Report of the
Defense Science Board Task Force
on

Smallpox Vaccine Down Select Process

Report Summary

May 2004

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This report is a product of the Defense Science Board (DSB). The DSB is a Federal Advisory Committee established to provide independent advice to the Secretary of Defense. Statements, opinions, conclusions, and recommendations in this report do not necessarily represent the official position of the Department of Defense.

OFFICE OF THE SECRETARY OF DEFENSE
3140 DEFENSE PENTAGON
WASHINGTON, DC 20301-3140

DEFENSE SCIENCE
BOARD

MEMORANDUM FOR THE ACTING UNDER SECRETARY OF DEFENSE
(ACQUISITION, TECHNOLOGY AND LOGISTICS)

SUBJECT: Final Report Summary of the Defense Science Board Task Force on Smallpox Vaccine Down Select Process

I am pleased to forward the Final Report Summary of the DSB Task Force on Smallpox Vaccine Down Select Process, which was chaired by Dr. George Poste. The Task Force was tasked to perform an independent evaluation of the Department of Defense and Department of Health and Human Services smallpox vaccine candidates.

The Task Force developed a set of scientific and manufacturing related criteria to evaluate the smallpox vaccine candidates. Using this set of evaluation tools, the Task Force was able to perform a qualitative evaluation of the smallpox vaccine candidates. The results of this evaluation are contained in the full report. Additionally, valuable the criteria matrix developed during the course of this study should be a valuable tool is accessing other DoD vaccine programs.

Furthermore, the Task Force strongly recommends that DoD continue to maintain a close relationship with a vaccine R&D group/company in order to respond to potential biological threats to our armed services.

I endorse the recommendations of this Task Force and propose you forward the report summary for distribution and comment.

William Schneider, Jr
Chairman

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I. INTRODUCTION: A SHORT HISTORY OF EFFORTS TO ERADICATE SMALLPOX

Early Attempts at Immunization and the Vaccinia Vaccine

In the 17th century, physicians in China blew powdered smallpox scabs into sinuses and prepared pills made from the fleas of cows. In India, physicians applied scabs to the scarified skin of the healthy. This technique migrated westward to Turkey where it was discovered by western physicians. Other early attempts to control smallpox included inoculation with material from smallpox lesions. This practice was known as variolation.

In 1796, Edward Jenner noted that milkmaids were free of the facial scars that marked most of the population of that time. The observation that they "cannot take smallpox" was attributed to the localized pox lesions that they developed in their hands. Jenner reasoned that infectious material from cowpox (caused by the vaccinia virus) lesions provided protection from smallpox (caused by the variola virus). He used it to vaccinate an 8-year-old boy. The boy later resisted infection, demonstrating the efficacy of the first vaccine.

The World Health Organization (WHO) Smallpox Eradication Program

Epidemics of smallpox inflicted mankind throughout history, and as recently as 1967, 10-15 million cases were still occurring annually in more than 30 countries. On 1 January 1967, the World Health Organization (WHO) launched the Intensified Smallpox Eradication Program. The program's initial strategy was to rely solely on mass vaccination, an approach that successfully eradicated smallpox in Western Europe, North America, Japan, and other areas. However, eradicating the disease via mass vaccination alone proved untenable in densely populated countries such as India. Nevertheless, forced to fight outbreaks in Kenya in 1966 and India in 1970 with a constrained supply of vaccine, the WHO developed a more effective strategy of surveillance and containment coupled with mass vaccination. This evolution in strategy eventually led to the elimination of smallpox. Smallpox is the only major human disease to have been eradicated.

The success of the eradication program required the capability to produce (at high volume) potent and reliable vaccines and an efficient and inexpensive means of delivering the vaccine. Three major technological innovations greatly facilitated the smallpox program: the development of the ability to mass-produce high-quality freeze-dried vaccine in several countries, the development of the hydraulic-powered jet injector, and the development bifuricated needle.

Although these innovations were milestones in the smallpox campaign, the program would not have succeeded without the ingenuity and creativity of the field staff, which surmounted a host of local problems. Important innovations such as smallpox recognition cards, watchguards, rewards, rumor registers, and containment books all came from fieldworkers.

The smallpox eradication program of 1967 was guided by a plan that embraced the two complementary approaches of mass vaccination campaigns and surveillance systems.

The WHO program functioned in a collegial structure of many independent national programs. As a result, programs differed greatly from one country to another, as well as from one time period to another.

II. CURRENT VACCINATION METHODS & INITIATIVES

Current U.S. Military Smallpox Vaccination

With the eradication of smallpox worldwide, vaccinations against this disease were ended. When it was learned, however, that the Soviet Union had weaponized smallpox and that other countries (including Iraq and North Korea) may have been able to obtain the virus, the United States determined that it was necessary to vaccinate its forces following procedures outlined in DoD Directive 6205.3, "DoD Immunization Program of Biological Warfare Defense." The DoD's Smallpox Vaccination Program is consistent with Food and Drug Administration (FDA) guidelines and the best practice of medicine. This program supports the national smallpox preparedness plans, but is tailored to the unique requirements of the Armed Forces. Under the program, DoD ensures preparedness by immunizing selected personnel. Selection is based on occupational responsibility; high-priority occupations include smallpox epidemic response teams and hospital workers and other designated forces having critical mission capabilities (for example, those forces essential to accomplishing the U.S. Central Command's mission).

Current Smallpox Vaccine Initiatives

On 2 October 2002 the Undersecretary of Defense for Acquisition, Technology, and Logistics (USD(AT&L)) requested the Defense Science Board stand up a task force to identify the criteria by which the Department of Defense would select the next smallpox vaccine from a list of various candidates available at the time. The DSB Smallpox Down Select Process Task Force (SDTF) stood up under the leadership of Dr. George Poste.[1]

The task force's terms of reference included several key parameters by which the SDTF would develop the criteria. These parameters included an assessment of:

- The cell line and viral strain to be used;
- Preclinical data;
- Vaccine production methodology, to include rates of production and surge capacity;
- Protocols for clinical trials, including adverse reaction rates;
- Cost issues related to production of the vaccine;
- Critical regulatory, legal, and ethical issues; and
- Any other relevant issues.

The task force met several times from December 2002 through October 2003 and developed insights into the status of the vaccine candidates. These insights allowed us to

[1] Appendix A contains the task force's terms of reference. Appendix B lists the task force membership.

inform some of the requests for information which would guide the specificity of the criteria, and their subsequent discriminatory power. In addition, we believe the companies actually benefited from some of the requests for data and feedback from the SDTF, and that this allowed us to better characterize the criteria as they applied to each of the candidate vaccines.

The appended chart contains the definitions the task force used in the analysis of the criteria. These definitions constitute a basis of consistent assessment of the criteria for all candidates. Appendix C also contains the important characteristics considered in studying each of the parameters, provides a risk assessment for that parameter as it applies to each product, highlights the preferred method the task force applied to that specific parameter, and lists the type of information requested from each candidate company as it related to that parameter at the time of the request.

III. RECOMMENDATIONS

1. Candidate overall assessment

The Task Force developed a matrix using the developed criteria (Appendix C). A matrix (containing proprietary information) was populated for the smallpox vaccine candidates. These matrices are contained in the full report.

2. DoD vaccine expertise

The Task Force strongly recommends that DoD continue to maintain a close relationship with a vaccine research and development group/company in order to respond to potential biological threats to our armed services.

Appendix A

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A. TERMS OF REFERENCE

THE UNDER SECRETARY OF DEFENSE

3010 DEFENSE PENTAGON
WASHINGTON, DC 20301-3010

ACQUISITION, TECHNOLOGY AND LOGISTICS

02 OCT 2002

MEMORANDUM FOR CHAIRMAN, DEFENSE SCIENCE BOARD

SUBJECT: Terms of Reference -- Defense Science Board Task Force on the Smallpox Vaccine Down Select Process

Request you form a Defense Science Board Task Force to perform an independent evaluation of the Department of Defense and Department of Health and Human Services smallpox vaccine candidates.

The Task Force should evaluate each of the three smallpox vaccine candidates to include the following type of issues.

1. Choice of cell line and viral strain used.
2. Preclinical data in appropriate animal models.
3. Review of vaccine production methodology to include rates of production and surge capacity.
4. Review protocols for clinical trials to include adverse reaction rates.
5. Review cost issues as they relate to production of the vaccine.
6. Review critical regulatory, legal, and ethical issues associated with the use of the vaccine.
7. Any other issues that the Task Force feels, based on its experience, are relevant.

The Study will be co-sponsored by me and the Assistant to the Secretary of Defense (Nuclear and Chemical and Biological Defense Programs). Dr. George Poste will serve as chairman of the Task Force. LTC Robert Borowski, USA, from the Office of the Deputy Assistant to the Secretary of Defense (Chemical and Biological Defense) will serve as Executive Secretary; and CDR Brian Hughes, USN, will serve as the Defense Science Board Secretariat representative.

The Task Force will operate in accordance with the provisions of P.L. 92-463, the "Federal Advisory Committee Act," and DoD Directive 5105.4, the "DoD Federal Advisory Committee Management Program." It is anticipated that this Task Force will participate in "particular matters" within the meaning of section 208 of Title 18, U.S. Code. The Defense Science Board will work with the General Counsel's office to resolve any potential or actual conflicts.

E. C. Aldridge, Jr.

Appendix B

Membership

B. TASK FORCE MEMBERSHIP

CHAIRS

Mr. John Dingerdissen	*Private Consultant*
Dr. George Poste	*Health Technology Networks*

MEMBERS

Dr. Barry Bloom	*Dean of the Faculty of Public Health*
Dr. Robert Couch	*Baylor College of Medicine*
Dr. Rebecca Devine	*Private Consultant*
Dr. Jerome Donlon	*Public Health Emergency Preparedness*
Dr. Dorothy Margolskee	*Private Consultant*
Dr. Richard Whitley	*University of Alabama*

GOVERMENT ADVISORS

LTC Robert Borowski	*Senior Medical Advisor, DATSD*

EXECUTIVE SECRETARY

Dr. Joseph Palma	*Deputy Assistant to the Secretary of Defense/CB*

DSB SECRETARIAT

CDR David Waugh	*Defense Science Board*

SUPPORT

Ms. Michelle Ashley	*SAIC*
Ms. Allison Balzano	*SAIC*
Ms. Cara Sievers	*SAIC*

Appendix C

Overview of Definition Criteria

C. OVERVIEW OF DEFINITION CRITERIA

Parameter	Important Characteristics	Parameters Driving Risk Assessment	Preferred method	Requested Information
Product specifications/ description	Liquid vs lyophilization; storage conditions; # doses per vial; potency (i.e. PFU/ml) to assure appropriate dose with bifurcated needle.	Availability of cold chain; ease of administration; best stability profile & longest shelf life.	Lyophilized product if more stable; $\geq$24 month shelf life (longer duration preferred); refrigerator storage of sufficient duration to allow vaccination of military in the field; 10^8 PFU/ml. Product, dose & method of administration (including dilution if applicable) must be fully licensed by FDA prior to use by DOD.	Product profile of candidate vaccines from companies.
Cell culture substrate	Cell type used; Master & Working Cell Bank characterization; number & results of release assays; vaccinia virus yields (PFU/cell)	Prior FDA approval (yes/no); Detailed history (i.e. GMP documentation of passages, sources of raw materials with especial note of animal-based products etc.); results of adventitious agent testing. Previously unapproved continuous cell lines (e.g. Vero) represent a regulatory risk. Virus infectivity/ cell productivity (PFU/cell) critical to assure manufacturing capacity & vaccine supplies.	Must pass required ICH guidelines, including full battery of adventitious agent testing selected on basis of cell passage history etc. Prior FDA approval & sourcing of original cell premaster from FDA or other approved source would be optimal to start premaster, master & working cell banks.	Details re cell line, characterization & release data. FDA reviews, comments re cell line.
Source of vaccine stock seed	Compliance with general ICH guidelines where possible. Identification of source; full history details (including passage descriptions, starting material lists & sourcing, with special note of animal derived components). Adventitious agent testing results available & acceptable.	ICH guidelines & general safety expectations drive regulatory risk assessment. Potential exists for unknown adventitious agents in original sample (associated with prior passage in animals).	Stock seed derived from demonstrated clinically-effective vaccine is preferred. Additional passages past the original vaccine lot, especially passages in cell substrates as opposed to animals (cow, sheep) may alter clinical efficacy/ safety profile. ICH guidelines should apply, including adventitious agent testing, sterility, potency etc. Results must be acceptable to FDA & clinical community with respect to vaccine safety.	Details re stock seed characterization & release data, including detailed list of adventitious agents in screening assay.
Source of vaccine stock seed (con't)	Vaccine virus chosen for expansion & subsequent use as seed lots.	Stock seed may require procedures to optimize sterility, etc. However, clonal selection could alter anticipated vaccine performance (either efficacy or safety).	Prefer vaccine stock seed that has not been cloned, since vaccinia virus characteristics that correlate with clinical safety & efficacy are unknown.	Details re vaccine stock seed source, history.

	Vaccine virus strain & association with clinical efficacy; # passages from original clinically-proven material	Passage history past clinically proven material may alter vaccine performance (especially efficacy)	Limiting cell-based passages to ~1or 2 past clinical material is preferred.	Details re vaccine relationship to clinically proven material, # & details re subsequent passages etc.
	Nature of passages (animal, cell-based, type of cells)		Prior animal passages preferable to cell-based passage if passage history extends past 1-2 cycles	
Seed lot analysis & release	Compliance with general ICH guidelines; development, validation (yes or no) & utilization of vaccinia-vaccine specific assays.	Historically, plaque assay, chick allantoic membrane (CAM), rabbit scarification & suckling mouse LD50 assays were used. Need to establish whether 2nd & 3rd will be required for release (may be hard to validate - may be possible to run as characterization "for information only").	Choice of potency assay(s) will need confirmation with FDA. Results from all assays would be useful for information, given lack of data correlating potency assays with clinical efficacy. Reincarnation of past assays may need standardization vs "gold standard" - because of difficulties with that approach, FDA may accept plaque assay as release & others for information only. Needs to be negotiated/confirmed.	Details re potency assays & their validation (if possible). Criteria for success. Release assays. Results. FDA correspondence, communications if any.
Master virus seed characteristics	Proposed identity & potency assays for release; extent of passage allowed past original stock seed; assay results compared to "gold standard"; nonclonal origin (but if needed "clean-up" from original stock seed, how was this done?)	Passage alters phenotype of vaccinia virus, with unknown impact on potency.	Conservative approach would minimize passages to 1-2 past stock seed, if possible. Productivity (PFU/cell) becomes a critical issue to minimize passage number. Anticipate yields of 10-50 PFU/ cell or better.	Details re potency assays & their validation (if possible). Criteria for success. Release assays. Identification of vaccine denoted as "gold standard". Assay results for both "gold standard" & for master seed.
cGMP production of cell banks	ICH & GMP compliance documented			ICH & GMP compliance documented
Manufacture of clinical material & incorporation of full scale manufactured vaccine in consistency lots/ Phase III clinicals	Process, scale, impact of scale on productivity, identity potency etc. Formulation definition, stability program & results.	Scale can impact vaccine performance (safety & efficacy parameters). Productivity (PFU/cell) is again a critical issue to minimize passage number, assure manufacturing capacity & subsequent vaccine supply. Shelf life of frozen product at least 24 months (longer is preferred). Acceptable stability at 2-8 degrees (refrigerator) for at	Phase III should be performed with consistency lots manufactured at full scale.	Documentation. Current status, process & purification steps; plans for scale up. Formulation development, results of stability testing etc.

		least 3 months required for military use.		
Preclinical safety assessment package.	Studies required by FDA - LD50, local tolerability. New guidelines include safety in 2 species (which) & reproductive toxicology studies. Will neurovirulence studies be required?	Safety evaluations on original vaccine did not require current-day standards. Monkey neurovirulence testing, reproductive toxicology studies may be required. If so, would need to compare results to a "gold standard" (Dryvax?). Method to show "equivalency" would need confirmation with FDA.	Wyeth "Dryvax" recently re-licensed & therefore may be acceptable as "gold standard". Discussions with FDA needed.	Results to date & plans. FDA communications if any.
IND status	Contents of IND filing. FDA response. General clinical plan & FDA feedback. Endpoints for safety, tolerability.		Any vaccine that has passed initial IND approval to proceed to Phase I is preferred to one still in preclinical (implies FDA initial approval of vaccine source, safety testing etc).	Development status of vaccine candidate. IND sections.
Clinical assays	Development & validation of immunogenicity assays, including measurement of antibody responses (ELISA, plaque neutralization) & cell-mediated responses (cytotoxic lymphocyte killing - CTLs and/or ELI-spot assay).	Development of cell-mediated immunity assays requires significant effort & care with respect to sample handling etc. For all immunogenicity assays, correlation of efficacy not established & will require attention during Phase I-II clinical trials (comparison to Dryvax-induced responses).		Information re current assay development, results etc.. FDA communications, if any.
Clinical studies & results	Safety, tolerability, comparison to Dryvax, including results of immunogenicity assays noted above.	Designation of "efficacy" parameters past "take". Will FDA require other immunologic assays as primary endpoints & if so, what will be the "cut-offs" for acceptable results, given no established correlation to clinical efficacy?	Phase I revaccination study in healthy adults followed by primary vaccination of naïve adults. Phase II rollout of vaccinations across age groups (including older adults & children ages 5-18 y.o.), with attention to take rates, immunologic assay results versus positive control (Dryvax, full strength) to determine size of Phase III.	Results of both safety & immunogenicity assessments to date. Populations studied & # subjects per age group. Frequency & size of cutaneous lesions associated with "take" & comparison to active comparator (Dryvax, full strength). Data regarding ELISA, plaque neutralization & cell-mediated immunity assays. Plans (or results) of Phase III clinicals. Level of commitment to Phase IV monitoring.
Clinical package for BLA approval	Extent of Phase III: FDA-required # of subjects by age; endpoints (& similarity to Dryvax?). Plans to provide Vaccinia Immunoglobulin (VIG) to manage potential adverse events in field use/ marketed use.	Safety: infrequent but severe adverse experiences (occurring at 10 - 70/10^6 doses) will not be characterized in Phase III. Efficacy: is "take" sufficient as a primary endpoint?	Because of concomitant vaccinations required for military recruits prior to deployment, label should provide guidance & allow concomitant administrations when possible. Availability of VIG should be assured prior to use in the field.	

Final manufacturing process & facility	Yield, consistency, capacity, cost.		Facility already inspected & approved by FDA preferred. Any documentation re FDA or other government audits of interest in assessing risk.	Status & plans.
Company history	Demonstrated record of FDA approvals for vaccines (yes/no); management capabilities, technical expertise for live virus vaccine development & manufacture; sophistication of key regulatory & research personnel	Successful manufacture & commercialization of live virus vaccines are extremely challenging activities. Until a company & its technical staff have demonstrated their success in bringing a live virus vaccine to market, their endeavor should be considered high risk. Demonstrated ability with small molecule drugs, biologics and/or protein-based vaccines should not be considered sufficient, given the unique requirements for live virus vaccine products.		Company history. CVs of management & key technical staff associated with project.
Company capabilities	Scale of manufacturing facility; demonstrated technical expertise; willingness to perform post-licensure studies; level of motivation	Technical staff expertise in live virus vaccines will drive level of risk. Major delays in program can be incurred if attention to detail & compliance with regulatory expectations are not taken into account.	Regulatory staff experienced in dealing with live virus vaccines & CBER requirements mandatory. Integration of regulatory, bioprocess, analytical, clinical, clinical assay groups mandatory. Availability of well-integrated, thoughtful strategy, plan & timeline with project details projecting out through BLA would provide some assurance of technical know-how.	
Other comments/ risks				

Appendix D

Acronyms

D. ACRONYMS

DHHS	Department of Health and Human Services
DoD	Department of Defense
DSB	Defense Science Board
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
ICH	International Congress of Harmonization
IND	Investigational New Drug
PFU	Plaque Forming Unit
SDTF	Smallpox Downselect Task Force
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USD(AT&L)	Undersecretary of Defense for Acquisition, Technology, and Logistics
WHO	World Health Organization