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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: Docket No. 00N-0074
Interim Rule: Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products [66 FR 20589, April 24, 2001]

Merck & Co., Inc, is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations.

In the course of bringing our product candidates through developmental testing and clinical trials, especially in recent years which have seen greater emphasis on and awareness of the special needs of the pediatric population, Merck scientists are regularly involved in issues affected by this proposal. Indeed, we have completed a number of pediatric programs that resulted in revised product labeling to include specific pediatric information while yet other such programs are underway. In addition, we are among the foremost manufacturers of pediatric vaccines in the world, and have conducted research that has led to the approval of vaccines for prevention of measles, mumps, rubella, varicella, hepatitis A, hepatitis B, and *haemophilus influenzae B.* Therefore, we are not only interested but we are well qualified to comment on this FDA interim rule to provide additional safeguards for children enrolled in clinical investigations of FDA-regulated products.

As stated in the preamble to the interim rule, the rule is "intended to bring FDA regulations into compliance with the provisions of the Children's Health Act of 2000…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, be in compliance with HHS regulations providing additional protections for children involved as subjects in research. Specifically, Title XXVII of the Children's Health Act of 2000 directs the Secretary of Health and Human Services to "require that all research involving children that is conducted, supported, or regulated by the Department of Health and Human Services be in compliance with Subpart D of Part 46 of Title 45, Code of Federal Regulations."

Assurance that children in clinical trials are afforded additional safeguards and protections is essential to pediatric research. MRL supports the regulatory provisions of this interim rule

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and believes that it will promote adherence to principles that are important in minimizing risk to pediatric research subjects. We are pleased to offer comments and recommendations in support of this rule.

In Section I of this letter, we are providing recommendations on issues for which FDA specifically solicited comments, including definitions of terminology, and provision of age-appropriate explanations of the therapy/intervention to be provided.

In Section II of this letter, we are providing general comments on:

- the role of IRBs in the selection of advocates for wards of the State,
- alternatives to public review and comment to allow studies to proceed that were judged by an IRB not to meet their requirements for IRB approval, and
- a mechanism to address the issue of "significant risk," as used in FDA's December, 1998 Pediatric Rule versus "minimal risk" and "minor increase over minimal risk" in the interim rule.

I. Specific Comments

FDA specifically solicited comments on a number of topics in the preamble to the interim rule. These included, among others:

1. The proposed definition of "guardian" at 21 CFR 50.3(s):

   FDA's proposed definition at 21 CFR 50.3(s) states: "*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.*" [Emphasis added]

   In 45 CFR 46.402(e) "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.*" Note that it does not include the language underlined above.

   In its preamble to the interim rule, FDA explains that it added language to the existing definition at 45 CFR 46.402(e) "because of concern that, in some cases, authorization to consent to general medical care may not extend to consent to participate in research." FDA points out that in its regulations at Section 50.3(l) and HHS's regulations at 45 CFR 46.102(c), the term "legally authorized representative" is used 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 states that

it'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."

Comment: FDA's concern that general medical care may not always include research presumably refers to the existence of differing State and local requirements for legal permission allowing children to participate in research. Under the HHS regulations on which this interim rule is based, IRBs have been and continue to be responsible for assuring that HHS sponsored or conducted studies involving children comply with Federal, State, and local legal standards regarding permission. It is unclear why a revised definition of *guardian* is deemed necessary in the parallel FDA regulation while no change is proposed for the existing definition in the HHS regulation.

In addition, when HHS sponsored research is also subject to FDA regulation, conflicting definitions of *guardian* in FDA and HHS will lead to confusion as to which definition applies in these instances.

Recommendation: The definition provided within 21 CFR 50.3(s) should be the same definition of *guardian* that appears at 45 CFR 46.402(e).

2. Whether "further definition" of "minor increase over minimal risk" should be provided.

Comment: While "minimal risk" is defined in regulations, we were unable to find any regulatory definition of the term "minor increase over minimal risk" in either the interim rule or in 45 CFR Part 46.

Recommendation: Clarification of the term "minor increase over minimal risk" should be provided. Because risk is relative to a number of factors, examples of some clinical investigations that would be considered to represent a minor increase over minimal risk in various situations would be useful. This is particularly important to minimize application of widely varying standards across the spectrum of IRBs.

3. Conducting placebo-controlled trials in children.

Section 50.52 addresses "Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects." FDA expressed the belief that clinical investigations involving placebos in children may be conducted in accord with Section 50.52. FDA invited comment on the issue of conducting placebo-controlled trials in children.

Comment: Merck supports the use of placebo-controls in clinical trials in children under certain circumstances and agrees with FDA that such studies may be conducted in accord with the terms of Section 50.52. Certain vaccines and a number of drug trials for certain non-life threatening medical conditions may require use of placebo designs in which the placebo does not provide a medical benefit. Specific circumstances should be evaluated between the sponsor and the Food and Drug Administration on a study-by-study basis. This position is consistent with the guidelines of the American Academy of Pediatrics on ethical conduct of studies in children.[1] Specifically, the guideline notes that research studies may be considered ethically permissible when they provide generalizable knowledge and, with respect to the determination of benefits and risks of research, that the benefits should be "construed broadly." The guideline also provides a discussion of the role of placebo and untreated observational control groups is studies involving children.

4. How to ensure that age-appropriate explanations for the purpose of obtaining assent are provided to children.

Comment: It is likely to be difficult to *ensure* for all clinical studies that age-appropriate explanations are provided to *all* children from whom assent is sought for participation in research. Section 50.55(a) requires the IRB to "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." Clearly, in order to make a determination about the adequacy of the provisions for soliciting assent, the IRB must be familiar with successful techniques for communicating information about medical interventions to children at various ages.

Recommendation: FDA should encourage the study and publication of techniques for securing the assent of pediatric patients.

II. General Comments

1. The text of proposed Section 50.56 ("Wards") states that "the *IRB must require appointment* of an advocate for each child who is a ward." [Emphasis added] However,

[1] Committee on Drugs, American Academy of Pediatrics, "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations (RE9503), Pediatrics, 95 (2), Feb. 1995, pp 286-294 (http//www.aap.org/policy/00655.html).

section II (I) of the preamble to the interm rule [*"Can Wards of the State Ever Be Included in Clinical Investigations?"*] states that "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." [Emphasis added]

> **Comment:** The text of the preamble to the interim rule goes beyond the meaning of 21 CFR 50.56 in that it specifies that an IRB *appoint* an advocate, and that the IRB-appointed advocate will essentially duplicate the role of an advocate who may already have been appointed by the State or any other agency, institution, or entity.
>
> **Recommendation:** The role of the IRB should be to review and confirm that an advocate who meets the requirements of Section 50.56 has been appointed. This need not be the same individual appointed by the State to serve as a guardian or *in loco parentis*. The IRB should be empowered to reject the selection of the advocate presented for confirmation if the IRB believes that individual to be unsuitable.

2. Section 50.54 addresses a process for FDA review and agreement to allow a study to proceed that an IRB has determined does not meet the requirements for IRB approval. It mirrors almost exactly the provision at 45 CFR 46.407, which makes provision to allow HHS supported or conducted research to be reviewed and permitted when an IRB has found that such a study does not meet the requirements for IRB approval. Under Section 46.407, approval for HHS to conduct or fund a study may be made by the Secretary after consultation with experts and opportunity for public comment. Similarly, Section 50.54 provides for the Commissioner of FDA to allow a study to proceed that was considered not to be in accord with requirements for IRB approval through a similar process including consultation with experts and an opportunity for public review and comment.

   The requirement for public review and comment as proposed in Section 50.54 does not recognize that research conducted or sponsored by the pharmaceutical industry, unlike Federally sponsored or conducted research, generally raises issues of commercial confidentiality. For Federally conducted or sponsored research, the requirement for public review and comment does not require the researcher to give up any right to protection of information in order to secure the Secretary's review. In contrast, the requirement for public review and comment of privately sponsored clinical trials requires sponsors to choose between public disclosure of otherwise confidential information or abandonment or revision of the program. Relinquishing a sponsor's right to confidentiality in exchange for the review may have the effect of discouraging pediatric studies in some instances.

Recommendation: Merck acknowledges the need for independent review of studies in these instances. However, the requirement for public review and comment of study proposals from private industry under Section 50.54 should be reconsidered in view of the commercial confidential nature of clinical drug development studies. A closed Advisory Committee meeting in which the committee may be supplemented with invited guests as deemed appropriate should permit full consideration of the issues and assure full protection of children without breaching the sponsor's right to protection of commercial confidential information. Closed sessions of this nature to discuss proprietary clinical design issues are already held by the Vaccines and Related Biological Products Advisory Committee and other FDA advisory committees.

3. The new additions to 21 CFR 50 Subpart D (Sections 50.50 through 50.56) require IRBs to determine the level of risk involved in studies involving children. Under the rule, IRBs can only "approve" studies that either do not involve "greater than minimal risk" (Section 50.51); studies that involve greater than minimal risk and provide direct benefit to the subjects (Section 50.52); or studies that involve greater than minimal risk and provide no benefit to the subject, but that contribute to generalizable knowledge where the risk is only a minor increase over minimal risk (Section 50.53).

   The background information in the preamble to the interim rule refers to FDA's December 1998 Pediatric Rule in which FDA argued that "the absence of pediatric labeling information for these drug and biological products [marketed products that could be used in children but lack adequate labeling] posed significant risk for children." [Emphasis added]

   Recommendation: FDA should clarify how its concept of "significant risk" posed by the use of *marketed* (but unlabeled) products in clinical practice, as described in the December, 1998 Pediatric Rule relates to the concepts of "minimal risk" and "minor increase over minimal risk" which IRBs must use as the benchmark in evaluating research proposals for pediatric drug development under the interim rule. The final rule should recognize that risk is relative to a number of factors. Assessment of the degree of risk to determine whether a study may proceed must be done on a study-by-study basis.

Summary

The assurance of safeguards for children in clinical trials is an important and essential element of human subject protection for a vulnerable population. In general, MRL believes the regulatory provisions of 21 CFR 50, Subpart D will provide additional assurance of adherence to important principles that will further minimize risk to pediatric research subjects. We have

made certain recommendations that we believe will improve this regulation as it applies to industry sponsored clinical trials of pharmaceuticals. These include: recommendations regarding the definition of *guardian* and *minor increase over minimal risk*; a recommendation to encourage the study and publication of techniques to ensure age appropriate explanations of research to children to obtain assent; the role of IRBs in evaluating advocates for Wards of the State; and consideration of alternatives to public review and comment to allow studies to proceed that were judged by an IRB not to meet their requirements for IRB approval.

We welcome the opportunity to comment on this interim rule and, if appropriate, to meet with you to discuss these issues.

Sincerely,

for Bonnie Goldmann

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