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Food and Drug Administration Clinical Misconduct Guidance

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

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

Dear Sir/Madam:

The Council on Governmental Relations (COGR), a non-profit organization comprised of 143 research universities, appreciates the opportunity to provide comment on the interim rule referenced above. We note the addition of new guidelines for pediatric clinical investigations to the FDA regulations, 21 CFR Part 50 and Part 56 and applaud the FDA's approach that is consistent with the Department of Health and Human Services (DHHS) rules in 45 CFR 46, subpart D. In this letter, we comment first on the interim rule and conclude with responses to the questions raised by the FDA.

Definitions

The changes required because of differences in regulatory authority and for clarification are reasonable. For example, including a separate definition of the term "ward" in Section 50.3 is consistent with the DHHS use of the word in Section 46.409(a). Other examples achieve consistency with DHHS regulations. They are the addition and amplification of a definition of "permission" to encompass the elements of informed consent and to highlight the need for parental permission, and the adoption of specific definitions of "assent", "children," and "parent".

Expanded Definition of "Guardian"

The FDA goal is to encourage studies on the efficacy of drugs and therapies to the benefit of pediatric populations. In the definition of the term "guardian," the FDA added a specific requirement that the guardian is authorized "to consent on behalf of a child to participate in research." We are concerned that this definition of "guardian" may result in unanticipated negative consequences. Many state laws do not specifically authorize legal guardians to provide consent for research, per se. The requirement that a guardian must be authorized "to consent on behalf of a child to participate in research" will unnecessarily prevent some children with guardians (i.e., those in states without a specific research authorization provision) from participating in research from which they could benefit directly. We recommend that the FDA implement a definition of "guardian" consistent with the DHHS definition in section 46.402 (e).

Determination of Level of Risk

The proposed section 50.51 describes clinical investigations not involving greater than minimal risk. It deviates in an important way from the DHHS section 46.404 that places the responsibility for determining the level of risk with the IRB. The proposed FDA regulations only require the IRB to find and document adequate provisions for soliciting assent and permission. Unless resolved, this section may create a set of circumstances in which the investigator and IRB disagree on the level of risk. While any disagreement will be resolved by the decision of the IRB, it may cause unnecessary conflict and confusion. Furthermore, this section appears internally inconsistent with the proposed FDA sections 50.52 (a) and 50.53 (a) in which the IRB assesses the nature and level of risk. For these reasons, we recommend that the language be consistent with DHHS section 46.404.

Assessment of Risk

The FDA has invited comment on appropriate criteria for IRBs to use in assessing greater than minimal risk in research that presents the prospect of direct benefit to the research participant and research that does not anticipate direct benefit but will likely yield generalizable knowledge. We believe that the regulations, as written, provide adequate protections for children in more than minimal risk research and provide IRBs with sufficient criteria for review. IRBs have been making assessments of increases over minimal risk and the balance between the prospects of benefit to the individual participant or generalizable knowledge and can continue to make those assessments on a case-by-case basis.

There is no need for further definition or elaboration of criteria in the regulations to aid the IRB in the determination of risk. The current regulations encourage IRBs to seek appropriate expertise to assist them in their deliberations (21 CFR 56.107 (f)). There are numerous guidance documents and materials available to the IRB to assist in its assessment of risk. The International Conference on Harmonization (ICH) **Guideline on Clinical Investigation of Medicinal Products in Pediatric Populations** (E11) offers a series of factors that should be considered in initiating investigations and trials in pediatric populations. Similarly, the DHHS **Institutional Review Board Guidebook** offers guidance to IRB members in assessing risks, generally (Chapter III, Basic IRB review) and in research with children (Chapter VI, Special Classes of Subjects). The American Academy of Pediatrics' (AAP) **Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations** describes special considerations for a variety of pediatric populations, e.g., dying patients, patients with chronically progressive diseases, etc., that will help lead IRBs through their assessments of pediatric protocols. The nature of the risk, the assessment of adult studies and their implications for pediatric studies, the availability of alternative treatments for children, and the establishment of pediatric endpoints for studies are all the types of questions for which IRBs can and will obtain expert advice and counsel. Additional criteria or definitions included in the regulation will not provide greater protections for research participants.

Appointment of an Advocate

The rule includes the appointment of an advocate for children who are wards of the state or any other agency. This requirement for an advocate is the same as DHHS 46.409 (b). The appointment of appropriate advocates in multi-site investigations is a challenge for the investigator and sponsoring institution but this requirement offers important protections for the research participants. We agree that the provision for the appointment of an advocate for children who are wards of the state should be retained in the FDA regulations.

Age Appropriate Explanations

Ensuring age appropriate explanations in any assent procedures is a significant part of the review process conducted by the IRB. Age-appropriate assent has long been a part of the DHHS regulations and current, available guidance will assist the IRBs in meeting their responsibilities. There is no need for further definition or elaboration of criteria to aid the IRB in ensuring age-appropriate explanations.

Placebo-Controlled Trials

The FDA has invited comment on the issue of conducting placebo-controlled trials in children. We understand and appreciate the on-going discussions concerning the use of placebo-controlled trials, generally, and applaud the FDA's sensitivity to this issue as it relates to investigations involving children. It is our position that the FDA should permit placebo-controlled trials. Placebo trials offer a powerful tool because they strengthen the conclusions that can be drawn about the effectiveness and safety of a drug or therapy in a study design that generally requires fewer subjects and can be conducted over a shorter period of time. The research community has established general guidelines for the use of placebo trials (e.g., ICH E10, Choice of Control Group and Related Issues in Clinical Trials). In addition to general standards, the American Academy of Pediatrics' (AAP) **Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations** has set specific standards for pediatric studies and endorses the use of placebo trials "if their use does not place children at increased risk." The AAP **Guidelines** offer good direction for IRBs in their review of pediatric placebo trials.

While placebo-controlled trials assume some subjects will not receive the test drug or therapy, there remains an opportunity of direct benefit for all participants. Conducted under the condition of not placing children at increased risk, a placebo-controlled trial can strengthen commonly used therapies by increasing efficacy or minimizing undesirable side effects. As the FDA notes, at a minimum, even those subjects not receiving the test product benefit from increased monitoring and care. IRBs, availing themselves of various guidelines and expertise, should retain broad latitude to determine on a case-by-case basis whether or not a particular placebo controlled study holds out the prospect of direct benefit to the proposed subjects. A prohibition or limitation on the use of placebo-controlled trials with children would not assist the FDA in

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achieving its goals of improving the labeling of drug and biological products for pediatric uses and encouraging studies on drugs and therapies that hold great promise for treating pediatric diseases or conditions.

Effective Date

We request clarification from the FDA on how to document the implementation of section 56.109 (h). The interim rule includes a required review of projects on-going on April 30, 2001 “either at the time of the continuing review or, at the discretion of the IRB, at an earlier date.” Does the FDA require specific, separate documentation, e.g., in the study file or in the minutes of a convened meeting, that a continuing study is in compliance with 21 CFR 50 Subpart D?

Economic Impacts

We would like to comment on the FDA’s Analysis of Economic Impacts. We believe that the estimates of additional time to be spent by IRBs to review and document the level of risk may be under-estimated. If the FDA anticipates that IRBs will simply note the level of risk in the minutes of a convened meeting as documentation of consideration then the estimate of one person-hour may be accurate. If, on the other hand, the FDA expects a more thorough documentation of what we know will be a much more complex discussion and review by the IRBs, we anticipate an increase of more than one person-hour of effort as a result of these regulations. The additional IRB responsibilities including ensuring age-appropriate explanations for assent and assessing strategies for the appointment of advocates when necessary, will add to the time spent by IRBs to ensure the safe conduct of pediatric clinical trials. Clarification from the FDA on the nature and scope of the documentation necessary may provide insight into the agency’s expectations and, as a consequence, its estimates of effort.

Thank you for providing us with the opportunity to comment.

Sincerely,

Katharina Phillips
President