

October 25, 2002

Dr. Greg Koski  
Dr. Leslie Ball  
Office of Human Research Protection

Dr. David Lepak  
Food and Drug Administration

RE: Review of 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"

Dear Drs. Ball and Lepak,

As requested, I have reviewed the materials submitted by the study sponsor, including the reports of studies conducted with adults, and testimony by representatives of HHS regarding bioterrorism readiness. My conclusions follow:

I do not believe that this protocol is approvable under 45 CFR §§46.404-.406 and 21 CFR §§50.51-.53. This vaccine poses more than minimal risk. The likelihood that children who participated in this trial will be made immune to smallpox is not sufficient promise of "direct benefit" to justify this risk under 45 CFR §46.405 and 21 CFR §50.52. These provisions require a weighing of risks and benefits for the particular child. In this case, I believe (and hope) that the likelihood that smallpox will be used as a weapon is sufficiently remote that the benefit to the particular child of being vaccinated does not outweigh the risks. Similarly, the otherwise healthy children who are to be enrolled in this study have no condition or disorder that would bring this study within the purview of 45 CFR §46.406 and 21 CFR §50.53.

I do, however, conclude that this protocol is probably approvable under 45 CFR §46.407 and 21 CFR §50.54. I will address the three regulatory criteria in turn.

- (i) "The research or clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." Sadly, while I believe that the risk that smallpox will be used as a biological weapon is small, I also believe that the risk is not zero. Based on publicly available data, it does not appear that new vaccine will be available in the foreseeable future. Given the limited quantity of vaccine currently available, it is important to determine the most dilute effective dose so that more children can be vaccinated in the event of attack. The critical distinction between the analysis under this section and that undertaken pursuant to 45 CFR § 46.405, is that the relevant benefit to meet the requirements of this subpart

is to the health of children generally, not to that of a particular child. Being able to save five times as many children would be an important public health outcome. Even the benefits to children generally would not suffice were it not for the facts that even though this vaccine is quite reactogenic, the incidence of serious adverse effects with long term sequelae appears to be quite low and that this protocol makes every effort to minimize these serious risks. It is reassuring that more dilute vaccine is effective in adults, but evidence from earlier smallpox vaccine trials in children (which showed them to be less likely to develop immunity than adults) as well as the more general history of studies of immunogenicity of vaccines in children would make it imprudent simply to extrapolate from the current adult trials. Another factor that warrants further investigation is the impact of covering the vaccination site with Opsite, particularly given that occlusive dressings were previously thought to be contraindicated.

Three caveats are implicit in the foregoing analysis. One is the risk of attack. If in fact, there is no real risk that smallpox will be used as a weapon, then this trial would confer no benefit to children generally and so could not be justified. The second is that I assume that a less reactogenic vaccine is not going to be available in the near future. The third is that I assume that Opsite would be used in the event of widespread vaccination. If not, then understanding its impact is not sufficient by itself to justify this trial.

- (ii) “The research or clinical investigation will be conducted in accordance with sound ethical principles.” This appears to be true.
- (iii) “Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR §46.408 and 21 CFR §50.55.” These seem appropriate. I, however, would delete the language about developing immunity as a benefit because I think/hope that the likelihood that these participants would actually need that immunity is quite low. This really is a study that is being undertaken to benefit children generally.

I would also point a couple of mistakes in the consent form for VIG. First, I assume that only two teaspoons of blood and not two tablespoons will be drawn. There is a “u” missing in the next to last line of the first page.

Please do not hesitate to let me know if you have any questions.

Sincerely yours,

Ellen Wright Clayton, MD, JD