

October 28, 2002

Greg Koski, MD, PhD
Director, Office for Human Research Protection
Office of Public Health and Science
Office of the Secretary
Department of Health and Human Services

David A. Lepad, MD, PhD
Senior Advisor for Clinical Science and
Director, Office for Good Clinical Practice
Office of the Commissioner
U.S. Food and Drug Administration

SUBJECT: 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. Koski and Lepad:

In response to your letter of October 11, 2002, I have reviewed the materials provided regarding the Division of Microbiology and Infectious Diseases (DMID), NIAID, NIH-sponsored protocol 01-650, a proposed multicenter, randomized dose response study of the safety and clinical and immune responses to Dryvax (vaccinia virus smallpox vaccine) administered to children 2 to 5 years of age.

Dryvax is currently an investigational drug, but was used until 1971 as a routine immunization for children in the United States. The vaccine is a live virus vaccine obtained from bovine lymph. The complications and efficacy of this vaccine in children are well documented in the literature. The 01-650 protocol proposes to initially study forty children age 2-5 years of age that will be divided into two groups. In the first group of 20 children the previously used WHO recommended standard vaccine and five skin punctures but with a semi-occlusive inoculation site dressing will be used. Results of immunogenicity and reactogenicity will be compared to historical experience in children and to recent data in adults using Dryvax and semi-occlusive dressings. The second group of 20 children will have a 1:5 dilution of Dryvax administered and the semi-occlusive dressing will be used. A potential second follow-up study with 60 additional children is proposed that will utilize the results of the initial study to further assess the 1:5 dilution and other dilutions (e.g. 1:10 and > 1:10) of Dryvax with or without the occlusive dressing.

I consider the research not to be approvable under HHS regulations 46.404, 46.405, 46.406 and the similar FDA regulations 21 CFR 50.51, 50.52 and 50.53.

46.404 is considered inappropriate because the vaccine has side effects, which make its use greater than minimal risk. 46.405 is considered inappropriate because the vaccine would not now offer direct benefit to a child since smallpox has (at present) been eradicated as a disease worldwide. An argument can be

made that the vaccine does offer direct benefit (e.g., protection from smallpox) to a child and thus could be approved under 46.405. However, in view of the absence of disease in the world for twenty-five years and the absence of a clear understanding or defined risk of the likelihood of a smallpox outbreak, be it accidental or bioterrorism, this argument is not compelling to recommend approval under 46.405. 46.406 is considered inappropriate because the risk of the vaccine is more than a minor increase over minimal risk (part a.) and that the vaccine does not present experiences to study subjects that are reasonably commensurate with those inherent in their actual or expected medical situations (part b).

I consider the research potentially approvable under 45 CFR 46.407 and 21 CFR 50.54.

Determination of the safety, clinical and immune responses of Dryvax in diluted form in children does represent a responsible opportunity to further the understanding, prevention or abbreviation of a serious problem that could affect the health and welfare of children.

The preservation of live smallpox (variola) virus in at least two sites in the world and the probability that live virus may exist in large quantities at other sites is a serious problem that affects the potential health and welfare of very large numbers of children. It is also important that a vaccine that may be used to protect children be tested in children. Thus, understanding that a diluted dose of Dryvax will be effective or that semi-occlusive dressings decrease spread but do not increase complications in children is important. While it can be argued that the power of this study is limited, that there is ample past experience with this vaccine in children, and that a 1:5 dilution and semi-occlusive dressing are satisfactory in adults and thus would be predicted to work in children, the data derived from the study would be extremely valuable and reassuring before beginning a mass vaccination program in the setting of a smallpox case.

The research must be conducted in accordance with sound ethical principles and adequate provisions should be made for soliciting the permission of parents and guardians. Issues raised during the two institutional reviews need to be fully addressed (e.g., risk to the child, parental screening, contact risk, liability, reimbursement for medical care, both parents' consent) before the study is begun. Consent must emphasize the risks to children and to contacts of these children. My belief is that the current consent form (part 4.) with phrases like "as with all vaccines" does not fully convey the serious risks of this vaccine to the parents. Dryvax is currently an investigational drug made from a nonsterile bovine product, administered using new techniques and methods (e.g., semi-permeable occlusive dressing) that might enhance vaccine reactogenicity or secondary complications such as superinfections. The risk to the child of serious injury and even death is low but not remote. The risk of spread to others in the family and outside the family is not negligible. For example, the exact procedure for the semi occlusive dressing (e.g. with sterile gauze first) is not clearly defined in the consent or protocol, nor is how changes of the vaccine site dressings are to be discarded by families and staff. These risks must be made very clear to the parents. Assent is judged not to be appropriate for this age child.

In summary, I consider the research can be approvable under 46 CFR 46.407 if it is deemed that a credible risk of a smallpox outbreak now exists.

Thank you for allowing me to review the material and participate in the panel.

Sincerely,

David S. Stephens, MD
Director, Division of Infectious Diseases
Professor and Executive Vice Chair,
Department of Medicine