

Comments on the NIAID Protocol,
"A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune
Responses of Dryvax® Administered to Children 2 to 5 Years of Age"

Steven Ebert, Pharm.D.
Infectious Diseases Pharmacist
Meriter Hospital
Clinical Professor of Pharmacy
University of Wisconsin
Madison, WI

As requested by Drs. Ball, Koski, and Lepay, the following are my comments pertaining to the "approvability" of the protocol named above, under 45 CFR 46.404, 46.405, 46.406, and 46.07 as well as 21 CFR 50.51, 50.52, 50.53, and 50.54. My comments come after fully reviewing the packet of information sent to me by DHSS, as well as a faxed copy of the minutes of the applicable Cincinnati Children's Hospital IRB meeting.

- I do NOT consider the protocol to be approvable under 45 CFR 46.404 or 21 CFR 50.51, "No greater than minimal risk". The risks of adverse effects associated with the vaccine including cellulitis, fever, disseminated vaccinia, vaccinia necrosum, eczema vaccinatum, and transmission of vaccinia to others are relatively small, but not (in my opinion) "minimal" in scope.
- I do NOT consider the protocol to be approvable under 45 CFR 46.405 or 21 CFR 50.52, "Greater than minimal risk, but presents the prospect of direct benefit to individual subjects". Although the risk of a terrorist release of smallpox appears to be a possibility, the likelihood of a participant in such a small study (40 subjects) who has become immune subsequently being exposed to smallpox is extremely small. Furthermore, the amount of the proposed payment to subjects' families for participation is not sufficient to offer "benefit".

I view the risks associated with Dryvax® immunization to a child, *given what is known about the vaccine in children at this point*, to be outweighed by the benefits ONLY IF the child had been exposed to smallpox or lived in a community where smallpox had been released.

- I do NOT consider the protocol to be approvable under 45 CFR 46.406 or 21 CFR 50.53, "Greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition".
 - 21 CFR 50.53 implies that the immunization should "present (an) experience to subjects that is commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations." Given the small chance of exposure to smallpox, I do not believe that that is the case.

- Studies in children conducted in the 1970's have tested the immunogenicity of Dryvax® at both full strength and diluted. These studies showed that immunization to young children usually resulted in vaccine "take" similar to that in young adults. 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 this study is unnecessary.
 - 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.
 - I fail to see how the proposed study will shed any new light on the "safety" of Dryvax®. Most of the severe reactions to the vaccine have occurred at a rate of 0.1-0.001%. Even if these severe reactions occurred at a 10-20-fold higher rate in the proposed study, the small number of subjects (40) would not allow for detection of this increased rate.
- Finally, I DO consider the protocol to be approvable under 45 CFR 46.407 and 21 CFR 50.54, "Not otherwise approvable but presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children."
 - The above concerns notwithstanding, the protocol will allow investigation of the 1:5 dilution in children using a five-insertion scarification method. Previous studies did not test this combination of strength and method. In addition, the study will evaluate a new semi-occlusive dressing applied to the immunization site.
 - I believe the study will be conducted in accordance with sound ethical principles.
 - Based on the protocol, I believe adequate provisions will be made for soliciting the permission of parents or guardians.

I feel that the "null hypothesis" associated with the study should be stated more strongly in the protocol.

I suggest that the term "safety" be removed from the title of the study. The number of subjects to be enrolled will not permit a reasonable estimate of the safety of the vaccine and/or technique.

Thank you for the opportunity to review this protocol.