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October 30, 2002

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Dear Drs. Koski and Lepay:

On October 11, 2002, you requested that I review several issues related to proposed research involving children under subpart D: "A Multicenter randomized dose response study of the safety, clinical and immune responses of Dryvax administered to children 2 to 5 years of age." I am writing in response to that request.

Understanding of the task: Specifically sought is opinion as to whether the proposed research is approvable under HHS regulations 45 CFR 46.404, 46.405, or 46.406 and under FDA regulations 21 CFR 50.51, 50.52, or 50.53 and the reasons for this opinion. If my opinion is that the research is not approvable under these regulations, an additional question concerns whether it could be approved under HHS regulation 45 CFR 46.407 and FDA regulation 21 CFR 50.54. In the latter instance, several conditions should be addressed including whether the proposed research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health and welfare of children, whether it will be conducted with sound ethical principles and whether adequate provisions are available for soliciting the assent of children and the permission of their parents or guardians.

All the designated regulations deal with research performed among children. HHS regulations 45 CFR 46.404-6 differ in assignment of potential risk to subjects involved in the research and potential for benefit. HHS regulation 45 CFR 46.404 addresses research

not involving greater than minimal risk. HHS regulation 45 CFR 46.405 addresses research involving greater than minimal risk to individual subjects but presenting the prospect of direct benefit to them. HHS regulation 45 CFR 46.406 addresses research involving greater than minimal risk to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition. FDA regulation section 21 CFR 50.51 provides for clinical investigation in which "no greater than minimal risk to children is presented" and adequate provisions are put forward for soliciting the assent of the subjects and permission of their parents or guardians. FDA regulation 21 CFR 50.52 provides for research involving greater than minimal risk that has the prospect of direct benefit to individual subjects. FDA regulation 50.53 provides for research involving greater than minimal risk that has no prospect of benefit to individual subjects but is likely to yield generalizable knowledge about the subjects' disorder or condition.

HHS regulation 45 CFR 46.407 and FDA regulation 21 CFR 50.54 detail rules for research not otherwise approvable that present an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children.

Background germaine to the opinion: NIAID proposes to study the safety and immunity of Dryvax, a vaccinia virus vaccine once recommended for universal administration to children, when administered to children 2 – 5 years of age. The study would take place at two of NIAID's sponsored patient enrollment sites, Harbor-UCLA Medical Center and Cincinnati Children's Hospital Medical Center. The proposal is to study the safety and immune response to Dryvax, both neat and diluted 1:5, in children enrolled at the above-mentioned sites.

While preparations for this study have been underway, a manufacturing supplement for a new 100-dose kit applicable to the use of this vaccine was approved by the FDA on October 25, 2002, thus effectively re-licensing Dryvax for use in the US. A vaccine consisting of Dryvax at a 1:5 dilution continues to represent an unlicensed use of the Dryvax vaccine and is scheduled to be used in the proposed protocol.

Reviewer summary and opinion regarding the issues posed by this proposed study. Should there be an intentional release of smallpox virus, the scenario by which such an event would occur is unknown. One could conjure up many theoretical scenarios under which this event might expose children. It may therefore become appropriate to provide post-exposure protection to such exposed children or even pre-exposure protection if additional information suggests that the likelihood of exposure were substantial.

Both of these scenarios raise the possibility that it may become necessary to prevent smallpox in children by vaccination. I believe that before Dryvax could be used in a larger number of children, the basic information that will be accrued by the conduct of the proposed study is essential. I believe that it is not acceptable to use data gathered from adults and extrapolate them to children. The cliché that children are not just "small adults" applies. For example, their immune responses may be different than 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 or pneumococcal conjugate vaccines.

Moreover, the planned dose of Dryvax for children is different from that used recently to immunize adults and few data are available to address pediatric responses to the proposed dose. There also may be different implications for safety among children in terms of biologic responses to the vaccine, e.g. rates of fever, and also in terms of environmentally driven issues related, potentially, to vaccine spread. People touch children differently than adults, in different ways, for different purposes and probably at different rates. Children may have different understandings of a "don't touch" directive after application of a semi-occlusive bandage to an immunization site than adults. Young children may not understand or comply with such a directive. It would be useful to define the occurrence of these behaviors and study their consequences.

The central issue for the opinion you have requested of me concerns assessment of real or potential benefit to a participating subject. For example, if the risk of exposure to smallpox in the relevant near future were 100%, it would be simple to understand the need to immunize relevant subjects rapidly. On the other hand, if the risk were known to be 0%, the proposed research would pose an unacceptable risk burden under all the regulations noted above.

Thus, for me, the difficulty is assessing the research in the absence of a more precise estimate of the actual risk for exposure to smallpox. In the absence of an actual event, this risk will unlikely be measurable with any precision, at least based on publicly available data. However, some assumption regarding risk must be made as it is impossible to understand the purpose of any smallpox preparedness program without doing this. It is my belief, therefore, that we are already operating on an assumption that the risk is > 0. All of the substantial recent concern regarding smallpox by government officials, the media, government advisory groups, and the general public is driven by an inherent assumption that the risk is > 0%. The decision to immunize adults at the CDC, St Louis and elsewhere makes sense only in light of such an assumption.

For children, in my opinion, an assumption of risk > 0% also provides the framework under which the research in the proposed safety and immunogenicity study can be justified. In this scenario, there <u>is</u> benefit to an immunized child. S/he would likely be protected in the event of an exposure, unless there were no "take" after vaccine administration.

Our society has applied a similar set of assumptions in the provision, for example, of a dose of IPV routinely to our children where the likelihood of exposure to wild-type polio is miniscule. The analogy is closer, however, in considering the use of OPV in the years before abandoning this vaccine for the increased safety of our current IPV program. We accepted the very small risk of VAP from OPV for many years. We continued to provide the benefit of immunization in the belief that the risk of exposure to wild-type polio virus was not 0 even when polio had not been seen in our country for many years.

Thus, I believe the studies proposed do provide potential benefit to the vaccinees and can therefore be justified under HHS regulation 45 CFR 46.405 and FDA regulation 21 CFR 50.52. That is to say, I believe there is more than minimal risk to individual subjects but there is a prospect of direct benefit to individual subjects.

I hope the opinion stated in this report is clear. I would be pleased to expand or clarify any part of this statement at your pleasure.

Sincerely,

Robert S. Daum, M.D., C.M.