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Dockets Management Branch (HFA-305)
Docket Number 02N-0466
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: A Multi-center, Randomized Dose Response Study of the Safety, Clinical and Immune Response of Dryvax[®] Administered to Children 2 to 5 Years of Age

Dear Drs. Crawford and Slater:

We write in response to the solicitation of public review and comment on the above-named research protocol, as announced on October 31, 2002 in the Federal Register, Vol. 67, No. 211, pages 26403-04. Our comments will ask and answer the following four questions.

- (1) Can the research study be approved by an IRB under one or more of the categories 45 CFR 46.404/21 CFR 50.51, 45 CFR 46.405/21 CFR 50.52 or 45 CFR 46.406/21 CFR 50.53? Our answer is no.
- (2) Will the research be conducted in accord with the primary "sound ethical principle" of research involving children, which holds that children should only be involved if the research question cannot be answered using adults? Absent significant modifications to the research design, our answer is no.
- (3) Will the research be conducted in accord with a number of secondary "sound ethical principles", assuming that the use of children in the research is necessary? Absent significant modifications to the research design and consent form, our answer is no.
- (4) Is the process of consultation being used to determine whether or not the research could be approved under 45 CFR 46.407/21 CFR 50.54 appropriate and ethical? Our answer is no.

We conclude that the proposed research should not be approved absent further public discussion of the need for using children to achieve the study objectives, and significant modifications of both the research design and consent documentation and process.

Question One: Can the research study be approved by an IRB under one or more of the categories 45 CFR 46.404/21 CFR 50.51, 45 CFR 46.405/21 CFR 50.52 or 45 CFR 46.406/21 CFR 50.53? Our answer is no.

With the exception of Dr. Fulginiti, who felt that the study should be approved yet failed to discuss the level of risk exposure, all of the consultants agreed that administration of the smallpox vaccine presents greater than a minor increase over minimal risk and thus could not be approved under sections 45 CFR 46.404/21 CFR 50.51 or 45 CFR 46.406/21 CFR 50.53. In effect, all of the consultants agreed that the study either must offer the prospect of direct benefit to the children enrolled in the trial (45 CFR 46.405/21 CFR 50.52), or meet the requirements for approval under 45 CFR 46.407/21 CFR 50.54. We agree with this assessment.

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In addition to the assessment of risk, the children to be enrolled in this study do not to have a “disorder or condition” as a requirement for approval under sections 45 CFR 46.406/21 CFR 50.53. This specific point was discussed by a minority of the consultants since the risk determination alone disqualified the study from consideration under this category.

Administration of the smallpox vaccine does not offer the prospect of direct benefit to the children to be enrolled in this research study. Only 2 of the 10 consultants (Daum, Baltimore) thought that the research offers the prospect of direct benefit to the children enrolled in the research. Although Dr. Fulginiti did not discuss the Subpart D categories, he clearly states that the research offers “no direct, immediate benefit to the children”. Dr. Daum argues for the prospect of direct benefit based on an analogy to the use of oral polio vaccine in spite of the known but small risk of vaccine-associated polio. However, this analogy is not useful. The oral polio vaccine was (and is) administered to children at the same time that polio disease occurs in many areas of the world. The benefits of that vaccine are, therefore, not theoretical. Dr. Baltimore argues that being immune from smallpox is a direct benefit even in the absence of a known bioterrorism-related risk for smallpox dissemination. Turning ethical concern for the “therapeutic misconception” on its head, Baltimore argues that parental perception of direct benefit based on the fear of smallpox dissemination is sufficient justification for an IRB to determinate that the prospect of direct benefit, in fact, exists. Contrary to Baltimore’s claim, Quigley appropriately asserts that the “parental instinct to protect a child should not be played upon as an impetus to enroll in this trial.” We do not know whether a conversation between consultants would have resulted in agreement on this point, as an the opportunity for such a panel discussion was never provided.

We agree with the majority of consultants that the research could not be approved by an IRB under categories 45 CFR 46.404/21 CFR 50.51, 45 CFR 46.405/21 CFR 50.52 or 45 CFR 46.406/21 CFR 50.53.

Approval under category 45 CFR 46.407/21 CFR 50.54 requires that “the research will be conducted in accordance with sound ethical principles.”

Although all of the consultants recommended that the research could be approved under section 45 CFR 46.407 and 21 CFR 50.54, there was little discussion of the “sound ethical principles” according to which the research must be conducted (apart from three of the four consultants with ethical and/or legal expertise). These “sound ethical principles” can be considered under two general categories: (1) the ethical principles that must be met for the research to be conducted in children at all, and (2) the ethical principles that must be met for the proper and ethical conduct of the research, assuming the use of children is ethically appropriate. Although the consultant’s discussion focused primarily on the second category, we must first ask and answer the first question of whether the research should be conducted in children at all.

Question Two: Will the research be conducted in accord with the primary “sound ethical principle” of research involving children, which holds that children should only be involved if the research question cannot be answered using adults? Absent significant modifications to the research design, our answer is no.

The primary ethical principle in conducting research involving children is that the scientific question(s) cannot be answered by using adults who are capable of consent. Assuming that consenting adults cannot be used, a secondary ethical principle in conducting research involving young children is that the scientific question(s) cannot be answered by using children who are capable of assent.

As stated in the protocol, the primary objective is to evaluate the cutaneous responses (take rates) after vaccination in children given undiluted and diluted (1:5 dilution) vaccine. Among the secondary objectives are the following: (a) to evaluate the immunological responses in children given undiluted and diluted (1:5 dilution) vaccine; (b) to ascertain the clinical and immunological responses and safety of 5 intradermal punctures with a bifurcated needle; and (c) to assess the safety profile in the vaccinated individual and assess the risk to contacts.

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The rationale for the study clarifies that a major concern is the risk of autoinoculation and secondary transmission from young vaccinees to contacts, with evaluation of the use of a semi-occlusive dressing to prevent such spread. The primary study endpoint is the clinical formation of a vesicle/pustule at the site of primary vaccination, and thus assumes efficacy based on this surrogate endpoint. The protocol states that the study is under-powered to examine differences between the groups receiving the undiluted and diluted (1:5 dilution) vaccine. In addition, the study is also too small to provide any meaningful safety data.

In examining whether children should be included in a study of smallpox vaccine, we ask the following five questions: (1) Is there a need to test diluted vaccine? (2) Is there a need to test the five-insertion scarification method? (3) Is there a need to evaluate a new semi-occlusive dressing applied to the site, in order to prevent secondary viral spread? (4) Is there a need to test children based on the possibility of a different immune response? Can one expect a different immunological response from children ages 2-5 years? Thus (5) are children as research subjects required to answer the research objectives?

Is there a need to test diluted vaccine? The need to test diluted vaccine is based on the public health concern to have an adequate supply of vaccine in the event of a terrorist attack. Whether the vaccine supply will remain scarce for the foreseeable future is a question of fact that could not be answered from the information provided. One of the consultants, Dr. Ebert, points out: "A newer version of smallpox vaccine is in development. I believe more useful information would be gained by delaying further testing in children until the new product is available." It is thus difficult to assess the need for this study absent facts concerning the reality of a terrorist attack, and the timeline for alternative vaccine development. Even so, unless one assumes that children would respond differently to the smallpox vaccine (addressed below), there would be no need to test the diluted vaccine on children.

Is there a need to test the five-insertion scarification method (i.e., 5 intradermal punctures with a bifurcated needle)? Although there is no discussion in the protocol as to why the 5 prick (as opposed to the 15 prick) method was being tested, one may assume that the shorter method has been selected for ease of administration and time efficiency. If so, there is no discussion of using intradermal jet injection as one possible method to be evaluated in the study. To the inexperienced observer, one would assume that this method would be even faster.

If the speed and efficiency of the 5 prick versus the 15 prick (or other method) is why the 5 prick method was selected, this hypothesis can be tested without introducing the risks of smallpox vaccine. It is possible that parents would not volunteer his or her child to be simply "stuck" without the presence of the vaccine; however, this hesitation illustrates the ethical problem with the parental perception of benefit from the vaccine. Testing the 5 prick method alone would make clear the public health benefit of the intervention without the prospect of direct benefit to the child. Furthermore, the comparative effectiveness of the 5 prick method in producing a vesicular response with either undiluted or diluted vaccine can be answered using adult subjects.

Is there a need to evaluate a new semi-occlusive dressing applied to the site, in order to prevent secondary viral spread? The previous adult study (n = 740) did not show an increase in adverse viral reactions or bacterial superinfection with the use of the semi-occlusive dressing. One would not expect there to be a difference between adults and children in the frequency of dressing-related adverse events, nor is the proposed pediatric trial powered (n = 40) to detect a rise in such adverse events. In addition, previous studies in adults demonstrated that two layers of the semi-occlusive dressing are required to obtain negative cultures from the top of the dressing. There is no reason to assume that viral penetration of the semi-occlusive dressing would vary between adults and children.

Thus the main reason to study the semi-occlusive dressing in children is to see if the behavioral differences results in a higher rate of autoinoculation and contact transmission. The rate of contact transmission will not be studied directly, as the children are being isolated in a way that will minimize such contacts when compared to the "real world" situation. The question then would be whether children of varying ages would be able to keep

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the semi-occlusive dressing in place during the 30-60 day period of post-vaccination viral shedding. Answering this question may not require vaccination with an active smallpox vaccine, unless one postulates that the presence of the vesicle would cause sufficient skin irritation to increase the likelihood that the child would remove the dressing. There is no discussion of whether there are alternative methods for mimicking a vesicle in order to reproduce the appropriate trial conditions without administering active smallpox vaccine.

Is there a need to test children based on the possibility of a different immune response? Can one expect a different immunological response from children ages 2-5 years? Three of the six infectious disease experts appear to disagree. Absent a panel discussion among them, it is unclear if they would have reached consensus on this point. However, the weight of opinion appears to favor the view that children have the same immunological response as adults, leaving the only difference that is then being tested as the 5 prick method (versus the 15 used on the adult studies).

Dr. Daum asserts that children's "immune responses may be different from those documented in adults. There are other vaccines where it is already known that the responses in adults do not mimic those in children, for example in the cases of diphtheria toxoid and pneumococcal conjugate vaccines." However, Dr. Halsey claims that "there is no biologically plausible reason to expect children 2-5 years of age to respond less well to this or any other live viral vaccine than adults if the vaccine virus and administration methods were the same." He asserts that "above two years of age there is no impairment of the immune response to any other live viral vaccine as compared to adults and children often respond better than adults." Halsey cites as evidence the fact that "there is no impairment in the immune response to measles vaccine, oral polio vaccine, yellow fever vaccine, mumps, or rubella vaccine in children ages 2-5 as compared to adults." Drs. Baltimore ("nearly all will respond to the undiluted and it is likely some or many will respond to the 1:5 based upon the adult data") and Ebert ("A recent study showed that old preparations of Dryvax[®] are still quite immunogenic in young adults. By inference, I would expect that the product would still be effective in young children, and that his study is unnecessary.") agree with Dr. Halsey's assessment. We do not know whether a conversation between consultants would have resulted in agreement on this point, as an the opportunity for such a panel discussion was never provided.

Thus, are children as research subjects required to answer the research objectives? Apart from the question of maintaining the intactness of the semi-occlusive dressing, there does not appear to be a reason that children are necessary to answer the other study objectives. This assumes that the immune response of a 2-5 year old child to a live smallpox vaccine is similar to that of an adult. Since there may be alternative methods for assessing the ability to maintain the intactness of the semi-occlusive barrier, it is unclear whether the administration of smallpox vaccine to children is necessary.

Question Three: Will the research be conducted in accord with a number of secondary "sound ethical principles", assuming that the use of children in the research is necessary? Absent significant modifications to the research design and consent form, our answer is no.

The research must be conducted in accord with at least the following four ethical principles: (1) the research design must minimize risk; (2) there must be adequate provisions for parental permission and child assent; (3) there should be adequate provisions for the treatment of research-related injury; and (4) the research subjects should control the disposition and use of biological specimens collected in the research.

The research design must minimize risk. Although a number of features have been put into place within the research protocol that minimize risk, several consultants point to additional questions that need to be addressed. Is there the need for a control group using undiluted vaccine? Is the response of the children to the undiluted vaccine predictable enough to eliminate the need for a concurrent control group? According to Dr. Baltimore,

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“nearly all [the children] will respond to the undiluted [vaccine].” Dr. Halsey asserts that “the fact that all children will respond to the undiluted vaccine renders the control group unnecessary.” In our view, if the main research question is the effectiveness of the 5 pin prick method, the two groups should be given the diluted vaccine with one group receiving 5 and the other group 15 pin pricks. Does the research require young children? In answer to Dr. Halsey’s question about the need to restrict school attendance, and thus study a population that is not attending school, the apparent answer is the unpredictability of children keeping the semi-occlusive dressing in place. Otherwise one could study older children and still allow for school attendance.

There must be adequate provisions for parental permission and child assent. We agree that there should be a two tiered process of parental permission, with a separate screening consent document. All language that suggests any prospect of direct benefit (such as references to “treatment”), or plays upon parental fear or desire to be a “good parent” by enrolling a child in the research, must be removed from the consent documents and process. The documents should contain a more appropriate description of the smallpox vaccine-related risks, including that they are more common than other vaccines. Finally, the process should optimize voluntary and informed parental permission. Among the more creative suggestions is to optimize the quality of parental permission through preferentially recruiting children of the adults who were enrolled in the adult trials. If an adult would not be willing to be exposed to the risks of smallpox vaccination, that same adult should not be exposing his or her child to those same (or greater) risks.

There should be adequate provisions for the treatment of research-related injury. Coverage for the costs any research-related injury must be provided, as these children are making a sacrifice for the public good in the absence of direct personal benefit. Any language that suggests the sponsor or institution is not responsible for any research-related injury should be removed.

The research subjects should control the disposition and use of biological specimens collected in the research. The testing of biological specimens should be limited to the purposes outlined in the research (and disclosed in the consent document). Explicit and additional consent should be required for any other testing, with provisions for the subject removing the specimen from the specimen repository at any point in the future.

Question Four: Is the process of consultation being used to determine whether or not the research could be approved under 45 CFR 46.407/21 CFR 50.54 appropriate and ethical? Our answer is no.

The federal regulations require both “consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law)” and the “opportunity for public review and comment” (45 CFR 46.407/21 CFR 50.54). For this consultation, the documents were mailed to the individual consultants who then delivered their reports. Although we understand that the individual consultants were permitted to contact each other, we suspect that this process did not allow for substantive exchange between panel members, either on points of scientific disagreement or for clarification of ethical arguments and/or claims. We have indicated in our analysis above where a substantive exchange on key scientific and ethical issues would have allowed for a more informed judgment about the research.

From the current documents, one cannot conclude that a concern raised by one consultant would not have been a concern for one or more of the other nine consultants. By way of analogy, the use of a focus group (of which a convened panel is a specific instance) is often recommended for qualitative research so that ideas raised by one panel member can be considered and developed further by the other panel members. This same approach informs the review of a research protocol by a convened meeting of an institutional review board (IRB) made up of members with different perspectives. Frequently only one member of an IRB expresses a concern which is then supported by the majority or a consensus of the IRB membership. It would be a serious error to conclude that a recommendation made by only one or two panel members reflects the opinion of only a minority of the panel.

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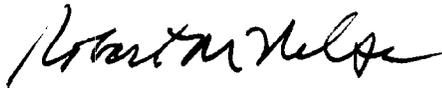
The lack of public discussion among panel members renders it impossible to determine whether the apparent differences of opinion would have been resolved, or to assess the relative merits of arguments for or against the divergent opinions. The scientific question of whether children ages 2-5 years have a different immune response from adults is absolutely essential in determining whether the research should be performed in children. The ethical and legal consultants did not have the benefit of hearing these different perspectives, nor did any of the panel members benefit from hearing a discussion among those with different views of the issue. In effect, it leaves the FDA and DHHS in the position of picking and choosing among the individual consultant's advice in order to support conclusions drawn by unnamed experts within either Department, thereby undercutting the moral justification of research conducted under 45 CFR 46.407/21 CFR 50.54.

The irony is that this consultative process may have been selected to avoid violating the Federal Advisory Committee Act (FACA). FACA is founded on the important principles of open government and public participation, especially when panel deliberations will have an impact on governmental policy. Although the public has adequate opportunity and access to the source documents in order to comment on this research, the manner in which the expert panel was conducted undercuts the moral legitimacy of the overall process.

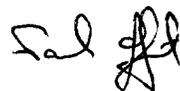
The FDA has considerable experience in the use of public advisory panels to provide a forum for deliberation and advice on issues concerning FDA-regulated products. Such a process should be established and used for research falling under sections 45 CFR 46.407 and 21 CFR 50.54. As is done now, existing advisory panels could be supplemented by appropriate subject-specific expertise. As schedules may conflict and prevent the participation of appropriate experts, written comments could be solicited ahead of time for consideration by the panel, with the ability to establish an audio-conference link with individuals whose schedules do not permit personal attendance. It is unclear why the existing FDA Advisory Panel structure, supplemented by individuals with appropriate subject-specific expertise, was not used for this panel. In fact, a meeting of the FDA Pediatric Advisory Subcommittee of the FDA Infectious Disease Advisory Committee was already scheduled for early November 2002 and cancelled due to lack of an agenda.

In summary, we conclude that the proposed research testing existing smallpox vaccine in young children should not go forward absent further public discussion of the need for using children to achieve the study objectives, and significant modifications of both the research design and consent documentation and process.

Sincerely,



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