A Multicenter, Randomized, Dose Response Study of the Safety, Clinical and Immune Response of Dryvax® Administered to Children 2 to 5 Years of Age *(sic)*

Consultative review—Attn: Dr. Greg Koski (OHRP) & Dr. David LePay (FDA)

This is an interesting study that raises substantive issues scientifically, politically, ethically, procedurally and from a regulatory perspective. The background is straightforward, if a bit complex.

Smallpox was eradicated clinically in 1977; routine vaccination has not been recommended in North America since 1971, and very few people have been vaccinated since 1982. There exists a vaccine that has been stockpiled since discontinuation of manufacture in the early 1980s; it was highly effective and reasonably safe, but there was a small incidence of very severe reactions and a considerable incidence of nuisance reactions. It is a crude product by today's standards, prepared from bovine (vaccine-strain cowpox) lymph; it has a large number of incidental proteins and a low but significant bacterial content; it contains antimicrobial agents. The stockpile has been variously described as sufficient for 7 million to 20 million doses when administered by rocking intradermal application of a bifurcated needle that had been dipped in the vaccine (or passed through a drop of vaccine on the skin).

The research stockpiles of smallpox virus were not all destroyed, and there is concern that there may be large amounts available for use in a hostile manner—either as "weaponized" aerosol or as delivered by suicidal human vectors. Moreover, it could be possible to reconstruct the virus from genomic information. There is therefore growing concern that the low population immunity to smallpox could make many countries (including the US) vulnerable to a terroristic introduction of the virus.

There are many reasons to believe that such a scenario is unlikely—most obviously the probability of "blow-back" outbreaks as the virus is spread within a mobile population (that is, the perpetrators' country of origin is likely also to be hit). However, recent graphic demonstrations of suicidal readiness among terrorists make the scenario hard to dismiss completely.

The obvious long-term solution would be to nullify the threat by vaccinating the population as had been done routinely prior to 1971. This has several practical problems:

- The number of doses available is insufficient to vaccinate the population, and gearing up production anew would not necessarily be fast;
- The vaccine that exists is old. It is not made to modern safety and purity standards, and there is at least the theoretical concern that safety and efficacy could have deteriorated (a low level of ongoing use to vaccinate people occupationally exposed to orthopox viruses has not demonstrated such problems convincingly, but there has been some concern that the adverse event incidence *might* be higher).
- Because the risk of terrorist use of smallpox is difficult to assess and is probably low, it is hard to be comfortable that the small but real incidence of serious vaccine reactions is tolerable

Thus, this solution seems best if it is done only after a modern sterile, axenic vaccine with demonstrated safety and efficacy—better that the old material—is available. That leaves a time window during which we're stuck with an insufficient vaccine stockpile.

An interim solution would take advantage of the fact that even post-exposure vaccination is highly protective against death; indeed, "ring" vaccination strategies were important to the eradication of clinical smallpox in places where universal vaccination was hard to effect. Even for this approach, the number of doses available is insufficient.

Taking that a step further, one could dilute the vaccine such that each recipient got a smaller number of virions, essentially removing the "dose cushion." Indeed, there have been studies with several hundred adults indicating that 1:5 and 1:10 dilutions of the vaccine still yield a high proportion of successful "takes."

There are no corresponding data in children, and such a response strategy would presumably include vaccinating children. The current investigators propose to compare undiluted vaccine with 1:5 diluted vaccine in 40 children between the ages of 2 and 5. This age range was chosen for several theoretical and practical reasons:

- Children over about age 8 are immunologically pretty mature, and generally respond as adults in vaccine trials; thus, it is argued, little is gained by doing adolescents first.
- Children under age 1 historically had the highest incidence of severe and life-threatening adverse reactions, so their exclusion seems appropriate—especially as long as the risk of bioterrorist use of smallpox remains speculative.
- Newly-vaccinated individuals shed vaccinia virus for as long as 30-60 days, so including children of school age would increase the risk of inadvertent secondary exposure to same.

The specific study under scrutiny would randomize children in this age range to receive routine vaccination or to undergo exactly the same procedure with a 1:5 dilution of the vaccine. Cutaneous evidence of "take" will be

recorded; special dressings will attempt to minimize inadvertent auto-inoculation at other sites (such as the eyes) or inadvertent allo-inoculation; samples will be obtained to measure seroconversion.

The principal difficulty in evaluating this study ethically and against the federal research regulations is the uncertainty of vaccine risk, the uncertainty of smallpox risk, and the dependence of benefit (of study participation) upon the reality of smallpox risk.

Two IRBs have approved the study, apparently judging the benefit of study participation sufficient to offset the risks. The decision at one center was not unanimous and was arrived at only after long and substantive deliberation. A third IRB found the study potentially meritorious, but also found that it could not approve it under 45 CFR §46.404, §46.405, or §46.406, and therefore forwarded it for special review under 45 CFR §46.407.

45 CFR §46.404 (21 CFR §50.51). Federal regulations provide that research involving children may be conducted if it entails no greater than minimal risk. Minimal risk is defined as risk that has no greater probability and magnitude of harm than do the risks of ordinary life (including such things as non-invasive diagnostic studies). The IRB referring the study for consideration under 45 CFR §46.407 did not feel that the research met the "minimal risk" criterion, and neither do I. But the argument is not entirely silly, so it warrants a few words of discussion. Childhood immunizations are among the risks of ordinary life, and this was once a routine childhood immunization. That being said, it was *discontinued* as a childhood immunization because it did have occasional severe reactions and the disease against which it was protective was no longer a threat. In the face of a consensus that the risk and benefit are not in appropriate *clinical* balance, it is hard to opine that this is "minimal risk" unless one really believes the smallpox risk to have become great enough to alter the clinical balance assessment. The referring IRB seems to have found that too speculative. Moreover, there are additional risks that are small, but that might be considered problematic in such small children (*e.g.* blood samples not co-ordinated with clinical need). Combining these factors, I agree that this would be hard to approve under 45 CFR §46.404.

45 CFR §46.405 (21 CFR §50.52). Federal regulations also provide that research may be performed on children in the face of greater than minimal risk, if that research also provides a benefit to the participants/subjects that is sufficient to offset the risk. This is the usual rubric under which clinical trials are approved, for example. This is a better fit to the protocol before us, but the referring IRB thought the benefits were too speculative to offset risk. Again, I agree with their assessment. The benefit to the subjects is that many of them will be successfully vaccinated and thus will be immune to smallpox.[•] That would be a huge benefit if there were in fact to be an attempt to use smallpox as a weapon, and if the child now being vaccinated were to be put in the line of transmission. The difficulty in accepting this as an offsetting benefit derives from the difficulty knowing whether this is a fantastically remote possibility or a real threat. As in considering 45 CFR §46.404, I do not find this argument completely without merit, but I find it inconclusive in supporting the approval of this research under this provision.

45 CFR §46.406 (21 CFR §50.53). Federal regulations also provide that research may be performed on children when there is risk without offsetting benefit (and by inference when there is risk with only partially offsetting benefit). For this provision to be applicable, the risk must be only a "minor increase" over minimal risk, the risks must be commensurate with the ordinary risk experience of the specific study subjects, and the research must be likely to yield important generalizable information about the subjects' "disorder or condition." The referring IRB opined that the risk was more than a minor increase over minimal risk; the denotational vagueness here is such that the point could be argued either way. Regardless of the decision on that specific point, I think the research fails to qualify under this provision because the subjects do not have an identifiable "disorder or condition." At the heart of this regulation is the concept that a benefit to the group to which the subject belongs might suffice to offset a small amount of additional risk that the subject bears. I agree with the assertion that a "condition" need not be medical to satisfy this regulation (it could be, for example, socioeconomic), but "normal children who lack smallpox immunity and might conceivably be exposed to a terrorist attack" is a descriptor of ALL children in the U.S., and seems beyond the regulatory intent.

45 CFR §46.407 (21 CFR §50.54). Having found it difficult to approve the research under 45 CFR §46.404, 405, or 406, the IRB appropriately turned to the provision allowing special consideration for research that seems appropriate

[•] Also mentioned in the consent documents is the benefit to *society;* that is not germane to the question of satisfaction of 45 CFR §46.405, because altruistic risk-bearing is ordinarily acceptable only for people who can be their own consent authority: altruism imputed in the absence of consent has other names, like "exploitation."

despite its failure to satisfy the requirement of one of the other categories. In order for this provision to be invoked, the IRB must find that

- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- the research will be conducted in accordance with sound ethical principles;
- adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians

and the Secretary of HHS must (after due consultation and a period for public comment) rule on the matter.[*]

The third bulleted point is the easiest to address. The children are all young enough that assent will not be sought. Instead, the emphasis is on making the experience of vaccination and blood drawing as non-threatening as possible.[†] Permission from a single parent is being sought, while the regulatory requirement under 45 CFR §46.408 is for *both* parents or guardians (if indeed there are two) to give permission. The consent form has problems, but is not beyond repair. **This point is therefore not satisfied, but the deficiency is remediable.**

The second bulleted point is more difficult of exegesis. What constitutes "sound ethical principles?" One may certainly find evidence of great care in the planning of this research. The group at greatest risk of vaccination complication—children under age two years—has specifically been excluded. The group that is useful to study but likely to spread vaccinia to others—school children—has also specifically been excluded. Care has been exercised to exclude others at risk, such as those with histories suggestive of diminished immune function. A dressing known to limit free shedding of virus is being used, to limit the risk of heterotopic autoinoculation or alloinoculation. Contingency plans have been put in place for the small possibility of a severe reaction requiring antiviral therapy (including off-label use of an anti-CMV drug with activity against vaccinia and including securing the availability of vaccinia immune globulin under IND). The consent form is better than most at frankly disclosing the fact that there are uncommon reactions that could be life-threatening. Safety monitoring is in place, though relatively few details are provided (specifically how one might decide that the adverse event experience is excessive). The sample size is appropriate for the primary endpoint.

The draft guidance document available indicates that risk/benefit balance must still be reasonable, that there must be a real reason that children must be used, that there should be special explanation or justification for risk-bearing research in *normal* children and in children deriving no direct benefit.

As I consider this, it appears that it becomes analogous in many ways to the calculus in considering 45 CFR §46.406: if the risk/benefit balance is not quite where you'd like it to be, or if it's hard to be sure just where that balance is, one asks if there is enough *public health* benefit to offset that problem and allow the research to go forward. **Thus, the concept of "sound ethical principles" is entwined with the question of opportunity to generate important knowledge; to the degree that they are separable, I think this study was planned with attention to sound ethical principles.**

This brings me to the first bullet: Does the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children? This is trickier than it looks at first blush. That is, a "serious problem" may be a problem that is especially severe or one that is especially common; smallpox would certainly qualify as "especially severe," given that it historically had a case mortality approaching 30%. But is it really a problem "affecting" the health or welfare of children? That depends upon the credibility one assigns the risk that smallpox will actually become a weapon of biological attack or bioterrorism. That is, smallpox is certainly not a problem that currently affects the health or welfare of children *directly*, but the *risk of smallpox* could be such a problem if it is credible enough. Guesses as to the likelihood of weapons use of smallpox vary widely; the most common opinion seems to be that it is just credible enough to worry about, given its potential to be devastating. I personally think it is very unlikely that it would be used by someone wishing to preserve his own people from harm, but that there could be people desperate enough to use it if cornered. An unanswerable question is whether anyone at risk to use it actually has access to it; more specifically on point, could anyone actually have the wherewithal to use smallpox as a weapon before we could develop a vaccine that's safer than the one being used in this study? The "reasonable opportunity" and "sound ethical principles" ideas again intersect—whose probability guesses about these unknowns should guide the Secretary? In the draft guidance document's discussion of "sound ethical principles," point #4 reads:

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[*] Allowing or disallowing the research under 45 CFR §46.407, or ruling that it is actually allowable under 45 CFR §46.404, 405 or 406

[†] It is mentioned that people specifically experienced in drawing blood from small children will be used, but I did not find mention of such comfort measures as EMLA

> **"It is essential to consider the perspectives of the children affected by the disorder or condition and their parents or guardians in deciding whether information to be gained from research upon children is of vital importance and relates to a serious problem affecting the health or well-being of children."**

In many other contexts we assert that the ultimate arbiter of the risk/benefit balance is the person bearing the risk: thus, there is a need for information and consent. A useful part of the process, here, may be to present the study to the parents/guardians much more pointedly, including language of the general flavor of: "We don't know if an attack by smallpox is a one-in-a-million chance or a one-in-fifty chance. The risk of serious harm to your child from the vaccine is very small, but it's high enough that we stopped using this vaccine when natural smallpox became rare. If you are unsure whether this study is important enough for that risk to be acceptable, you should think about it and remember that you're entirely free to say 'no.'" A reminder that risk is being accepted for a speculative benefit would have the advantage of being forthright, while at the same time gauging whether that is an acceptable scenario from the perspective of the subjects' parents or guardians (whose risk tolerance may be different from that of the investigator or from mine).

Also within the concept of "reasonable opportunity" are the concepts of scientific validity, timeliness and feasibility. Scientific validity here is good insofar as the primary endpoint of vaccine "take." Twenty subjects in each group will yield a fair idea whether the diluted vaccine will retain enough potency to be a good public health tool in children. With respect to safety, the study is unlikely to be informative (even though "safety" is listed first in the [garbled] title). The serious adverse events in routine smallpox vaccination occurred at incidences of one in tens of thousands, and fatalities occurred at a few per million. A 40-person sample has only about a 35% chance of detecting a serious event occurring at an incidence of 1%, and an incidence of about 7.5% is necessary for that sample to have a 95% probability of detecting it. The study is otherwise feasible; timeliness is a more complex issue.

The study is timely if it is anticipated that there will be a long enough time until a new vaccine is available—such that this study can be completed and a strategy based on its results can be in place for a significant period of time (put simply: if it won't be a waste of time). The study is *not* timely if the next generation of vaccine will be ready to enter clinical trials before the proposed study can be carried out or very soon after its completion—a possibility that has specifically been suggested in some news reports and even congressional testimony (but about which I have no primary information).

I believe that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, but I recognize that (a) the actuarial nature of the problem may lead to differences of opinion, including selective acceptance of the study risks by prospective participants, and (b) if a new vaccine is close to readiness for clinical trials, this proposal may not be timely.

Nitty-gritty: Returning briefly to the third bullet, the consent process deserves a bit more scrutiny in a special case such as this one. The most serious issues are:

- Satisfying the regulatory requirement that both parents/guardians grant permission unless one is unavailable (etc.)
- Responding to the unusual nature of the risks in this study by frankly disclosing that uncertainty about the likelihood of smallpox attack make all the benefits—both personal and public-health—highly speculative.

A few less-important consent issues are also worthy of attention:

- The last sentence on the first page is incorrect. "5 times as much Dryvax" and "5 times as many vaccine doses" are not equivalent concepts.
- Formulaic wording in places introduces confusion rather than clarity
- Describing the vaccine study as "experimental treatment" is disingenuous
- Benefits description is also problematic: listing altruistic satisfaction as a benefit in a study of children ages 2-5; listing smallpox immunity as a benefit *before* saying that there may be no benefit; listing "no benefit" possibility only in terms of immunization failure; listing the absence of charges for research procedures as a benefit; listing non-interference with routine care as a benefit
- Heading of "alternatives" section is confusing, and is obviously meant for a study that is standing in place of customary therapy
- Discussion of retained samples has no information about confidentiality and privacy
- Blanket consent is given for unlimited use of surplus samples *even if* the "no" box for such use is checked (concept is re-introduced downstream from options)
- Blanket consent is solicited for record review and photocopying, rather than what is actually needed—permission for record review for data verification; why this insensitivity to privacy?
- Exculpatory language is used in Section 10

<u>Conclusion:</u> I concur with the referring IRB's findings that this study is hard to approve under 45 CFR §46.404, 405 or 406. I also concur that it is potentially approvable under 45 CFR §46.407, though I would be more restrictive.

- **Because the public health danger addressed by the study is extremely speculative, the benefits of participation are also very speculative and frank disclosure of this issue is essential to making sure that the risk/benefit balance the investigators have deemed acceptable is also acceptable to the parents or guardians of the children being studied.**
- **Further, if the study is in fact not timely because of the pending availability of a more modern vaccine for testing, it should not be done.**

<u>Comment:</u> As implied by some of my comments above, I am concerned about the precedent that would be set in allowing this study. It should be unusual that a substantive risk be allowed to be borne without offsetting personal benefit by someone incapable of being his or her own consent authority. The justification of the risk in terms of public health benefit is highly speculative, so I may well have advised differently—denying even my very tentative and conditional acquiescence—if the product being tested were one for which we did not have an extensive safety record. In this specific case, we can say with fair confidence that the risk of truly threatening adverse event is quite small, and that safety profile has been considered in selection of the specific target population for study. Also in this specific case, we can say that the vaccine under study *was* in the relatively recent past a standard childhood immunization, so it *would* 30 years ago have been considered an ordinary risk of childhood. Those considerations were key in reaching my conclusion.

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