

**THE ALIANCE FOR HUMAN RESEARCH PROTECTION  
(AHRP)**

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**FDA Docket Number 02N-0466 Comments re: Proposed smallpox vaccine trial to test the safety of Dryvax administration to children 2 to 5 years of age**

Recent public and professional debate about smallpox vaccine and its risks provides the framework for evaluating the ethical justification for conducting clinical trials on children. Dryvax is a particularly impure product made of live vaccinia virus harvested from the pustules of calves infected with (it is believed) cowpox. Although the vaccine, which is scratched on the skin, only causes mild infections in most people, in a small but significant number the infection caused serious adverse reactions similar to the complications of the disease they were designed to prevent: painful, disfiguring skin disorders, blindness, neurological impairments and death.

**Smallpox Vaccine Risks:**

Smallpox vaccine is the most highly reactive vaccine that has ever been routinely used in humans. Routine vaccination against smallpox was terminated in about 1971 because of severe adverse side effects from the vaccine and a low risk of exposure to smallpox. Fever lasting for 4 to 14 days can be expected in 70 percent of children inoculated.<sup>1</sup> Based on data from a 10 state survey in 1968,<sup>2</sup> the Center for Disease Control (CDC) estimates that for every 1 million people vaccinated for the first time about 1,000 experienced reactions that, while not life-threatening, were serious, requiring medical attention: vaccinia rash (outbreak of sores due to accidental touching) on the genitals or face, including the eyes, where it can damage sight or lead to blindness; widespread vaccinia may be spread through the blood; toxic or allergic reaction. The most recent data reveals that following vaccination, children 1 to 4 years of age are particularly at risk of suffering from widespread blotchy macular rashes.<sup>3</sup>

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Furthermore, CDC estimates that between 14 and 52 people per 1 million people vaccinated for the first time experienced potentially life-threatening reactions. Eczema vaccinatum: serious widespread infection with vaccinia lesions over the body of patients with eczema or a history of eczema. Clinically, these patients are similar to burn patients, losing fluid, serous exudate, and electrolytes through their skin. Children < 5 have a greater risk than other age groups—44 cases

(out of one million vaccinated). Fatalities have occurred in patients who were not themselves vaccinated, but were close household contacts of recently vaccinated siblings etc.<sup>3</sup> Vaccinia necrosum (infection of skin with tissue destruction) frequently leads to death. Finally, post-vaccinal encephalitis (inflammation of the brain), for which there is no effective treatment and no complete recovery. Approximately 15% to 25% of those who are stricken with post-vaccinal encephalitis die, and 25% suffer permanent brain damage.<sup>1</sup> No one knows what percentage of smallpox vaccine recipients today will suffer severe complications. But a recent study of adult primary vaccinees revealed that 36% were sufficiently ill to miss work, school, or recreational activities.<sup>4</sup>

#### **Ethical / moral considerations:**

Experts say the vaccine can be administered 3-4 days AFTER exposure to the smallpox virus and still "prevent or decrease the severity of clinical disease."<sup>5</sup> Careful risk/benefit analysis is, therefore, critical toward making the best decisions regarding who should be vaccinated, and when. Adults have the right to choose whether or not to be inoculated against smallpox--children do not have the legal right to exercise free choice. Therefore, to meet ethical / moral standards, those proposing the Dryvax vaccine experiment—exposing 2 to 5 year old children to the hazards of the vaccine—must provide compelling evidence of an imminent risk of smallpox exposure for the children sought. Absent such evidence there is no justification for exposing children to the severe, painful, possibly irreversible, risks of the vaccinia virus. This is especially the case with children who are at greater risk of severe reactions because of their lesser understanding of preventive measures and ability to follow instructions.

Dr. Paul Offit, Chief, infectious diseases section of Children's Hospital of Philadelphia, and a member of the Center for Disease Control (CDC) Advisory Committee on Immunization Practices, has seen babies who suffered adverse reactions to smallpox vaccine. He says that in the absence of a single case of smallpox anywhere on earth, the vaccine is too risky to use:<sup>6</sup> "I would never give that vaccine to my children because right now there is no disease out there."<sup>7</sup> Don't children of less knowledgeable parents have a right to be similarly protected from harm?

#### **Other risks: Accidental infection of third parties**

Because vaccinia virus is a live virus, there is the risk of its inadvertent transmission by touching parts of the body or from contact with a vaccinated person whose lesion is in the florid stages. Unvaccinated adults and children are at risk of contacting the virus. Lesions of inadvertent inoculation occur most commonly on the face, eyelid, nose, mouth, genitalia, and rectum. Lesions in eczematous skin, in disrupted skin, and in the eye pose special hazards, as the infection can be extensive and a threat to eyesight. [Accidental transmission infection in other parts of resulting

from the vaccine is the most frequent complication of smallpox vaccination.<sup>3]</sup> The Dryvax package insert states that 577 cases occurred among a million vaccinated children aged <5 years. Furthermore, those who came in contact with the virus were at increased risk of contacting a more severe form of eczema vaccinatum than those vaccinated because those vaccinated were screened out. The CDC reports that in one case, six cases of eczema vaccinatum resulted through contact with one vaccine recipient.<sup>1 [p.11]</sup>

Some, but not all, complications from vaccinia virus can be treated with vaccinia immune globulin (VIG), a substance taken from the blood of previously vaccinated people. But there is a shortage of VIG. According to the World Health Organization "The risk of adverse events is sufficiently high that vaccination is not warranted if there is no or little real risk of exposure. Vaccine administration is warranted in individuals exposed to the virus or facing a real risk of exposure. A safer vaccinia-based vaccine, produced in cell culture is expected to become available shortly."<sup>8</sup>

#### **Dryvax stockpile problems:**

Dryvax, the vaccine to be used in the proposed experiment on 2 to 5 year old children was pulled out of storage after approximately thirty years. Dryvax stockpiles had been freeze dried and stored in glass tubes to be mixed with a liquid diluent just before vaccination using a bifurcated needle that allows droplets of the vaccine to be scratched onto the skin. In 1999, the CDC discovered that some U.S. Dryvax vaccine stockpiles had badly deteriorated: rubber stoppers on the glass storage tubes had decayed and vacuum pressure had been lost while the liquid diluent had changed color and there were only one million bifurcated needles to administer more than 15 million doses.<sup>9</sup> The journal, Science, reported that one fourth of the stockpiled vials "are suspect."<sup>10</sup>

In the June 22, 2001 the CDC confirmed that previous methods of vaccine production using calves are no longer being used: "The traditional method for producing vaccines on the scarified flank of a calf is no longer acceptable because the product inevitably contains some microbial contaminants, however stringent the purification measures."<sup>11</sup> New vaccinia virus vaccines will be grown in laboratories using other cell tissues such as human fibroblasts (from fetal connective tissue cells).<sup>12</sup> CDC indicated that new cell-culture vaccinia virus vaccine will be evaluated for safety and efficacy by direct comparison with Dryvax using appropriate animal models, serologic and cell-mediated immunity methods and cutaneous indicators of successful vaccination.

In 2001, the CDC began inoculating its staff with smallpox Dryvax vaccine, but allegedly stopped, because the adverse reactions were greater than anticipated. The CDC has not provided critical information from its recent experience, about the rate of local and systemic reactions, their type

and duration. Without such up to date, current data, neither the public nor medical professionals are able to make a reasoned risk/benefit decision about using this vaccine.

**Proposed Dryvax trial on 2 to 5 year old children is unnecessary and unethical:**

Not a single case of smallpox has been reported anywhere in the world, thus the risk is, at best, speculative. Given the history of serious adverse reactions in adults and particularly in children, given also the complicating risk factors of the Dryvax vaccine, it is all the more astonishing that the government is giving its blessing to an unprecedented clinical trial in which the smallpox vaccine will be tested in small children. To justify the exposure of children — who are not volunteers — to the very real serious risks associated with the smallpox vaccine, evidence must demonstrate a credible risk to smallpox exposure for these children. If there is no evidence of a real risk of a smallpox attack, then the experiment is wholly unethical for it would put the children and others at risk without a potential benefit. Indeed, the overwhelming negative response by the public and media to the trial announcement — should preclude conducting the trial.<sup>13 14</sup>

A fundamental ethical principle under The Nuremberg Code and federal regulations is that any experiment in which human beings may be at risk must be justified by showing that the information sought is "unprocurable by other methods or means."<sup>15</sup> The purpose of the study, it is claimed, is to test the safety and immune response of Dryvax vaccine, by comparing full strength to a 1:5 dilution in children 2 to 5 years of age. But Dr. William B. Carey, Clinical Professor of Pediatrics at the Children's Hospital of Philadelphia, who spent 31 years in primary pediatrics care between 1957 and 1989, disagrees. Dr. Carey personally gave almost all the immunizations his patients received, including thousands of smallpox vaccinations up until about 1970. Dr. Carey raises two important points that seem to have been overlooked by those who considered the proposed trial on 2 to 5 year old children. He points out that it may not be necessary to dilute the vaccine at all because there is enough vaccinia virus in each individual vaccine tube to provide several doses. Dr. Carey points out, that unlike immunizations preparations for tetanus or measles, of which one must inject all the liquid that is provided to each person, the smallpox vaccine vials always contained far more vaccine than one could use for a single administration. He remembers that doctors had to discard the excess. On some occasions, as when a whole family had to prepare for an overseas trip, it was possible to divide one vial for all members with good takes for all. This knowledge seems to have been overlooked in the present debate. But in light of the experience, he says, "we must ask whether it is at all necessary to be considering the use of dilution to solve the supply problem. Besides, any necessary testing could be done on unimmunized adults 20-30 years of age, who can be fully consenting."<sup>16</sup>

One of the panel experts who reviewed the proposal pointed out, the proposed study will not shed any new light on the 'safety' of Dryvax because it lacks a sufficient number of subjects. He notes that even if the severe reactions in this study were to occur at 10-20 fold higher rate, "the small number of subjects (40) would not allow for detection of this increased rate." [Steven Ebert, Pharm.D] Furthermore, he notes, studies had already shown that "immunization to young children usually resulted in vaccine 'take' similar to that in young adults." Since a recent study showed Dryvax to be immunogenic, one can, by inference, expect that it would still be effective in young children. Therefore, this one panel member concludes: "this study is unnecessary."

An examination of the protocol and reports by the panel of experts, underscores the pitfalls of the current research protection system: those who evaluate clinical trials through the lenses of the federal regulations (45 CFR 46.404—408; 21 CFR 50.51-54) tend to ignore the overarching moral issues. By focusing entirely on the imperfectly formulated regulatory sections in isolation, they tend to approve experiments in which the welfare of some children will be compromised—as if they were "canaries in the mines"—contradicting the Maryland Court of Appeals landmark decision, which affirmed the right of children to be protected from research that is not in their best interest.<sup>17</sup> All too often research gatekeepers accommodate research proposals that expose children to pain and risk of harm, by accepting a claimed "benefit from study participation" where none can be demonstrated. This tendency reveals a systemic flaw and a deep schism between those who approve research and those who are recruited for research. Vulnerable, less fortunate children are unprotected from experiments involving hazards to which experts acknowledge they would not subject their own children.

The significant risks posed by exposure to the vaccinia virus vaccine do not fall into any of the permissible categories of research under Federal Regulations (45 DCF 46.404-406). Yet, two institutional review boards (IRBs) approved the study, apparently rationalizing the risks by speculating a benefit of study participation — even when none can be shown. One expert who reviewed the experiment, Dr. Robert S. Baltimore, (Yale University) claims: "In this study the participants [2 to 5 year old children] are self selected for great interest in becoming immune to smallpox," adding, "they will have received considerable information about the risks..." Dr. Baltimore further argues: "Unless these studies are done the children who are vaccinated in an emergent situation... will not be able to give informed consent." But, as Dr. Baltimore must surely know, children are NOT "self-selected" volunteers, and they are precluded from giving legally valid informed consent to research until they reach the age of majority, 18. Dr. Baltimore brushes aside the hazards associated with the smallpox vaccine, stating: "The minor discomforts of the vaccine are seen in many vaccines but do not represent a major concern."<sup>18</sup>

Dr. Baltimore's statement should give rise to deep concern among ethical and responsible professionals and government officials about whose children are being conscripted and the context and conditions of their recruitment. His statement and expectations from 2 to 5 year old children is bereft of the understanding that most parents—even those with minimal education-- have about the capabilities of such young children. The UCLA Human Subjects Submission Form states how recruitment will occur: "parents will be approached during the child's well care visit...Secondarily, we may enroll children from the surrounding community with notification of the child's primary care provider." What compelling (but misleading) argument and/or inducements will cause parents to suspend their intuitive parental caution and enroll their 2 to 5 children in a vaccine trial that is fraught with hazards and discomfort in an unnecessary vaccine dilution experiment?

**Consent Form Misleads and Misinforms Parents:**

The "informed consent" form presented to parents misrepresents the fact that the children sought—in Cincinnati and Los Angeles — are not at any particular risk of exposure to smallpox, and would, therefore, be unlikely to benefit from the vaccine if no attack occurs. Furthermore, the consent form fails to provide parents with forthright, illustrated information about the nature of the known severe adverse reactions to the vaccine.<sup>19</sup> Parents are told about \$120 in reimbursement and a \$40 gift certificate for those children who complete the study—even before they are (nonchalantly) "informed" about risks. Indeed, the report by Dr. Neal Halsey, a member of the expert review panel, notes, "The consent document should provide more complete information and avoid language that minimizes the potential risks from this vaccine. Specifically...there is no mention that 1/3 of adults who received Dryvax had sufficient discomfort and /or inability to use their arm that they missed school or work. " Furthermore, the consent form misinforms and misleads parents with repeated false assurances: "As with all vaccines or drugs, there is the possibility that your child could develop an allergic reaction..."

The consent documents fail to inform parents about plans underway requiring states to submit plans for providing rapid response clinics to vaccinate the public, should a smallpox infection occur in the United States. Therefore, it is untrue to claim that pre-emptive vaccination offers any benefit for these children.

**If the Informed consent document is inaccurate, the research is unapprovable.**

As has been noted, the consent documents for the smallpox vaccine trial mislead parents about the extent of risk and likelihood of severe adverse side effects. This is another example of the inadequacy of the research review process by local institutional review boards (IRBs) to protect the interests of children. IRBs had approved the faulty consent documents. This case

demonstrates the special need for additional oversight to protect children from harmful experiments. The Alliance for Human Research Protection has called for the establishment of independent, Children Protection Committees (in addition to review by IRBs) to serve as the child subjects' advocates, monitoring their selection, assessing the reasonableness of their parents' consent, and ensuring that the informed consent signed by parents is in fact informative.

**If a bioterrorist attack occurred, would the smallpox vaccine protect these children ?**

The rationale given to parents who would be solicited to volunteer their children for Dryvax vaccine demonstrates how they can be misled to believe their children are at risk of exposure to smallpox, and the vaccine trial will protect them. But there is no evidence of a known risk of exposure to smallpox for these children. Therefore, the potential benefits of vaccination do not outweigh the risk of vaccine complications. Universal vulnerability to the rapid spread of smallpox — if released anywhere—may continue to deter its use. Knowledgeable experts, such as Meryl Nass, MD, have pointed out that although the vaccine is effective against the outbreak of smallpox as a natural disease, the situation in biological warfare may be very different, and the precautions used against the former may be of little use against the latter. The terrorists' goal is to maximize virulence: they may enhance infectivity by selecting (or creating) pathogens to which genes for antibiotic resistance and vaccine resistance may have been added. This means that protective measures that are effective in routine disease situations may fail when confronted with a bioterrorist attack. Terrorists may pick any number of pathogens for which there is no vaccine — such as, tularemia, plague, ebola, or an encephalitis virus—rather than a pathogen for which the targeted population has been vaccinated, or maintains a vaccination capability.

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<sup>1</sup> Centers for Disease Control. June 22, 2001. Vaccinia (Smallpox) Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP) 2001. Morbidity & Mortality Weekly Report

<sup>2</sup> Lane JM, et al. Complications of smallpox vaccination, 1968: results of ten statewide surveys. *J. Infectious Disease*, 1970; 122: 303-9.

<sup>3</sup> Lane JM. Editorial. Smallpox vaccination served great purpose, but was not always benign, *Infectious Disease News*, March 2002

<http://www.infectiousdiseaseneews.com/200203/frameset.asp?article=quested.asp>

<sup>4</sup> Frey SE. et al Clinical responses to diluted and undiluted smallpox vaccine. *New England Journal of Medicine*, April 25, 2002, 346: 1265-1274.

<sup>5</sup> Henderson DA, Inglesby TV et al. June 9, 1999. Smallpox as a biological weapon (Consensus Statements of the Working Group on Civilian Biodefense). *Journal of the American Medical Association*. 281:2127-37.

<sup>6</sup> Manning A. Smallpox vaccine carries a dose of risk. *Daily Times of Pakistan*. Nov 28, 2002.

[http://www.dailytimes.com.pk/default.asp?page=story\\_28-11-2002\\_pg4\\_13](http://www.dailytimes.com.pk/default.asp?page=story_28-11-2002_pg4_13)

<sup>7</sup> Chase M and Hill G, Ugly Side Effects of Smallpox Vaccine Color Terror Plans, *Wall Street Journal*, Oct 21, 2002, front page.

<sup>8</sup> World Health Organization. 2001. Smallpox. *Weekly Epidemiological Record* 76.

<sup>9</sup> Garrett L. 2000. Betrayal of Trust. New York: Hyperion.

<sup>10</sup> Marshall E. Bioterror Defense Initiative Injects Shot of Cash. vol 283 pp 1234-5).

<sup>11</sup> Henderson DA, Inglesby TV et al. June 9, 1999. Smallpox as a biological weapon (Consensus Statements of the Working Group on Civilian Biodefense). *J of the American Medical Association*.

<sup>12</sup> Gillis, J, Okie S U.S. mounts smallpox vaccine push. *The Washington Post*. October 28, 2001.

<sup>13</sup> Altman L, At the Health Department, the Messengers Still Stumble *The New York Times*, October 8, 2002:

<http://www.nytimes.com/2002/10/08/health/policy/08DOCS.html?pagewanted=print&position=top>:

Elias M, Smallpox vaccinations: A shot in the dark *USA TODAY*, October 7, 2002

[http://www.usatoday.com/news/health/2002-10-07-smallpox-vaccines\\_x.htm](http://www.usatoday.com/news/health/2002-10-07-smallpox-vaccines_x.htm)

<sup>14</sup> FDA website: <http://www.fda.gov/ohrms/dockets/dockets/02n0466/02n0466.htm>

<sup>15</sup> Principle 2, Nuremberg Code. <http://ohsr.od.nih.gov/nuremberg.php3>

<sup>16</sup> Carey WB. Personal correspondence.

<sup>17</sup> Maryland Court of Appeals. Higgins vs. Kennedy Krieger Institute, Aug. 16, 2001.

[www.courts.state.md.us/opinions/coa/2001/128a00.pd](http://www.courts.state.md.us/opinions/coa/2001/128a00.pd)

<sup>18</sup> Baltimore R Opinion. <http://ohrp.osophs.dhhs.gov/dpanel/baltimore.pdf>

<sup>19</sup> CDC slides at: <http://phil.cdc.gov/Phil/results.asp?page1>