October 17, 2002

Leslie K. Ball, M.D.
Office for Human Research Protections
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Rockville, MD 20852
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RE: DMID 01-650 protocol "A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune Responses to Dryvax Administered to Children 2 to 5 years"

Dear Dr. Ball:

I am writing in response to your e-mail requesting information on the rationale for approval of the study referenced above by the Kaiser IRB. A summary of the deliberations and decisions regarding this protocol, under Subpart D regulations - Additional Protections for Children Involved as Subjects in Research, are noted below:

On July 16, 2002 the Kaiser IRB reviewed this study designed to evaluate the dose-response and safety of smallpox vaccine in children two to five years of age. The Kaiser IRB was concerned about the virus being carried in saliva and asked the investigator to screen for children who have a propensity to bite. The Kaiser IRB also asked for clarification on Question #30 of the IRB application which appeared to be missing a word. In addition, the Kaiser IRB requested a final version of the recruitment letter that would be sent to the potential subject's parents. The Kaiser IRB noted that the answer to Question #6 of the IRB application indicated that patient charts (medical records) would be reviewed in conjunction with this study. However, the response to Question #27 stated that no access to databases or medical records would be required for this study. Therefore, the Kaiser IRB asked for clarification on this issue. The Kaiser IRB also asked the investigator to provide the filing number of the investigational drug (Dryvax®) being used in this study. Finally, the Kaiser IRB reminded the investigator that all informed consent documents would need to be translated into Spanish after the English versions were approved.

In accordance with §46.405, research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects, the Kaiser IRB determined that the risk to

subjects was justified by the anticipated benefit to the subjects and the relation of the anticipated benefit to the risk was at least as favorable to the subjects as that presented by available alternative approaches (none of which currently exist in the prevention of smallpox). In addition, as the potential subjects are aged two to five years old, the IRB did not feel these children are capable of providing assent. Informed consent shall be documented by the use of a written consent form approved by the Kaiser IRB and signed by the subject's legally authorized representative. A copy shall be given to the person signing the form.

On July 29, 2002 the principal investigator responded to the Kaiser IRB and agreed to exclude children who have a propensity to bite from the study along with children who have behavioral, developmental, or psychiatric conditions which preclude subject compliance with the protocol. The principal investigator also submitted a revised and corrected IRB application, as well as a final version of the letter that would be sent to the potential subject's parents. The investigator also provided the IND filing number for Dryvax®. In addition, the investigator also explained that due to the extensive nature of the post-vaccination instructions, only 20 English speaking subjects would be recruited for this pilot study.

On August 2, 2002 the investigator's response as described above was reviewed by a Subcommittee of the Kaiser IRB and subsequently approved on August 5, 2002.

Please let me know if you have any additional questions or need further information regarding this study.

Sincerely,

Eric Macy, M.D.
Chair, Institutional Review Board
Kaiser Permanente Southern California