treatment was provided based on state laws which

allow physicians to **treat** adolescents for sexually transmitted diseases without parental involvement. However, when new drugs became available only under **research** protocols, these adolescents would not have been afforded the potential benefits that might have accrued from participation in the clinical trials if parental permission were required. As is well known today, these research studies were life prolonging and enhancing for participants. Clinicians responded to this problem by asking IRBs to invoke section 408(c) of the regulations to permit the research to proceed without informing the parents of subjects who requested confidentiality. IRBs along with clinical research teams created methods to assure that the adolescents understood the potential risks and benefits of the research, appointed nurses, social workers, or others independent of the research team to be counselors to the adolescents, and carefully monitored the conduct of the research. Research protocols went forward based on the informed consent of the adolescent.

The Society for Adolescent Medicine, the clinical society which represents health professionals who specialize in the care of adolescents, in the early 1990s created a series of meetings to review this issue and provide helpful guidance to IRBs. Their recommendations are published in a special issue of the Journal of Adolescent Health entitled "Guidelines for Adolescent Health Research" (1995;17:264-269). NHRPAC's view on this issue is consistent with these recommendations.

NHRPAC Guidance

NHRPAC strongly urges the development of a "guidance" for dissemination by HHS and FDA to IRBs to clarify appropriate implementation of section 408(c) in order to protect the interests of adolescents and children who are research subjects.

Conclusion

In conclusion, NHRPAC believes that section 408(c) of 45 CFR 46 Subpart D has been an important part of the regulations to protect the interests of children as research subjects. We STRONGLY believe that in specific circumstances the consent of the mature adolescent, without parental involvement, IS SUFFICIENT to permit research to proceed as long as procedural safeguards are in place to protect the interests of the subjects. We request that the FDA aggressively interpret its legal authority and adopt this section of the regulations as part of the additional safeguards for children in clinical investigations of FDA-regulated products. Adoption of this section for application to research proposals involving mature adolescents does not eliminate informed consent. Rather it creates a process to allow the adolescent to consent to participation in a research study without requiring concurrence of a parent in specific instances in which involvement of a parent would not be in the best interests of the adolescent.

Thank you very much for your consideration. We would be happy to meet with FDA staff to discuss this issue further.

Sincerely,

Mary Faith Marshall, Ph.D.
Chair, NHRPAC

cc: David Lepay, FDA
Greg Koski, OHRP
Duane Alexander, NICHD
NHRPAC Members
NHRPAC Children's Workgroup