Report on Biological Warfare Defense Vaccine Research & Development Programs

July 2001

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Executive Summary

Section 218 of the Floyd D. Spence National Defense Authorization Act for Fiscal Year 2001, Public Law (PL) 106-398 (at Appendix A) requires the submission of a report to the congressional defense committees on the acquisition of biological defense vaccines for the Department of Defense (DoD). As required by section 218, PL 106-398, this report addresses: 1) the implications of relying on the commercial sector to meet the DoD's biological defense vaccine requirements; 2) a design for a government-owned, contractor-operated (GOCO) vaccine production facility; 3) preliminary cost estimates and schedule for the facility; 4) consultation with the Surgeon General on the utility of such a facility for the production of vaccines for the civilian sector and the impact of civilian production on meeting Armed Forces needs and facility operating costs; and 5) the impact of international vaccine requirements and the production of vaccines to meet those requirements on meeting Armed Forces needs and facility operating costs.

Since 1998, senior leadership has amplified the focus on resolution of difficulties in securing a ready and reliable access to safe and effective vaccines for use against biological warfare agents. As part of the DoD's vaccine initiative, DoD contracted with Science Applications International Corporation (SAIC) to select an independent panel of experts to assess the DoD acquisition of vaccine production programs and report their recommendations for improvement to the Deputy Secretary of Defense. The panel prepared a report to reflect its independent opinions for consideration by DoD. This report (at Appendix B) discusses vaccine industry constraints and concludes that the size and scope of the DoD program is too large for either DoD or industry alone. It recommends the application of a combined, integrated approach by DoD and industry, coupled with better alignment with industry best practices. The Department is studying the Panel's recommendations.

Substantial advancement has been accomplished in defining the scope and operating concepts for a DoD GOCO vaccine production capability. A preliminary 25-year life cycle cost estimate for such a facility would be approximately $1.56 billion. This estimate includes approximately $386 million for designing, building and validating the facility, $915 million for operations and $259 million for other government costs. The facility would accommodate three bulk vaccine production suites and modular design would allow for expansion. A preliminary projected schedule would allow for production to begin approximately seven years after project start, with the current anthrax vaccine having highest priority. Moreover, the Department consulted with the U.S. Surgeon General about the development of a GOCO vaccine production facility and in his letter (at Appendix C), he encourages DoD to proceed with its plans.

The actions above have significantly aided in analyzing the issues associated with securing vaccines to protect our forces.

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Introduction

Over the past decade, since the Gulf War, it has become most evident that the Department of Defense (DoD) must secure ready and reliable access to safe and effective vaccines for protection against biological warfare agents. Vaccines, coupled with effective immunization policy for safeguarding the force from biological warfare agents, are the most effective technological method for enabling successful force projection to any global region where vital interests of the United States are contested.

Since 1998, senior leadership from the Department of the Army—the DoD executive agency for biological warfare defense—and from the Office of the Secretary of Defense has amplified our focus on resolution of difficulties in securing a ready and reliable access to safe and effective vaccines for biological warfare defense. It is a policy imperative that vaccines—regardless of their source of manufacture—that are intended for force health protection are licensed by the Food and Drug Administration (FDA). The current DoD vaccine acquisition strategy focuses on the development of eight vaccines: Anthrax Vaccine Adsorbed (AVA), Smallpox, Plague, Tularemia, Multivalent Botulinum, Next Generation Anthrax, Ricin, and Multivalent Equine Encephalitis.

As a part of the DoD's vaccine initiative, DoD contracted Science Applications International Corporation (SAIC) to select an independent panel of experts to assess the DoD acquisition of vaccine production programs and report its recommendations for improvement to the Deputy Secretary of Defense. Additionally, substantial advancement within the DoD and across federal, non-DoD agencies has been accomplished in defining the scope and operating concepts for a DoD government-owned, contractor-operated (GOCO) vaccine production capability. These actions together have significantly aided in analyzing the issues associated with securing vaccines to protect our forces.

The following report is organized according to the report content requirements prescribed by section 218 of Public Law 106-398 (Appendix A), which are in bold type.

1. **The Secretary's evaluation of the implications of reliance on the commercial sector to meet the requirements of the Department of Defense for biological warfare defense vaccines.**

In the congressional hearings on the Department of Defense's Anthrax Vaccine Immunization Program before the Senate Armed Services Committee on July 12, 2000, and before the House Armed Services Committee on July 13, 2000, the former Deputy Secretary of Defense, Mr. Rudy de Leon, testified that he asked the Acting Assistant Secretary of Defense for Health Affairs and the Director of Defense Research and Engineering (DDR&E) to contract with a private organization to provide an independent review of the Department's management of vaccine procurement. The purpose was to provide for an independent third party to give the Department both advice and to further ensure that our efforts are credible, consistent and effective with the use of public monies in this area.

The DDR&E funded this study and assigned the study support task to SAIC using an existing contract delivery order. A panel of experts, with expertise in the scientific, regulatory and industrial aspects of vaccine production, and Federal procurement, was assembled by the contractor, SAIC, to conduct the study. SAIC solicited nominees from industry and the government for potential panel members and contacted them about their willingness and availability to participate in the vaccine study effort. SAIC's recommendations of potential panel members were reviewed and accepted by DoD. The Panel Chair was fully responsible for and directed the Panel's effort. DoD and the SAIC staff provided support and assistance as requested by the Panel Chair.

On November 29, 2000, the panel of experts presented their findings to the then Deputy Secretary of Defense, that the scope and complexity of the DoD biological warfare defense vaccine requirements were too great for either the DoD or the pharmaceutical industry to accomplish alone. To put in perspective, within the United States, vaccines are currently licensed to protect against approximately 20 diseases, whereas the DoD biological warfare defense program alone requires vaccines to protect against almost an equal number of disease-causing, biological warfare agents. In addressing this requirement, the Panel agreed with the DoD vaccine acquisition strategy, which focuses initially on a limited set of approximately eight vaccines. The Panel recommended that a combined integrated approach whereupon DoD would work closely with the vaccine industry and national scientific base, both private and public, to develop and produce the vaccines that DoD needs would be a more effective acquisition strategy. The Panel reported that this approach must draw upon the acquisition management expertise of the DoD, incorporate the best practices of the pharmaceutical industry, and draw on national scientific and technical strengths.

At an eight-vaccine scale, the Panel estimated that the DoD acquisition of vaccine production program would require between $2.4 and $3.2 billion in research and development costs over a 7- to 12-year period. The Panel also agreed with the DoD plan to consider construction of a dedicated GOCO production facility with an initial production capacity of three to four products, pilot production and scale-up capacity. Resources for a GOCO were roughly estimated by the Panel at $370 million in initial construction. This estimate is very much in line with the DoD's estimate of $386 million in military construction (MILCON) for a GOCO vaccine production facility.

The independent panel felt strongly about the benefits of long-term government commitment, increased resources, innovative DoD business and program management practices, and effective participation by established pharmaceutical industry leaders in vaccine discovery, licensure, and manufacturing. However, it must be recognized that many of the Panel's recommendations are at variance with Departmental policy, the existing vaccine acquisition strategy, as well as acquisition and procurement practices. The report[1] prepared by the independent panel is provided at Appendix B. The Department is studying the Panel's recommendations.

2. A design for a government-owned, contractor-operated facility for the production of biological warfare defense vaccines that meets the requirements of the Department for such vaccines, and the assumptions on which that design is based.

A 35 percent design for a GOCO vaccine production facility (VPF) was completed for the DoD in 1993. Shortly thereafter, the DoD vaccine acquisition strategy was changed to a prime systems contractor, rather than a GOCO, approach. This was done in anticipation that established private sector pharmaceutical manufacturers would support DoD vaccine production requirements. This strategy has not worked as well as expected. The 35 percent design prepared in 1993 was used as the basis for a November 2000 concept study and estimate prepared by Bio-Pharm Technologies, a division of Day and Zimmerman, International, Inc. (DZII). The purpose of the latter study was to develop a new conceptual cost estimate and schedule for design, construction, fit-up, and qualification to FDA regulatory requirements for vaccine development, licensure, and manufacturing as promulgated in Title 21 Code of Federal Regulations (21CFR), Food and Drugs.

Major planning assumptions used for the November 2000 conceptual study and estimate for the DoD GOCO VPF included the following.

- Large, well-established, pharmaceutical industry (i.e., vaccine) manufacturers are unlikely to reverse their decades-long trend of relatively inconsequential support of DoD vaccine production requirements.
- DoD must develop and acquire a second, licensed manufacturing source for anthrax vaccine adsorbed (AVA) and other high priority vaccines for force protection.

[1] Volume I summarizes the discussions and findings of the independent panel. Volume II contains copies of briefings and documents provided to the Panel, and was not prepared or approved by the panel. Therefore, it is not being forwarded.

- DoD critical needs and reliance on vaccines for force protection, coupled with the two previous assumptions, dictate that the DoD be the federal lead agency for the GOCO VPF.
- The GOCO facility must contain flexible and expandable manufacturing capacity for licensed production of eight DoD-critical vaccines, including AVA, which is licensed to BioPort Corporation, Lansing, Michigan.
- Licensed vaccine production should begin in fiscal year (FY) 2008 with early emphasis on AVA manufacturing.
- The DoD GOCO must contain three bulk production suites, one for each of the following processes:
  - spore-forming bacteria (i.e., AVA)
  - microbial fermentation
  - tissue culture (viral vaccines)
- GOCO manufacturing capabilities must be sufficiently flexible to support expansion that is sufficient to accommodate high priority needs for protection of civilian populations, both foreign and domestic, and to effectively respond to changing biological weapons threats.
- On-site capabilities for animal testing are necessary.
- On-site quality control laboratories are necessary.
- Support spaces (administrative offices, warehouse, and utilities) must be sufficient for an eight product scale and expandable to accommodate potential contingencies.

Table 1 shows the vaccine production assumptions of the first eight DoD-critical products. An architectural drawing showing the relative space utilization for the different functions is shown in Figure 1. Alternative designs will be solicited and evaluated as one of the bases for selecting the contract operator(s) for the facility.

Table 1. Vaccine Production Assumptions

Product Name	Production Process
Anthrax Vaccine, Adsorbed (AVA)	Bacterial spore-forming
Smallpox Vaccine	Cell culture
Plague Vaccine	Recombinant fermentation
Tularemia Vaccine	Fermentation
Multivalent Botulinum Vaccine	Recombinant fermentation
Next Generation Anthrax Vaccine	Recombinant fermentation
Ricin Vaccine	Recombinant fermentation
Multivalent Equine Encephalitis Vaccine	Cell culture

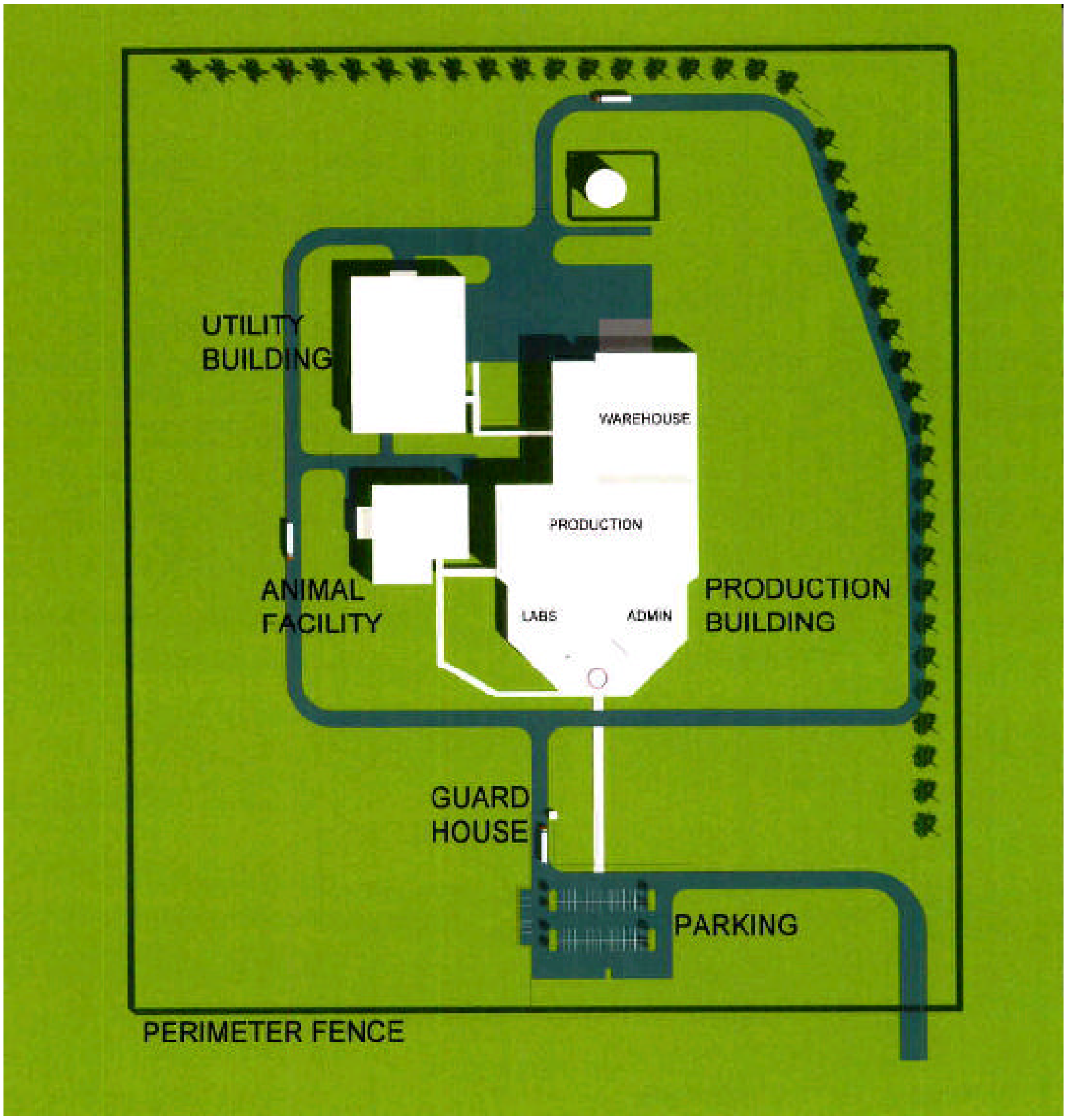

Figure 1. Architectural Drawing of DoD GOCO Vaccine Production Facility

3. A preliminary cost estimate of, and schedule for, establishing and bringing into operation such a facility, and the estimated annual cost of operating such a facility thereafter.

Using data provided in the concept study and estimate prepared by DZII, Science Applications International Corporation (SAIC) prepared a life cycle cost estimate (LCCE) for the design, construction, FDA qualification, and operation through FY 2026 of a DoD GOCO VPF. SAIC applied the following ground rules, assumptions, and major constraints to develop the LCCE.

- Ground Rules:

  - Cost estimates are developed in base year 2000 dollars (BY00$)
  - January 2000, Office of the Secretary of Defense (OSD) Inflation Indices were used.
  - The DoD GOCO VPF life cycle is 25 years starting in FY02.
  - Licensed production will start not later than FY08 and priority will be given to AVA production.
  - No surge capacity is planned for the GOCO VPF. However, maximum production rates are planned for each suite. This equates to a "dedicated suite" concept for vaccines that are planned.
  - No contingency requirements are planned in the LCCE.
  - Only DoD biological defense vaccines will be produced in the 25-year life cycle for the GOCO VPF.

- Assumptions:

  - National Environmental Policy Act (NEPA) compliance will require 2 years. However, design can be initiated after the first year's NEPA activity.
  - Site selection will require approximately 6 months and may start in FY01. The LCCE assumed a generic site.
  - Vaccines will be stored in vials at the GOCO VPF—no bulk storage—until released for use.
  - Product yields are based on technical estimates and likely to change.
  - AVA capacity during the first year of operation is 50 percent.
  - Product shelf life was assumed to be 3 years for AVA and 2 years for all other vaccines.
  - The Joint Vaccine Acquisition Program biological warfare defense vaccine development and licensure schedule, dated 3 October 2000, was used.
  - The GOCO VPF will be built using military construction and a design-build (i.e., "turn-key") contracting strategy.
  - The acquisition strategy will include competitive award to two contractors and subsequent performance competition with down-select to one contractor at 35 percent design point.

- Major constraints:
  - Assumptions for each vaccine to be produced:
    - Tier 1**:** Current requirements
      - AVA for entire force
      - 300,000 Troop Equivalent Doses[2] (TEDs) for other vaccines
    - Tier 2: 3 million TEDs for force protection
      - 2.4 million for U.S. forces + 0.6 million for Commanders Reserve, Other-than-U.S.-forces, and Canada-U.K.-U.S. Memorandum of Agreement
      - Stockpile plus annual requirement for several vaccines
      - Basis for the GOCO facility design
    - Tier 3: 300 million TEDs for civilian protection
      - Approximation for total U.S. population
      - *Beyond the baseline operating scope of the GOCO facility design*
  - Vaccine production will be as shown in Table 1 and use the three suites at maximum capacity as needed to fulfill requirements.
  - Fermentation with spore-producing bacteria (i.e., AVA) requires a dedicated production suite.

Preliminary costs for designing, building, and validating the GOCO VPF are estimated to be $386M ($CY). The LCCE for operations would be approximately $915M over the 25-year life cycle that equates to an average annual operating cost estimate of $36.6M. The LCCE for other government costs are estimated to be $259M ($CY). A preliminary projected schedule is shown in Figure 2.

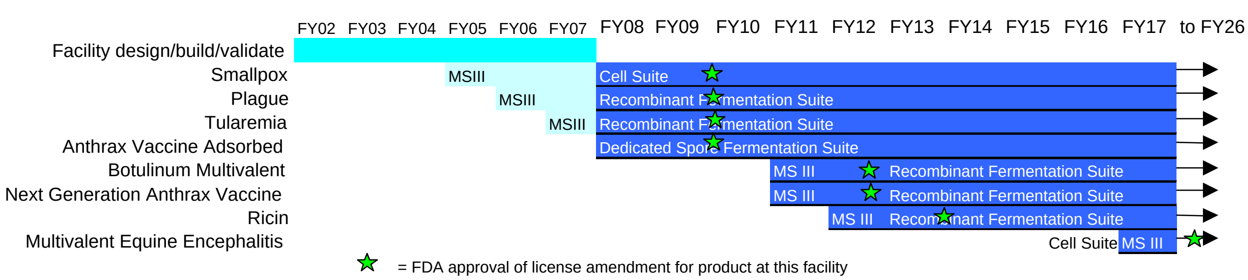

Figure 2. DoD GOCO VPF Product Schedule

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[2] Troop equivalent dose is defined as the number of vaccine administrations required to reach the required immunity. Boosters are not included.

4. A determination, developed in consultation with The Surgeon General, of the utility of such a facility to support the production of vaccines for the civilian sector, and a discussion of the effects that the use of such a facility for that purpose might have on:

(a) the production of vaccines for the Armed Forces; and
(b) the annual cost of operating such a facility.

Relatively early in the process of considering DoD alternatives for vaccine acquisition, the Department established a Federal Interagency Advisory Group on the DoD GOCO VPF. Participants, in addition to those from DoD agencies, have included representatives of the White House [Office of Science and Technology Policy, National Security Council, Office of Management and Budget], Federal Emergency Management Agency, Department of Health and Human Services (DHHS) [National Institutes of Health, Public Health Service, Food and Drug Administration, Centers for Disease Control and Prevention, and the Office of the Assistant Secretary for Health and The Surgeon General]. This group, chaired by the Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense (DATSD(CBD)), has served as a highly effective and productive forum for discussions concerning U.S. vaccine acquisition—particularly vaccines for defense against biological warfare agents—for force health protection and public health needs for the civilian sector.

The DATSD(CBD) met with The Surgeon General of the United States on January 5, 2001 to discuss the status and plans for a DoD GOCO VPF for force health protection against biological warfare agents. They also discussed the issues posed in point 4, above, particularly, the utility of the GOCO for production of vaccines for the civilian sector and effects that might have on production of vaccines for force health protection and facility costs. The Surgeon General has addressed these points in a letter at Appendix C.

The Surgeon General recognized that biological warfare agents, even if targeted at a military force, could cause severe, primary or collateral civilian casualties. He agreed that a GOCO VPF could assure the availability of the vaccines for fulfilling military needs, as well as eventual use in the civilian sector, should such a contingency arise. The Surgeon General also observed that civilian participation could contribute to the successful planning and operation of the GOCO VPF. The Surgeon General stated that it is important that the GOCO VPF have sufficient flexibility to accommodate evolving production requirements, both for new vaccines and for fulfilling future civilian sector needs.

The DoD GOCO VPF will manufacture FDA-licensed vaccines. The FDA licensure requirements for vaccines intended for both DoD and civilian sector needs are stipulated in 21 CFR. The Surgeon General noted in his letter that the lists of biological weapons agents confronting the civilian sector are very similar to those under consideration by the DoD in its planning for the DoD GOCO VPF. Vaccines manufactured in the DoD GOCO VPF will be effective when used by civilian populations for their FDA-licensed indications.

The Department welcomes the continued support and participation of DHHS in our GOCO VPF planning. We agree that such civilian support and participation contributes to successful design, construction, and licensed production of vaccines for force health protection against biological warfare agents. Fulfilling armed forces vaccine requirements and applying the GOCO vaccine production capacity to meet civilian sector requirements—beyond those production requirements for the armed forces—should enhance successful operation and contribute to public acceptance.

Finally, the DoD GOCO VPF design is intentionally flexible and planned to accommodate changing production requirements, both in quantity and vaccine diversity. Annual operating costs for vaccine production are proportional to the production requirements and until the expanded production requirement is defined, there is no solid basis for estimating increased annual operating costs. Despite this, it should be noted that there is a great deal of agreement between cost estimates developed in the DoD GOCO VPF LCCE and the report by the independent panel of experts (Appendix B) who place annual operating costs of vaccine production at between $35M and $50M per vaccine. There may be economies of scale in expanding the GOCO once it is in licensed production, rather than in de novo construction for added capacity or product diversity.

5. An analysis of the effects that international requirements for vaccines, and the production of vaccines in response to those requirements, might have on:

(a) the production of vaccines for the Armed Forces; and
(b) the annual cost of operating such a facility.

The DoD GOCO VPF would produce vaccines licensed by the FDA. Most commonly, vaccines licensed by the FDA are acceptable for their licensed indication in worldwide populations. Some nation states have testing requirements that are different from, or are in addition to, FDA requirements and those would have to be addressed on a case-by-case basis. Since the primary objective of the DoD GOCO VPF would be to produce vaccines to meet armed forces health protection against biological warfare agents, and since DoD use is not impacted by other than FDA licensure requirements, there should be no impact on production for the armed forces. As with the DoD GOCO VPF annual operating costs to support civilian sector needs, the annual operating costs are expected to increase in proportion to the size and diversity of the international vaccine requirements. Unless and until such requirements are characterized, realistic vaccine production capacity and the associated cost estimates cannot be provided.

APPENDIX A

Public Law 106-398 – October 30, 2000
Floyd D. Spence National Defense Authorization Act
For Fiscal Year 2001
Section 218. Report on Biological Warfare Defense Vaccine Research and Development Programs

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APPENDIX A

PUBLIC LAW 106-398 – OCTOBER 30, 2000; FLOYD D. SPENCE NATIONAL DEFENSE AUTHORIZATION ACT FOR FISCAL YEAR 2001

SEC. 218. REPORT ON BIOLOGICAL WARFARE DEFENSE VACCINE RESEARCH AND DEVELOPMENT PROGRAMS.

(a) REPORT REQUIRED - Not later than February 1, 2001, the Secretary of Defense shall submit to the congressional defense committees a report on the acquisition of biological warfare defense vaccines for the Department of Defense.

(b) CONTENTS - The report shall include the following:

(1) The Secretary's evaluation of the implications of reliance on the commercial sector to meet the requirements of the Department of Defense for biological warfare defense vaccines.

(2) A design for a government-owned, contractor-operated facility for the production of biological warfare defense vaccines that meets the requirements of the Department for such vaccines, and the assumptions on which that design is based.

(3) A preliminary cost estimate of, and schedule for, establishing and bringing into operation such a facility, and the estimated annual cost of operating such a facility thereafter.

(4) A determination, developed in consultation with the Surgeon General, of the utility of such a facility to support the production of vaccines for the civilian sector, and a discussion of the effects that the use of such a facility for that purpose might have on--

(A) the production of vaccines for the Armed Forces; and

(B) the annual cost of operating such a facility.

(5) An analysis of the effects that international requirements for vaccines, and the production of vaccines in response to those requirements, might have on--

(A) the production of vaccines for the Armed Forces; and

(B) the annual cost of operating such a facility.

(c) BIOLOGICAL WARFARE DEFENSE VACCINE DEFINED - In this section, the term “biological warfare defense vaccine: means a vaccine useful for the immunization of military personnel to protect against biological agents on the Validated Threat List issued by the Joint Chiefs of Staff, whether such vaccine is in production or is being developed.

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APPENDIX B

Department of Defense Acquisition of Vaccine Production Report to the Deputy Secretary of Defense by the Independent Panel of Experts Volume I – December 2000

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Department of Defense Acquisition of Vaccine Production

Report to the Deputy Secretary of Defense by the Independent Panel of Experts

Volume I

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DEPARTMENT OF DEFENSE ACQUISITION OF VACCINE PRODUCTION (AVP)

REPORT TO THE DEPUTY SECRETARY OF DEFENSE BY THE INDEPENDENT PANEL OF EXPERTS

VOLUME I

DECEMBER 2000

This document reflects the independent opinions of the Vaccine Study Panel and should not be construed as the official position of the DoD.

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EXECUTIVE SUMMARY

By memorandum dated July 20, 2000, the Deputy Secretary of Defense tasked the Director, Defense Research and Engineering and the Assistant Secretary of Defense for Health Affairs to jointly contract with a private organization or panel of experts to conduct a comprehensive study of the Department of Defense (DoD) acquisition of vaccine production (AVP). The study was to focus on review of the following areas:

- Vaccines to protect Service members against biological warfare threats as well as infectious diseases.
- A comparison of current Department efforts with best business practices in the biologics industry, and if/how the Department can leverage the best aspects of the private sector programs from industry.
- A determination whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.
- The development of recommendations for how the Department should best develop and oversee a vaccine production program.

An independent panel of experts (the Panel) was established and assessed DoD's AVP requirements and ongoing programs, management, and acquisition processes against U.S. vaccine industry best practices.

The Panel found that:

- BW and endemic diseases are proven, high consequence threats to military operational effectiveness.
- Vaccines are the lowest risk, most effective protection; they enable force projection and are superior to antibiotics or other treatments.
- DoD's current AVP approach is insufficient and will fail.
- A new approach can make this program work.

The size and scope of DoD vaccine requirements for force protection are exceptionally large. DoD requires new vaccines to protect against 15 or more biological warfare (BW) and endemic diseases. By comparison, vaccines licensed for use in the U.S. protect against about 20 diseases and Merck & Co., Inc. manufactures 9 licensed vaccines. The size and scope of the DoD program is too large for either DoD or industry alone. A combined, integrated approach drawing on industry, DoD, and national scientific strengths and assets is essential.

DoD needs to consolidate and integrate its vaccine research, development, and acquisition programs for BW defense and endemic disease protection. Success requires a tailored acquisition model and infusion of technically qualified staff at all levels. A Joint Program Executive Officer must have responsibility and authority for the program and report to a designated acquisition executive, a Vaccine Acquisition Executive reporting to the Under Secretary of Defense (Acquisition, Technology and Logistics). The DoD vaccine acquisition program should be managed as an Acquisition Category I program and—on an 8 vaccine scale—requires a $3.2 billion research and development program. A government-owned and contractor-operated vaccine production facility is an essential element of the DoD program. DoD senior leadership must meet with and solicit industry support for its vaccine requirements.

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1.0 INTRODUCTION

In response to a memorandum dated July 20, 2000, from the Deputy Secretary of Defense (DEPSECDEF), the Director, Defense Research and Engineering (DDR&E) and the Assistant Secretary of Defense (Health Affairs) [ASD(HA)] jointly took action establishing the independent panel of experts (Attachment II of Appendix A) to review Department of Defense (DoD) acquisition of vaccine production (AVP). The Panel operated independently of the DoD and consisted of diverse scientific, manufacturing, and regulatory expertise. It was supported by the Deputy Assistant to the Secretary of Defense for Chemical/Biological Defense [DATSD(CBD)] and the Director, BioSystems, Office of the Deputy Under Secretary of Defense (Science and Technology) [ODUSD(S&T)] and by Science Applications International Corporation (SAIC) under a contract with the Office of the Director, Defense Research and Engineering (ODDR&E). The DEPSECDEF requested that the study by the independent panel of experts focus on the following areas:

- Vaccines to protect Service members against biological warfare (BW) threats as well as infectious diseases.
- A comparison of current Department efforts with best business practices in the biologics industry, and if/how the Department can leverage the best aspects of the private sector programs from industry.
- A determination of whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.
- The development of recommendations for how the Department should best develop and oversee a vaccine acquisition production program.

The summary of the approach and process used in conducting the review and assessment is provided in Appendix A. This volume summarizes the discussions and findings of the Vaccine Study Panel. Volume II contains copies of briefings and documents provided to the Panel.

2.0 SCOPE OF TASK AND GENERAL UNDERSTANDING

The scope of the Panel's review and recommendations regarding the DoD's AVP was defined by the DoD sponsors as full life cycle, from discovery [science and technology (S&T)] through development, manufacturing, production, procurement, storage and distribution, sustainment, and useful life of vaccines. It included the DoD's vaccines for force health protection program areas of biological defense (i.e., medical countermeasures to BW threats) and defense for infectious diseases of military importance (i.e., medical countermeasures to naturally occurring diseases, endemic to different areas of the world, that adversely impact health across the full spectrum of military operations). The salient facts bearing on the problem of DoD's AVP are summarized in Table 1.

Table 1. Facts Bearing on the Problem of DoD's AVP

➢ BW and endemic diseases are proven, high consequence threats to military operational effectiveness
➢ Vaccines are lowest risk, most effective protection – Better than antibiotics or other treatments – Enable force projection
➢ Current approach is insufficient and will fail
➢ A new approach can make this program work

Inclusion of vaccines for both the biological defense program (BDP) and the infectious disease program (IDP), from a force health protection, readiness, and business perspective, had particular relevance because of the first two facts bearing on the problem. Despite perceptions of some differences between the BDP and IDP in the areas of threat, resources, industrial base, and organization and management, vaccines are a unifying technology solution that effectively and efficiently defeat these threats to the force.

The Panel focused its effort on the best way for DoD to administer, manage, and execute the DoD AVP, consistent with good medicine, efficiency, business practices, technology, priority, urgency, and cost. It included, as they apply to DoD and industry, consideration of varying aspects of:

- threat generation,
- requirements definition,
- investment and execution strategy,
- planning, programming, and budgeting (PPB),
- life-cycle process for vaccines (cradle-to-grave),
- regulatory requirements,
- process for making informed decisions, organization and reporting chains, and
- assigned responsibilities, authority and accountability.

In addition, the Panel considered industry's process and capacity for manufacturing vaccines, as well as opportunities (e.g., medical need, shared opportunity, and profit) for DoD to leverage industry capabilities and engage the commercial vaccine industry in supporting its BDP and IDP vaccine needs.

3.0 INDUSTRY BEST PRACTICES FOR VACCINE PRODUCTION

The major vaccine manufacturers licensed in the U.S. are Wyeth-Ayerst International, Inc., a division of American Home Products; SmithKline Beecham; Pasteur Merieux Connaught, a division of Aventis; and Merck & Co. Inc. The primary drivers behind the major vaccine industry's best practices and investment decisions are public health (i.e., medical need for a particular product); potential profitability (i.e., return on investment); and technological feasibility (i.e., access to a technology and its maturity). Resolving high priority public health needs fulfills humanitarian concerns and, in turn, ensures sufficient annual sales to provide a return on investment and potential for long-term profits. Since the cost (approximately $300 –

$400 million) for the research, development, and clinical trials is similar across vaccines, the industry wants first to select a medical need for which there will be high acceptability for the vaccine within the medical community. This is an important difference between industry and DoD. Although DoD generally has prioritized requirements for vaccines, it does not necessarily have the option of determining which vaccines it will develop. Resolving medical need to protect the force and enable force projection is a key DoD consideration. While industry can choose which needs to address, DoD must address threats.

The market life for older vaccines is 15–20 years [Anthrax Vaccine, Adsorbed (AVA) is approximately 30 years old]. Newer vaccines are projected to have a market life of 10–15 years. This is an element in industry's investment strategy and decision-making process. The $300 to $400 million is a cost estimate for development of a vaccine that takes 7-12 years (discovery through licensure) and does not include any associated facility capital investment. Market life is becoming shorter while development schedules remain relatively fixed and development costs increase. This translates into potentially dramatic decreases in return on investment.

It is estimated that clinical trials represent 30% - 40% of the total vaccine development cost necessary to capture every possible observation and to be able to address them to the Food and Drug Administration (FDA) in terms of demonstrated safety, potency, and efficacy. Demonstrating safety and efficacy is considered a critical part of the cost of doing business. It demands extensive quality assurance (QA) and quality control (QC) support as well as rigorous reporting.

Technology drives the early decision to develop a vaccine, forces early emphasis on process development, and defines the manufacturing process. As a result, options are tested and evaluated as early as possible. Maximizing product progress is a common industry goal in reducing risks and costs. Due to the underlying complexity of the technical processes, once a decision is made to take a vaccine candidate out of discovery and move forward, industry intensely manages the product stream from discovery through production and licensure and brings its full corporate resources to bear on the project. Risks are reduced to a manageable level prior to making the decision to go forward from the S&T base (i.e., discovery), and industry will shut a project down if it determines there is a problem. The decision to discontinue is normally based on feasibility — an analysis of technical risk. Such technical risks are mitigated by maintaining a robust S&T program of alternative constructs for products in development. Technology base activities typically receive quarterly reviews while developmental testing activities are more heavily scrutinized. Scientific and technical decisions account for the major impacts on vaccine development and licensure costs and schedules.

Decision making (responsibility, authority, and accountability) is vested by corporate executives in the management team overseeing execution of the process; that is, *industry delegates decision making to the management team collocated with the discovery and development project teams*. A generic representation of the industry model is shown in Figure 1. The management teams are multidisciplinary, typically led by a scientist with in-depth expertise and experience, and many establish written agreements or "contracts" with each of the project teams executing the different components of the overall process. Industry emphasis on individual performance and accountability is reflected in compensation reviews that commonly incorporate consideration of both team and individual performance and accomplishment.

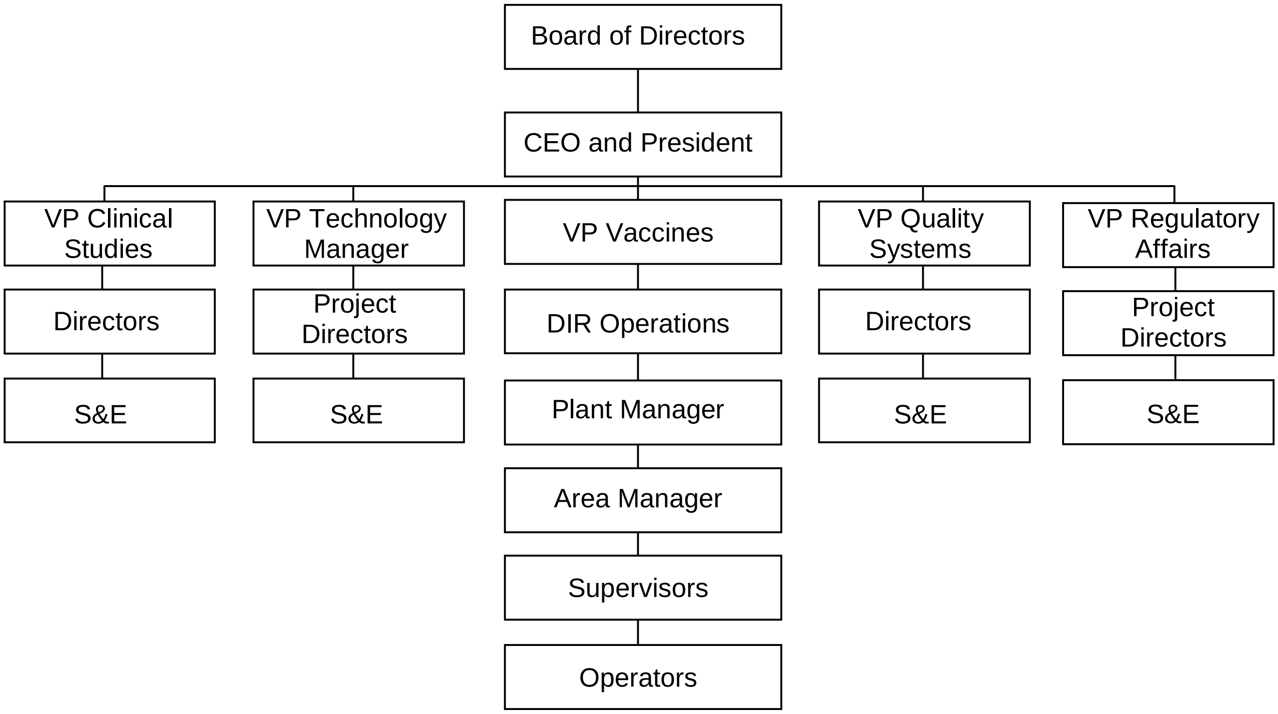


Figure 1. Generic Industry Organizational Model for Managing Vaccines

The management philosophy and approach used by industry, as summarized in Table 2, gives the management team and project teams maximum flexibility (applying the right people, skills, and resources during and at any time in the process) and accountability for success. This approach has proven highly effective and efficient within the industry.

Table 2. Industry Management Benchmarks

➢ Goal is quality product
➢ Scientific expertise at every level
➢ Problem focus for continuing improvement – Rapid assessment and decisions
➢ Mitigate risk at every stage
➢ Commitment to development and production follows successful discovery phase
➢ Empowered and accountable management teams

Another of the keys to industry's success is effective integration of all vaccine life cycle activities as outlined in Table 3.

Table 3. Successful Vaccine Acquisition

Industry Best Practices effectively integrate:
➢ Policy
➢ Product life cycle components – Research – Development – Production – Licensure – Sustainment
➢ Resources
➢ Management

The generic elements of vaccine development (discovery through production and licensure) used in industry are depicted in Table 4 and shown in a time-phased manner in Appendix B. Although specific steps may be carried out or be titled differently, this table provides a succinct overview of activities in the process. Due to the high technical risks associated with biologicals, industry generally does not consider transitioning a candidate vaccine from discovery (i.e., the industry phase corresponding to DoD's S&T phase) to product development until:

- The candidate has successfully passed Phase 2 clinical trials, and
- Solid progress has been made in the manufacturing process.

Table 4. Elements of Vaccine Development

Capacity	Function	Comments
Discovery Research	Determine mechanisms of immunity Define immunization technologies	In and out of house Develops pipeline
Vaccine Development Laboratory Research	Preclinical evaluation of immunization technology Refinement of technology	In house: requires state-of-the-art, broadly based science capability
Vaccine Manufacture Process Development	Establish technology based manufacturing process Optimize process Produce research lots	Integration of research, manufacturing, and process engineering
Phase 1 Clinical Trials	Determine initial safety and biologic activity	Intense clinical research program in a confined environment
Phase 2 Clinical Trials	Determine safety and biologic activity (immunogenicity) in modest size study group	Established clinical research program in field site clinic programs
Phase 3 Clinical Trials: A	Definitive efficacy, extended safety	Established clinical research programs, multiple sites, where disease is prevalent
Manufacturing process and assay validation	Ensure accuracy of manufacturing process and product testing	Interactions between quality control, quality management, research, and manufacturing programs
Ongoing process and assay development	Address problems arising in clinical trials, manufacturing, and testing	Consistent ongoing dimension of vaccine development; requires application of state-of-the-art research capability to problem solving
Facility development	Construction and operation of facility for scaled up manufacture	May occur before consistency lot manufacture, or for postlicensure change
Process scale up	Enhance manufacturing to commercial levels	Major process engineering issue
Phase 3 Clinical Trials: B	Consistency lot evaluation	Established clinical research programs in large field site(s)
Communications with FDA, Vaccine Advisory Committee	Define development, manufacturing, and licensing requirements	Ongoing throughout development process
Communications with vaccine recommending bodies (e.g., AFEB, ACIP)	Determine potential for vaccine usage	Determines strategy for clinical trials, manufacturing scale, and logistics
License application	Prepare and submit ~100 volume document to FDA	Defines in detail every aspect of vaccine manufacture, testing, preclinical and clinical evaluation, and the operation of all aspects of the manufacturing facility; >100FTE, >1yr
Phase 4 Clinical Trials	Determine safety of vaccine in general use	Field epidemiology at site(s) of use
Ongoing process development	Address issues that arise and ongoing product quality	Always required to address stability and related issues, and problems that arise

Each vaccine is managed on an individual basis since its associated technologies and processes tend to be very different from other vaccines. *In this regard, a manufacturer would rarely transition from discovery more than one technology lead for a potential vaccine at a time; however, every discovery program has multiple backup technologies to fall back on in those cases where the lead technology may fail.* This is true from concept to feasibility analyses throughout the investigational new drug (IND) process. Further, industry exercises integrated development production strategies that involve only a limited number of vaccines at any one time. The major supporting business practices used by industry to maximize the probability of successfully getting a vaccine to market are identified in Table 5.

Table 5. Business Practices for Product Success

➢ Product focus, not budget focus
➢ Funding stability
➢ Up-front multiyear commitment
➢ Flexible “reprogramming” authority (dollars and type)

Every vaccine needs a champion and the more champions there are the better the chances of success. *An axiom of the vaccine industry is that success demands that the staff at every level be “highly” qualified and that they be adequately compensated.* Normally there is a discovery team, not “one inventor” for a product. The discovery team serves in an advisory role during the manufacturing, testing, and production phase, but they do not lead any of these activities. The advisory role entails no more than 5% of the discovery team’s time. Industry wants their S&T discoverers to remain at the bench to the fullest extent possible, as this is where their contributions will be greatest. *Interestingly, industry often allows up to 20% of discoverers’ time to be spent pursuing independent study and research.*

Successful vaccine production is linked clearly with absolute control of the overall process, and in terms of manufacturing, it is associated with repeating the process over and over – producing a vaccine on a regular basis. Acquisition strategies that plan production for every third or fourth year are widely viewed as unrealistic and technically unfeasible. The vaccine manufacturing process does not lend itself to long breaks in production (i.e., greater than a year) since manufacturing vaccines entails three interdependent elements – validated process, scientific art, and team skills. Manufacturing start-up costs can be as high as $20 - $30 million per product and likely would have to be repeated any time there is a break in production lasting longer than 1 to 2 years. Further, it must be recognized that from an FDA perspective, if vaccines are not continuously produced so that FDA can inspect at any and all stages of manufacturing, then compliance and license problems are more likely to occur.

The vaccine industry was among the first to try outsourcing. Companies having the capacity and capability tried outsourcing manufacturing but have since pulled these operations back in-house. Unlike outsourced manufacturing of chemical pharmaceuticals, outsourcing of vaccine manufacturing was found to be fraught with difficulties, inordinate process control risks, and added overall costs. As a result, the major vaccine producers limit or do not outsource manufacturing at all. Most do not believe they will be able to operate as virtual companies for the foreseeable future. Outsourcing for other non-manufacturing activities, such as conduct of clinical trials, is possible and economically feasible.

The pharmaceutical (i.e., drug) industry has had excellent success with outsourcing its manufacturing processes. This is thought to be due to the straightforward nature of the chemistry in the manufacturing processes for drugs. The vaccine industry does much in-sourcing (in-licensing), while looking outward for ideas (e.g., buy into patents and collaborative partners). Some of the small biotechnology companies, by necessity, do outsource steps in their processes, and this is likely to continue. *It is critical that DoD carefully assess the risk associated with any strategy for the AVP that includes any major element of outsourcing*.

Pharmaceuticals (drugs) and biologics (vaccines) are different and the biologics investment and risk are incompatible with outsourcing as a preferred option. *The unique problems associated with process control during the manufacturing of vaccines provide a basis for industry's reluctance to outsource.* Industry's experience in three areas underscores their concern.

- Late changes to the vaccine manufacturing process may require additional clinical trials for safety and efficacy.
- Taking a validated process from one vaccine facility and trying to replicate it in another facility is a major undertaking, requiring revalidation of product safety and equivalence.
- Renovating and modernizing an old vaccine facility can take several years and requires revalidation of product safety and equivalence.

A wide variety of difficult scientific issues need to be addressed in a coordinated and timely fashion in the course of vaccine development. In general, precedents established previously in the course of addressing scientific problems associated with development of other vaccines are of little relevance to development of a new vaccine. In contrast, drug development tends to be much more standardized.

Industry considers people and process to be the cornerstones of successful vaccine projects. The benchmark standard of investment in human resources for an 8 product (vaccine) scale is 2,500 people with exceptional and specialized skills. This includes all aspects of the vaccine process from discovery through production and licensure. Table 6 provides a summary of the industry's benchmark investment in human resources. There is a national and international scarcity of personnel with the requisite skills and expertise needed by the vaccine industry. As a result, the industry provides extremely attractive compensation packages in their efforts to attract and retain the most qualified. Recent college graduates can have starting salaries of $40,000 to $50,000 and individuals with process validation experience are attaining salaries in the $100,000 to $120,000 range. Industry provides continuing education and training programs and expects their senior technical production personnel to be qualified in several areas of vaccine production (e.g., manufacturing, validation, and regulatory affairs).

Table 6. Industry Benchmark for Human Investment (8 Product Scale)

➢ 2,500 people
➢ Exceptional and specialized skills
– Scarce national pool
➢ Competitive compensation
➢ Special human resources programs – Recruit, train, and retain

Industry's benchmark estimate of costs associated with the major components of a vaccine program is summarized in Table 7. The estimate covers the major areas [e.g., research and development (R&D) and capital investment cost for facility] of consideration supporting a vaccine program. Process and facility improvement, an integral and critical part of industry's investment, is estimated at 5%-10% of the operational budget per year. Industry considers this cost in its market analysis and expects to fully recoup this investment from their sales of vaccines. The R&D cost estimate of $300M-$400M includes discovery through production and licensure of a single vaccine. The cost estimate of $370M to build and equip a vaccine facility includes the required initial production, laboratory, and support suites to produce three to four vaccines.

Table 7. Industry Benchmark Cost Estimates for Vaccine Programs

Element	Cost/Product
R&D	~$300M - $400M
Facility capital costs	~$370M initial*
Additional production, labs, and support	~$75M - $115M**
Manufacturing Operations and Maintenance	~$30M - $35M/year

*First 3 vaccines
**For each vaccine beyond initial 3-4

The FDA has changed a great deal over the last 10 years. Personnel from the FDA's Center for Biologics Evaluation and Research (CBER) used to conduct pre- and postlicensure inspections. Due to concerns with the regulatory oversight process, the FDA recently established Team Biologics, principally consisting of field inspectors, which now conducts biannual compliance (postlicensure) inspections. In the process of change, it is commonly perceived that the focus shifted from identifying problems and finding solutions for their resolution to one of establishing absolute compliance backed up by detailed record keeping. A warning letter that is issued by the FDA to a facility today is taken very seriously by the industry. In fact, some individuals view receipt of a warning letter as the potential end of their career. *The vaccine industry considers the regulatory environment to be extremely demanding but a necessary part of business and a part of their established best business practices.*

The research, development, and acquisition (RDA) process for vaccines — regardless of whether it is practiced by the private sector or DoD — is extraordinarily complex, highly technical and regulated, and difficult to articulate to those outside the vaccine business in a manner that enables them to grasp the complexity, interrelationship, and dependencies of the steps in the process (Figure in Appendix B and Table 4), let alone the overall problems encountered in getting a potential vaccine from discovery to market. The difference is that vaccines as biologics are produced by microbial or mammalian cells that require absolute control over the myriad aspects of production (as compared to the relative ease of control of chemical reactions and purification of drugs). In the absence of such understanding, it is difficult to fully assess the magnitude of the impact of regulatory requirements and scientific problems encountered during the process (e.g., preclinical testing, clinical trials, and scale-up manufacturing) on a program. Further, it may preclude meaningful interpretation and appreciation of why one vaccine succeeds and another fails, and hinders informed application of lessons learned in strategic and tactical decision making.

4.0 DOD ORGANIZATION, MANAGEMENT, AND CAPABILITIES

Although centralized program oversight in DoD is laudable and important, the number of organizational entities that are directly influencing the biomedical S&T BDP and IDP [U.S. Army Medical Research and Materiel Command (USAMRMC)] seems unnecessary and counterproductive (Figure 2). The same is true for the Joint Vaccine Acquisition Program (JVAP). For example, DoD organizations influencing these programs include DDR&E, DUSD(S&T), DATSD(CB), Defense Threat Reduction Agency (DTRA), ASD(HA), Joint Nuclear, Biological, Chemical (JNBC) Defense Board, Joint Services Integration Group (JSIG), Joint Services Materiel Group (JSMG), The Surgeons General, and Joint Program Office for Biological Defense (JPO BD). Further, the resultant organization has seemingly fragmented the DoD vaccine RDA program. It has placed leadership decision making for medical BDP products largely in organizations that lack the requisite level of medical and technical expertise. Similarly, leadership decision making for medical ID vaccines is in organizations that are missing the requisite level of Defense materiel acquisition expertise. Only a very limited number of offices have effectively integrated expertise in medical and technical matters with the requisite levels of Defense acquisition expertise. This impacts on the seamless delivery of vaccines in DoD.

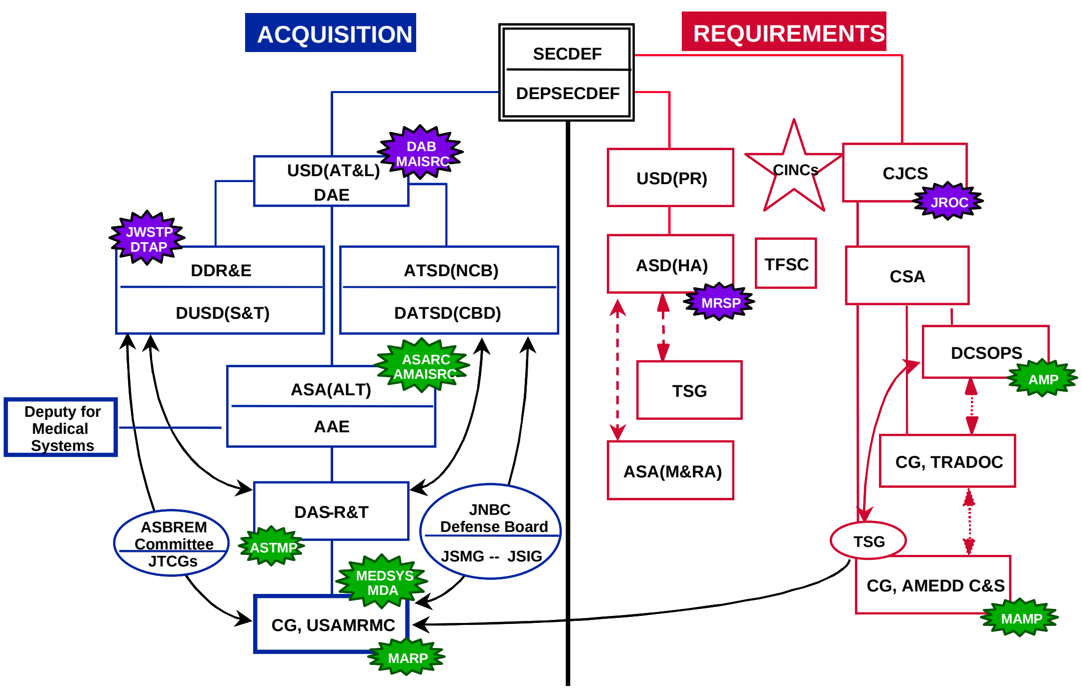
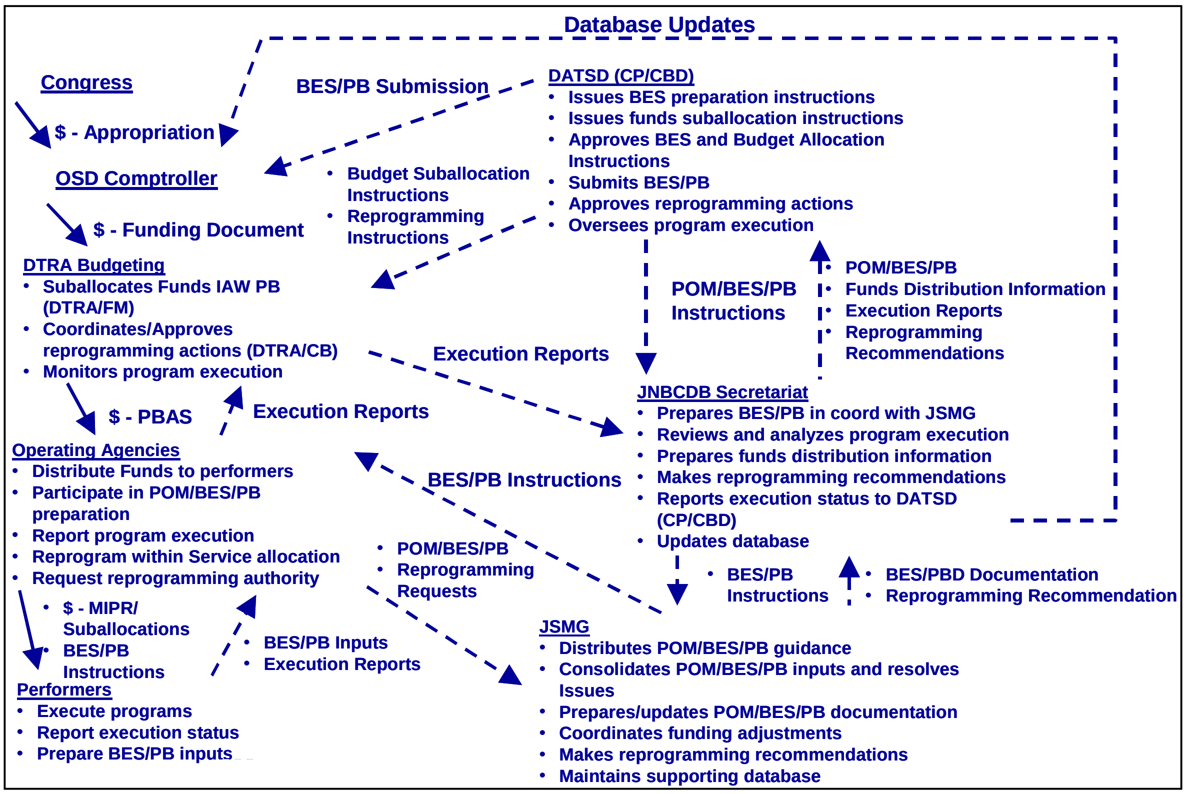


Figure 2. DoD Management Organization for Biomedical Science and Technology BDP

With regard to the organization and management, there is fragmentation of the DoD AVP within and across the Office of the Secretary of Defense (OSD) and the Services. Examples include:

- BDP. OSD controls the funding for BDP vaccines, and DATSD(CBD) has oversight of the full life cycle of the BDP, the Army is the Executive Agent for the BDP, the S&T aspects of the BDP vaccine program are executed in the USAMRMC, advanced development through production is executed through the JPO BD, and procurement of resultant products is with Defense-wide procurement dollars. JPO BD authority is diluted by the oversight structure and has no effective reprogramming authority. The seemingly complex process for managing BDP funds is depicted in Figure 3. There is limited biomedical expertise and knowledge in the JPO BD reporting chain, and in the JSIG, JSMG, and JNBC Defense Board. There is no qualified medical authority over BDP vaccine decisions.



JSMG Hand Book of Standard Operating Procedures, Fig IV-I, Page 19

Figure 3. DoD Funds Management Process for BDP

- IDP. The DUSD(S&T) has oversight of the S&T program for IDP vaccines. There is no OSD-level assigned responsibility for the program beyond S&T, with resultant consequences for proponency, oversight, and management of associated development and acquisition activities. The Army is the Lead Agent and resources the program while USAMRMC executes the Lead Agent program responsibilities (S&T through production) through the Services' biomedical laboratories and contracts. Procurement of resulting products is made with Operations and Maintenance, Army (OMA) dollars to fulfill Army requirements. Each service specifies its own vaccine requirements for protection against infectious diseases and is responsible for their vaccine procurements. *The USAMRMC provides biomedical matrix support to the Joint Vaccine Acquisition Program, Project Management Office (JVAP PMO).*

- The BDP is managed under Defense Acquisition Board oversight as an acquisition category (ACAT) I program while the IDP is managed as an ACAT IV non-major program.

Within DoD, the varying degrees of experience, multiple organizations with program responsibilities, associated levels of oversight [e.g., Congress, OSD, Services, and Major Commands (MACOMs)], decision making, reporting requirements, and PPB structure and system do not lend themselves easily to the streamlined process and flexibility used by industry in taking a candidate vaccine from discovery to market. Hence, there is high risk in DoD's current approach to vaccine acquisition. Further, the scope of the BDP AVP and associated schedule of vaccine procurement raised questions of practical feasibility. The investment strategy is not one that is consistent with industry best practices and raises questions about whether the risks associated with such a strategy were fully explored or understood, and if so, how they were mitigated. *Given industry's success with extremely short oversight and decision-making chains of responsibility and accountability, the DoD must reexamine its diversity in structure for overseeing, managing, and executing its vaccine program.*

The threat issues and associated problems identified during and following the Gulf War deserved congressional and OSD scrutiny. There have been many valuable lessons learned as a direct result of this scrutiny. It appears, however, that the organization put in place by DoD to "fix" the BDP AVP issues may in fact have become an impediment to efficient and effective vaccine program management, execution, and success. There is an identified threat list to support the BDP, and the IDP would benefit from a similar threat list. *Since disease threats, regardless of source (e.g., BW and ID), can have catastrophic impact on military operations, an integrated list of BW and ID threats deserves consideration in planning, proposing, and budgeting for the most urgent medical vaccine needs*.

DoD's practices for managing its vaccine programs contrast sharply with industry's best practices (Section 3, Table 2) and pose some inherently high risks to success. Factors contributing to the high risk nature of the DoD approach are summarized in Table 8. It is contrary to the vaccine industry's well-established business success model that ensures a single empowered and accountable individual (project manager) in charge of program, focused (non-diffuse) cross-functional management, and a clear picture of the medical need. DoD practices diffuse management, making it difficult to establish clear lines of responsibility, authority, and accountability. In addition, the DoD lacks the level and depth of scientific oversight and talent needed to manage and execute the vaccine programs. This is exacerbated by a relatively scarce national pool of exceptional and specialized expertise and DoD's noncompetitive compensation packages.

The DoD BDP vaccine acquisition strategy, utilizing a prime systems contractor (PSC) with outsourcing for components of the manufacturing process via multiple subcontracts, differs from that normally followed in the vaccine industry. It does not mean, however, that this strategy won't work. Rather, it may experience considerable delays and must have more intense technical oversight if it is to be successful. *Simply stated, the DoD BDP vaccine acquisition strategy is considered a high-risk approach.*

Table 8. Reasons Why DoD AVP Program Is at Risk of Failure

➢ Approach is contrary to business success model – No one in charge – Diffuse management – Fragmented program
➢ Lack of integration from discovery through licensure
➢ Lack of essential scientific oversight and talent
➢ Insufficient capture of industrial base
➢ Goals and dollars do not match

The expertise within DoD to address DoD's vaccine needs appears to have become fragmented and difficult to sustain, with the preponderance of expertise resident within the Army and Navy biomedical research communities. The uniformed biomedical scientist has historically been a major participant and contributor in the DoD vaccine research, development, test, and evaluation (RDT&E) process (e.g., leadership, management, and program execution). This seems to have changed with abolishment of the draft, and the military downsizing (1980s and 1990s) wherein priority has been placed on warfighter and health care delivery personnel authorizations. Uniformed biomedical scientists now routinely leave the services to sustain their professional growth and opportunities or take on a diversity of nonbench and non-RDA assignments to remain competitive from a promotion perspective. During the past 10 years, not a single military biomedical scientist has been promoted to the rank of a Flag Officer. This reflects fewer opportunities for biomedical scientists to reach senior leadership positions where their expertise and experience can benefit DoD, and is another disincentive for remaining in the military. Further, the civilian biomedical S&T workforce is relatively stagnant with long years of service, and recruitment and retention of replacements with the competencies needed to address DoD's vaccine RDA needs are extremely challenging. The DoD compensation and benefits package for civilians is not competitive with industry. The national pool of required biomedical S&T expertise is limited and extremely expensive. While some companies have had success in recruiting qualified personnel for the vaccine industry, DoD in many cases, simply cannot compete with the biotechnology firms, biopharmaceutical industry, or academia for the very best talent under existing compensation constraints and career opportunity. *The DoD is experiencing difficulty recruiting and retaining required military and civilian biomedical scientists, and has lost a critical mass of senior uniformed scientists that were well founded in the DoD biomedical RDA process.*

There is a general lack of integration in and across the DoD vaccine programs, from discovery through licensure. The USAMRMC has a pilot plant at Walter Reed Army Institute of Research (WRAIR) that supports the military infectious disease vaccine effort and the JVAP uses the PSC to satisfy its biological defense pilot plant vaccine production needs. Additionally, the JVAP and U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) have used the National Cancer Institute (NCI) pilot lot production facility located at Fort Detrick, Maryland, and the National Institute of Allergy and Infectious Diseases (NIAID) has used the pilot production facility at WRAIR. While this may seem curious, it underscores the technical necessity of integrating the discovery and development phases and the importance of proximity to these processes. Both WRAIR and USAMRIID have strong S&T programs supporting the IDP and BDP, respectively. Industry best practices for success mandate integration of policy, all elements of a product's life cycle, resources, and management as summarized in Table 3.

It is clear that the DoD has not had a successful strategy or commitment to effectively capture the vaccine industrial base. The key existing impediments to industry taking on DoD's vaccine needs are summarized in Table 9.

Table 9. DoD AVP Impediments to Industry

➢ Size & scope of program
➢ Industrial base at full capacity
➢ Idle manufacturing
➢ Risk to industry – Efficacy risk – Program stability – Perceptions – Political
➢ Defense procurement practices

Finally, the DoD's goals for the AVP do not match the programmed and budgeted resources. Industry maintains a robust discovery base and commits itself to full and stable resources when it transitions a lead candidate from discovery to development and production. Benchmark costs associated with vaccine discovery, production, facilities, and maintenance in industry were discussed in Section 3 and summarized in Table 7.

A best business assessment model was used to evaluate the degree of DoD's compliance with industry's best practices for managing and executing vaccine programs (Figure 4). The rationale for the assessment of DoD's compliance is provided in the figure.

Industry Best Practices	Assessment of DoD	Rationale for Assessment
Integrated-Discovery Through Licensure	R	Piecemeal process
Scientific Talent	Y	Good S&T, inadequate development and production
Technical Qualifications of Management	R/Y	Vaccine Acquisition ≠ Weapons System Acquisition
Management Focus and Accountability	R/Y	Fragmented and Multilayered below DEPSECDEF
Funding Stability	R	Annual allocation and frequent decrement drills
Funding Commitment	R	Development/Acquisition not funded following discovery
Flexible Reprogramming	R/Y	Limited by Congress
Focus on Product Quality	Y	Goal G; Execution R

G = Green - Full Compliance
Y = Yellow - Moderate Compliance
R/Y = Red/Yellow - Low Compliance
R = Red - No Compliance (High Risk)

Figure 4. Business Model for Assessing DoD's Compliance with Industry Best Practices

5.0 INTEGRATION OF DOD AND INDUSTRY VACCINE OBJECTIVES

Partnering with DoD to produce vaccines is considered a high-risk venture by industry. Some of the reasons for this industry perspective are identified in Table 10. Industry's existing and projected vaccine streams are considered to be strong and growing, with few exceptions. If industry takes on development and production of a DoD vaccine, it will have to displace medically needed, competitive and profitable products – an industrial base vaccine capacity issue – that market analysis demonstrates will satisfy a public health need, grow and provide a reasonable return on investment. In this regard, DoD will need to fulfill industry's needs and expectations. *Vaccine manufacturing companies have to grow and growth is more predictable and easier to manage as a Company initiative than one in support of a DoD vaccine initiative*.

Table 10. Reasons Why DoD AVP Is Considered High Risk by Industry

➢ Instability of DoD programs, associated resources, and commitment
➢ DoD acquisition model and resource system PPB, as well as associated categories of funds, do not align with industry's best practices for vaccine discovery and production
➢ Industry's experience with DoD's unwillingness to resource infrastructure and process sustainment costs associated with vaccines unique to DoD
➢ DoD's episodic capacity requirements and associated risks in maintaining capability
➢ DoD acquisition process that seems to emphasize budget, not quality
➢ Difficulties with and shortcomings of Defense procurement practices
➢ Proposal preparation and submission costs and processes
➢ Government regulations [e.g., cost accounting and National Environmental Policy Act (NEPA)]
➢ Public perceptions (e.g., mistrust) of DoD

The DoD must acknowledge industry practices and factors that motivate industry, capture industry interest and incentives, and invest its own corporate resources in the process if it has any hope of involving the major and successful industrial vaccine manufacturers in solving its vaccine requirements. The Panel is confident that many leaders in the vaccine industry are willing to help DoD and will not be opposed to DoD building its own vaccine production facility once they are familiar with DoD's requirements and AVP program rationale. With regard to capturing industry's interest and willingness to address DoD's vaccine requirements, the following resource and policy-related topics that impact potential incentives are offered for consideration. They represent a critical aspect of an integrated strategy to resolve DoD's vaccine requirements.

5.1 Resources

5.1.1 Market Needs

It is important for DoD to market to the public health needs that industry views as important whenever possible. The industry would likely have interest in vaccines to prevent diseases of high public health impact [e.g., malaria, Human Immunodeficiency Virus (HIV), and perhaps hepatitis E and smallpox]. A single manufacturer probably would not want to take on more than one of these vaccine needs at a time. They already have an existing and projected stream of scheduled vaccines to meet customer needs and company goals. Further, the staffing and production capacity support their planned vaccine schedules, and would not generally support vaccine needs beyond this capability. *If the medical need were perceived as important enough to industry, they might partner with DoD to accommodate a DoD vaccine requirement*. There may also be specific vaccine-related technologies that would capture the interest of industry. Regardless, the DoD would need to carefully market their specific needs to industry. In this regard, *previous DoD Requests for Proposals (RFPs) have not worked well in the vaccine industry – because they go in at the wrong level or have an approach that is inconsistent with industry's experience for success.* For example, the JVAP solicitation was considered by many in industry to be "way too big" – it had too many products being scheduled over too short a timeframe. The number of products and schedule were simply viewed as very "high" risk and did not capture industry interest.

5.1.2 Size and Scope of DoD Vaccine Requirement

The scope of the DoD vaccine requirement is very substantial by any measure. The BDP requires new vaccines to protect against 10 or more BW threat agents and at least 5 new vaccines are needed to protect against endemic diseases of military importance. Considering that vaccines are licensed in the U.S. to protect against about 20 different diseases, the DoD requirement for approximately 15 new vaccines represents a staggering technological undertaking. The overall requirement by comparison is larger than that of the vaccine operations of Merck & Co. Inc., which produces 9 vaccines. The Panel used a scale of 8 vaccines for estimating the resources needed for the DoD vaccine program. The DoD program operating at this scale requires about $3.2B in R&D funds. The assumptions for these rough-order-of magnitude estimates are shown in Table 11. Given that industry has virtually no excess capacity, it is clear that the size and scope of the DoD vaccine program itself preclude even major manufacturers as a single source of DoD vaccines.

Table 11. Industry R&D Funding Benchmark Estimates (8 Product Scale)

- R&D Funds – $3.2B
  - ~8 successful vaccines (7-12 years each)*
  - ~$300 - $400M/product R&D to licensure
  - ~2 products/year to start
  - ~4 products/year at year 4
  - ~8 products/year when mature

*BD and MIDRP require >8 vaccines total; study scale was 8 vaccines

5.1.3 Capital Investment

The vaccine industrial base is operating at near full capacity and the major manufacturers have no reason to invest in expanding that capacity beyond that needed to support their vaccine schedule. Adding capacity requires significant capital investment and it can take 3 to 5 years to get new or modernized facilities operational and processes validated for facility and product licensure. *The financial cost of failure and rewards for success are great and industry invests its capital accordingly*.

The DoD has a need for many vaccines that have limited potential for marketability elsewhere. Each of these vaccines will need a dedicated production capability. It is possible that products that use similar production technologies can be manufactured in the same facility; however, most products will require unique production technologies and a dedicated production suite and/or facility.

In the vaccine industrial environment, incentives are needed for successful partnering between DoD and a vaccine manufacturer. Such incentives include creative capitalization and guaranteed product demand and revenue streams. If DoD demonstrates a long-term commitment to making a capital investment to expand the industrial base vaccine capacity, industry will likely respond. *For example, DoD could target selected expansion of industry's capacity by providing the fiscal resources, under competitive contracting, for major manufacturers to design, build, and equip a modular-type facility on their premises for the production of certain vaccines to meet a DoD requirement*. This is one of the least intrusive approaches and has the advantage of drawing on the manufacturer's resident expertise for managing and producing vaccines and would minimally affect the investment concerns of company shareholders. Some of the important elements of incentive-based contracts that would facilitate industry interest in participating in DoD's AVP are summarized in Table 12.

Table 12. Contracting to Capture Industry Interest in DoD AVP

➢ Longest multiyear contract possible
➢ Government-provided facility
➢ Incentive-based contracts
– Award fee
– Industrial R&D
– Intellectual property to contractor
– Third-party sales

5.1.4 Infrastructure Maintenance

The DoD cannot expect industry to invest its resources to maintain the infrastructure (e.g., facilities, equipment, and personnel) or modernize its facilities in order to meet DoD vaccine needs. Lessons learned demonstrate that such expectations inevitably lead to a loss of capability and source of vaccines. For example, Wyeth Laboratories manufactured Adenovirus Vaccines (Types 4 and 7) for DoD, the sole customer for the vaccines. When DoD determined it would not make the investment in renovations of the outdated facility necessary to continue production, Wyeth Laboratories made a decision in 1995 to discontinue manufacturing. As a direct result, the vaccine supply ran out, the DoD has not found an alternative supplier, and there has been a resurgence of acute respiratory disease epidemics in military (Air Force, Army and Navy) and Coast Guard trainees due to adenoviruses. Unfortunately, the prospects of remedying this force health protection problem in the near to mid-term are not good.

The requirement to sustain a vaccine facility infrastructure and provide for facility modifications (e.g., to meet regulatory compliance requirements) should not be underestimated. Failure to fully plan for continuing these activities will be disastrous for the DoD vaccine program, with a loss of production capability and years to get a process revalidated and a facility licensed by the FDA. Hence, infrastructure and modernization planning and resourcing must be integral parts of the overall DoD vaccine acquisition strategy.

5.1.5 Adoption of Vaccine Industry Product Development Process

It may well be to DoD's benefit to carefully consider industry's successful approach to vaccine development and not, therefore, place burdensome constraints on their process. *The vaccine industry uses a process that reduces S&T-related and manufacturing process risks early, before a decision is made to take a candidate forward for development, manufacturing, and marketing.* Decision making is vested with the management team charged with overseeing the process to get the product manufactured, licensed, and to market. Once a decision is made to take a product forward, the management team intensely manages the project teams working the various steps in the process (e.g., manufacturing, clinical trials, and regulatory) and plans on achieving licensure of the product within 3-6 years. INDs for vaccine candidates have a success rate of 20% or less and the resources required to carry a product to market are enormous. Estimates for the discovery, development, manufacturing, and testing required to achieve licensure of a single safe and efficacious vaccine are estimated at $300 - $400 million over 7 to 12 years. *Rarely would industry consider transitioning a candidate vaccine out of discovery (i.e., the industry phase corresponding to DoD's S&T phase) before it has successfully passed Phase 2 clinical trials and solid progress has been made in the manufacturing process.* The technical risks are otherwise considered too high. The DoD should be aware of the critical nature of the integrated life cycle development approach to vaccines. This approach involves a commitment to long-term development of a vaccine, once a candidate transitions from discovery to development and production.

5.1.6 Multiyear Contract Awards

A key strategic incentive for industry is the guarantee from DoD of a continued product production requirement and associated revenues through provisions utilizing multiyear contract awards. This may take statutory relief but is absolutely necessary in order for industry to maintain the manufacturing proficiency, personnel, and level of expertise needed to manage and produce a particular vaccine. The vaccine manufacturing control process does not lend itself to extended breaks in production since the process involves three interdependent elements – validated process, scientific art, and team skills and proficiency. If the acquisition strategy for a vaccine results in extended breaks in vaccine production, the art, technical skills, and proficiency required for a validated process will be compromised, if not altogether lost.

5.1.7 Commercial Sales of Vaccines

Vaccines are currently the most effective and practical way of protecting an at-risk population from a BW or ID threat. From a readiness perspective, vaccines are an enabler of force projection. Accordingly, there is a high probability that foreign military forces will want to acquire DoD-developed vaccines.

With regard to vaccines that generally have unique utility (e.g., biological defense) to the DoD, there may be some policy (e.g., DoD and State Department) limitations on the global sales of such vaccines. In terms of DoD, this most likely would be associated with vaccines that are developed and manufactured with DoD's RDA resources. The DoD does consider potential vaccine requirements for joint operations with U.S. allies; however, it does not incorporate the total vaccine requirement of its allies in its acquisition strategy. This does not preclude consideration of such requirements where the sale of vaccines to military allies is contemplated. Depending on U.S. national policy for defense preparedness requirements of its home front, there may be a rather large market requirement for biological defense vaccines. The spectrum of BW threats for which vaccines are needed is represented in Table 13.

Table 13. BW Threats

➢ Smallpox
➢ Anthrax (existing product)
➢ Anthrax (next generation product is desired)
➢ Plague
➢ Venezuelan Equine Encephalitis (VEE), Western Equine Encephalitis (WEE), and Eastern Equine Encephalitis (EEE) combined
➢ Coxiella burnetii (Q fever)
➢ Tularemia
➢ Botulinum toxin A, B, C, E, F
➢ Staphylococcal Enterotoxin B (SEB)
➢ Ricin
➢ Brucella
➢ Others

The ID threat to the military force depends on the diseases endemic to the particular area of deployment. History has shown that when troops are deployed to new geographic areas the probability of disease outbreaks is high, with high risk to decisive military operations. Vaccines that are developed by DoD to protect U.S. Forces from endemic infectious diseases during deployments throughout the world may also have a potential commercial sales market, depending on the fiscal strength of the country involved. Further, the United Nations International Children's Emergency Fund (UNICEF) and other humanitarian support efforts may want to purchase such vaccines when they become available. The IDP needs vaccines to protect against a wide spectrum of threats such as those shown in Table 14.

Table 14. Infectious Diseases of Military Importance

➢ Malaria
➢ Shigellosis (and other enteric bacterial infections)
➢ Dengue fever
➢ HIV
➢ Hepatitis E
➢ Others

With few exceptions, there are only very limited worldwide public health requirements for those vaccines that are most needed by the BDP and IDP. Generally, those countries that might have the greatest need are also those least able to afford large vaccine procurements. For example, a plague vaccine developed for the BDP might be effective against endemic plague outbreaks such as occurred recently in India. In such an instance, the U.S might be asked to provide the vaccine as a humanitarian initiative. As noted above, it is also likely that as vaccines are licensed by the DoD, both foreign military sales and sales for protection of indigenous populations and dependents of military service men and women will become an area of increased potential for commercial sales. Realization of such potential is confronted by both the relatively small size and non-recurring nature of foreign military vaccine requirements. Additionally, DoD would not normally conduct clinical trials to support product use by non-DoD personnel, people outside of the age range of 18-50 years. The absence of such data could be expected to restrict the commercial sales potential of DoD vaccines.

DoD should clarify its policy on industry rights to foreign military sales of BDP and IDP vaccines, domestic civilian use of BDP and IDP vaccines, and international and domestic commercial sales of IDP vaccines. In this way, industry can estimate potential market size in reaching a decision whether or not to develop a DoD vaccine.

5.1.8 Personnel Requirements in Vaccine Discovery and Production

The importance industry places on having the right people, the right technical skills, the right depth of expertise, and the right compensation packages to optimize success is reflected in one major manufacturer's workforce consisting of approximately 2,500 individuals dedicated to the management, discovery, process development, manufacturing, testing, production, and related regulatory support of an average of eight products. That number exceeds the total authorized personnel strength of USAMRMC in support of its biomedical RDT&E program activities for IDP, BDP, Military Operational Medicine, Medical Chemical Defense, Combat Casualty Care, and Congressionally Directed Medical Research Programs and probably exceeds the total number of DoD civilians performing medical RDA activities. The biomedical RDA expertise for vaccines is extremely limited, expensive, and draws largely from academia and industry. The starting salary for recent college graduates entering the vaccine industry is reported to be in the range of $40,000 - $50,000 per year. Individuals with sufficient experience to qualify for process validation positions may start at $100,000 - $120,000 per year. If DoD's vaccine requirements were to be met internally, DoD will need to implement compensation policy changes and provide the resources needed to capture and retain the best talent, with particular emphasis on manufacturing, testing, clinical trials, and regulatory compliance. The Panel does not believe that DoD can recruit, retain and manage the skilled personnel needed in advanced development of vaccines and recommends that development be effected by a combination of industry and GOCO.

5.1.9 GOCO Facility

In view of the size of DoD's vaccine program, the limited available industrial vaccine capacity and the limited industry interest in most DoD vaccines, it is likely that DoD will need to develop committed vaccine production facilities. The Panel was informed that the DoD has programmed resources for a proposed GOCO vaccine production facility. The proposed GOCO was viewed as an essential, partial remedy for DoD. However, it also raised a question about how the JVAP's PSC fits with, or would be linked with a GOCO. There was no immediate linkage defined. With regard to the PSC, the contract base is for three products. All other vaccines are options under the contract. Currently the three base products on the contract along with two product options are being developed.

Several of the salient considerations in locating, designing, building, and operating a GOCO facility to produce vaccines are summarized in Table 15. *Programming a vaccine production facility is considered the easiest part of establishing the overall capability for vaccine development, manufacturing, and supply. What goes in the facility and how the facility is managed are considered the most difficult and critical components of the process. It is important that planned processes drive the design of the facility.*

Table 15. Factors in Planning for a GOCO Vaccine Production Facility

➢ Shell/buildout to process and manufacturing scale
➢ Expandable
➢ 3 to 4 products/processes capacity
➢ Pilot production/scale-up – 2 products at one time
➢ Inherent clinical, regulatory, QC & QA elements, applied research laboratory capability
➢ University/industry corridor location is essential – Northeast coast lowest risk

Staffing a GOCO vaccine production facility with the level and depth of expertise needed to manage and manufacture (process teams) vaccines was thought to be an extremely difficult challenge for DoD, let alone the vaccine industry. The Panel believes that the DoD must attract, train, and retain a technically competent cadre of vaccine expertise. In this regard, it is likely that a greater than normal number of DoD staff will need to fill key positions in the GOCO as a part of this initiative. The needed expertise is in very short supply and the DoD would have to compete very aggressively with industry for those limited assets.

With regard to having the right mix and depth of expertise, it is clear that both technical and management skills are critical to the success of any vaccine R&D program including a GOCO. Scientific training does not necessarily enhance one's acquisition management skills and, most assuredly, acquisition training does not add to one's scientific acumen. Further, with the exception of project management skills, the scientific and management skills and experience needed to operate a successful vaccine program are decidedly different from those needed to run a weapon systems program. Even within the biomedical disciplines, few are appropriate to vaccine production. *Vaccines (i.e., biologicals) are different from weapon (i.e., hardware) systems and should not be forced-fit into or equated with such acquisition programs.* These points become critical in terms of staffing and operating a DoD GOCO vaccine facility for success.

It is also important to keep in mind that project leaders and managers in the biopharmaceutical industry identify and surface issues immediately upon identification. Success (e.g., cost, schedule, and performance) is based on timely resolution of problems. *Industry's approach of having the decision maker on site facilitates this process, as does the culture that rewards the practice of not hiding risks and technical, process, and regulatory problems. Further, the constant turnover of DoD Program Managers (PMs) (i.e., continuity of leadership issue) in a* *program creates its own impediments to achieving cost, schedule, and performance objectives.* Turnover of PMs may contribute to an environment of deferring problem resolution. In general, in the vaccine industry, the same team sees a product through the equivalent of DoD's development and manufacturing (production) acquisition phases. *From the foregoing perspectives, management (e.g., DoD project management office) of a DoD GOCO vaccine facility would benefit from alignment with the vaccine industry's management culture, processes, and best practices.*

Industry does not build a facility for a specific vaccine until clinical trials have proven safety and proof of concept and process issues have been resolved. When industry builds a new facility, they plan 3 to 6 years for getting the first vaccine produced and another 12 to 18 months to get the product licensed. Typically, it costs an additional 20%-30% per year for the first year or two to get a manufacturing process up and running. Thus, for a $100 million dollar facility, a manufacturer might expect to expend $20 – $30 million a year to get a process operational during the first couple of years. During this period, 20%-25% of the product will be discarded due to product variability. During normal operations, about 5%-10% of the product may be discarded due to variability from lot to lot. This loss is higher than that experienced (1%-2%) in the pharmaceutical drug manufacturing process. It is important to realize that discarded product is lost revenue to the manufacturer. Typical capital investment costs associated with vaccine facilities are provided in Table 16.

Table 16. Industry Capital Investment and O&M Funding Benchmark Estimates (8 Product Scale)

➢ Capital funds ≥$370M – ~$300M construction for manufacturing – ~$70M construction for labs – ~$75-$115M for each additional vaccine after the initial 3-4 – ~5%-10% infrastructure maintenance/year at year 8
➢ Operations and Maintenance funds – ~$300M/year for 8 vaccines

Importantly, the Panel agrees with the concept and scope of the proposed DoD GOCO. In general, a modular approach (i.e., using identical modules to duplicate a capability as the means to increase production capacity) is recommended in building a vaccine production facility. Dedicated manufacturing is preferred to multiple product suites. Ideally, the strategy would include limiting production–as opposed to development–to one or two (maximum) initial products. It is extremely important to gain experience and demonstrate success with one product before taking on others. The level and depth of expertise necessary to achieve success should not be underestimated. It would be prudent to focus on a single technology, and a related technology if two products are envisioned at the outset.

Involving the facility and process operators in the design, building, and equipping of a new facility (e.g., GOCO) is critical to the operational success of any vaccine production venture. As occurs in industry, infrastructure and modernization must also be integral parts of the budget supporting any DoD GOCO vaccine production facility. *The requirements for sustaining a* *vaccine facility infrastructure and facility modifications (e.g., to meet regulatory compliance requirements) should not be underestimated.*

There are a number of risks that must be managed in a DoD GOCO vaccine production facility. These include factors such as facility design and construction, dedicated versus multi-use facility, past performance of contractor, technical maturity, process validation, performance requirement, cost, and schedule. A risk assessment process and plan are needed to effectively oversee, manage, and mitigate them. A GOCO should only be one part of the DoD strategy for AVP. However, the Panel considers a GOCO as an essential element in DoD vaccine procurement.

5.2 Policies

5.2.1 Confidentiality

Industrial vaccine manufacturers hold certain pieces of critical technical and business information as trade secrets. These secrets largely derive their value from the fact that they are not known to others who could disclose or use them for their own benefit. Therefore, the holders of this information are extremely sensitive to the release of this information to any others, especially if they are unsure whether confidentiality will be maintained. For these reasons vaccine manufacturers insist that any recipients of confidential trade secret information sign nondisclosure statements that specifically lay out and create the confidentiality obligations of the recipients. It is also important to note that any government employee who discloses confidential information received as part their official duties are subject to criminal prosecution under 18 USC 1905.

5.2.2 Management of BW Perceptions and Treaty Compliance Issues

In addressing DoD vaccine requirements to protect against BW threats, an upfront and agreed upon public affairs plan is essential in overcoming any negative perceptions (e.g., risk to population in the area of vaccine production) about DoD's BDP. Further, the industry does not want to be wrongly tainted by any suggestion it might be producing BW agents for DoD and it is opposed to any potential inspections imposed by BW conventions under the pretext that they might be producing BW agents instead of manufacturing vaccines to protect against such agents. If such inspections are or will be required, industry would be seriously concerned from both the perspective of potentially losing proprietary/trade secret manufacturing information, and the potential perception of being involved in an offensive instead of defensive program. Hence, such inspection activities would have an adverse impact on the industry's image and growth and would not have the support of their shareholders.

5.2.3 Use of Non-U.S. Owned or Based Manufacturers

It is essential that DoD is clear on its position regarding the country of ownership of a vaccine manufacturer, as well as non-U.S. manufactured vaccines that comply with FDA licensure requirements. Two of the four major vaccine manufacturers, SmithKline Beecham and Aventis, are non-U.S. companies. This becomes important in terms of potential implications for DoD vaccine supplies where a foreign-based owner of a U.S. company may, for whatever reason, unilaterally end production of DoD's vaccine. Similarly, political and corporate considerations could end abruptly DoD's access to vaccine supplies contracted through non-U.S. based vaccine manufacturing facilities even if U.S. owned.

5.2.4 User Acceptance of Vaccine

The question of user acceptance of a BDP vaccine was raised, particularly with respect to the Department's experience with the anthrax vaccine. The data from longitudinal studies of vaccines used by the DoD in immunizing its force do not suggest there has been a problem with regard to adverse events or health care problems. The incidence and type of adverse reactions (e.g., sore arm or slight swelling at the site of injection) associated with the administration of the anthrax vaccine appear to have been similar to those experienced with other vaccines. The primary concern to DoD is not having safe, licensed vaccines to protect its forces from both the BW and ID threats.

Despite the scientific and health care data that support the fact that there is no unusual risk associated with the immunization of individuals with the anthrax vaccine, it is felt that gaining user acceptance could be a potential problem with each BDP vaccine. The public seems to question the reasonableness of DoD's mandatory immunization policy for anthrax, and this has been reflected during Congressional hearings. Further, the public has little basis for appreciating the impact of infectious disease epidemics on military operations and health care delivery. All this seems to underscore the importance of having a risk mitigation plan that clearly communicates to the user (military recipients and commanders at every level), as well as the public in general, the benefits, immunization rationale, and potential risks of each new vaccine.

It is also important that the DoD establish a policy for when and how all the vaccines in their portfolio will be administered. Figure 5 summarizes the current vaccines licensed in the U.S., including those administered to U.S. Forces. Adding to this list, the vaccines identified as required for force health protection against BW and endemic disease threats will generate a seemingly overwhelming number of potential vaccines that might be administered to individual members of the Armed Forces. Clearly, an immunization policy that stipulates the procedures (e.g., number of inoculations and routes of administration, and booster requirements) and phasing of vaccine administration is required.

Current U.S. Licensed Vaccines		
Childhood Vaccines	**Deployment Readiness**	**Additional**
• Diphtheria Pertussis Tetanus	• Hepatitis A	• BCG
• Measles-Mumps-Rubella	• Cholera	• Rabies
• Polio-Salk and Sabin	• Japanese encephalitis	
• Hepatitis B	• Typhoid	
• H. influenza B	• Yellow Fever	
• Pneumococcus	• Influenza	
• Varicella		
Basic-Training	**Biological Defense**	
• Meningococcus	• Anthrax	
• Adenovirus	• Vaccinia	

Figure 5. Current U.S. Licensed Vaccines

5.2.5 Use of IND Vaccines

The DoD has previously relied on using some BDP vaccines under IND status where safety and efficacy have been established in laboratory models, and safety, but not necessarily efficacy, has been ascertained in man. The use of such investigational vaccines requires Presidential approval. This is a difficult issue and one that is fraught with potential problems (e.g., logistical and political). In overcoming this issue (i.e., perception of a service member as a guinea pig) of vaccine use under an IND, the DoD must place increased program emphasis on identifying and demonstrating surrogate markers of immunity (i.e., protection) in man that are acceptable to the FDA and work with the FDA to achieve sufficient human safety and immunogenicity data, as well as efficacy data in animal models, to provide licensure of all DoD vaccines.

5.2.6 Vaccine Liability and Indemnification

It is generally true that potential liability is a concern to industry in addressing DoD's vaccine needs, particularly as it relates to a product for which efficacy cannot be demonstrated in man; that is, where surrogate markers and/or surrogate models must be used to provide presumptive evidence of efficacy; and where there is no way to quantify exposure risk in terms directly related to a vaccine's claims of efficacy, as is the case with BW threats. This problem is associated almost exclusively with the BDP where the BW threat agent is not typically associated with an endemic disease in a population, as is often the case with those diseases of concern in the IDP.

Litigation cases involving vaccines, however, have historically been associated with adverse outcomes, not matters of efficacy. This does not in any way lessen industry's concerns over potential litigation where there may be no reasonable way to quantify the risk (e.g., the potential exposure levels that might be experienced in BW attack) in terms that are directly related to a vaccine's claims of efficacy.

Given the experience with BDP immunizations during the Gulf War, there are implications for policy in terms of removing immunizations from the context of conflict that might also lessen industry's concern. The adverse effects of immunizations during basic training and during mobilization prior to deployment are viewed just as that – adverse reactions. They do not get complicated by other factors (e.g., stress, exposure to environmental contaminants, and illnesses).

Since indemnification is available, albeit on a case-by-case basis, it makes sense for companies to ask and expect to receive it from the government. Indemnification should be a guarantee for any vaccine manufacturer that is contracted to develop and produce a vaccine to meet DoD's unique requirements. *Indemnification, limited to that for military use and not commercial sales, coupled with sound contract provisions, must mitigate industry's concern in this area.*

5.2.7 Vaccine License Holder

Historically, the FDA regulatory process necessitated that the holder of a biological license be responsible for all submissions to the FDA, manufacturing, clinical trials, and production of the vaccine. Recent changes in industry practices that are related to the emergence of small biotechnology companies have led to new FDA guidance for industry and associated cooperative manufacturing agreements. As a result, a sponsor may now hold a biological license but not conduct any of the actual steps in the process (e.g., manufacturing and clinical trials).

Although the concept of a virtual company is seen within the pharmaceutical industry, it is currently viewed as difficult to implement and has not gained widespread support. This difficulty is due to the intense management and control needed to effectively and efficiently take a vaccine from discovery to market. A major contributing factor accounting for this difficulty is the need for integration of multiple, state-of-the-art, developmental research efforts to address complex scientific issues unique to each vaccine throughout the course of development. The complexity of the vaccine manufacturing process is also a critical issue. Although there are validated technological processes for controlling the manufacturing process for a vaccine, repetition of the process and an element of art in the underlying S&T seem crucial to success. This problem is evidenced by the vaccine industry's troublesome experience with replicating the same product results with the same process in another manufacturing facility or difficulty during start-up in their own new facilities.

In the absence of the depth of expertise and experience needed to oversee a virtual vaccine operation and inherent problems with outsourcing aspects of the overall process, such operations have enormous attendant risks for failure. The risks to DoD in not holding the biological license for a product are probably minimal except in the case where it may become necessary to have another manufacturer produce the vaccine. It is felt that well thought out and tight contract provisions, along with enforcement, could largely mitigate the risk associated with this single exception.

6.0 FINDINGS AND RECOMMENDATIONS

DoD must adopt industry practices, capture industry interest, and invest its own corporate resources in the management and execution of the AVP program if it has any hope of solving its vaccine requirements. This may well require changes in DoD policy and organization, legislation, and statutory commitments. The issues of U.S. national preparedness and the potential use of DoD vaccine stockpiles to meet national needs were discussed; however, it was not considered to be within the scope of the Panel's charge to include this in the overall recommendations for DoD's AVP. Nevertheless, the Panel hoped that its recommendations and DoD's planning tools would have practical utility and application to other agencies involved with national preparedness.

A combination of industry, government, and an integrated approach from discovery through production and sustainment are essential to the success of DoD's vaccine programs. The critical elements of a combined integrated approach to DoD's AVP strategy are summarized in Table 17.

Table 17. Elements of a Combined Integrated Approach to DoD AVP

➢ Management/development skills of industry
➢ Acquisition skills of DoD
➢ Scientists from Federal, academic/industry labs
➢ Exploit industry development/manufacture where possible
➢ GOCO for development/manufacture of remaining products

This strategy should include the vaccine industry's involvement as well as that of DoD and other government agencies. It is also important not to inadvertently lose any capability in the process of implementing any new vaccine acquisition strategy. A balanced strategy is quintessential to success and should include a multipronged approach. The Panel's goal in recommending the following management structure was to make it consistent with current DoD acquisition management structure, (but lean and responsive!) and to invest management with the strong technical expertise and advice essential for success in vaccine development. The Panel considers that the principal weaknesses of the current DoD AVP program are the current diffuse management structure and the lack of technical expertise in management beyond the S&T phase.

Specific recommendations include:

- Mainstream BDP and IDP vaccine programs as integrated ACAT I programs to ensure visibility, competitiveness with other programs, and that warfighter needs are satisfied in a timely manner (Table 18).

Table 18. Industry-Based Management Model for DoD AVP

➢ Tailored Acquisition Model – OSD VAE – Oversight (ACAT I)—technically qualified – Strategic Vaccine Board advises VAE
➢ Vaccine Acquisition Review Council (VARC) and Defense Medical Requirements Council (DMRC)
➢ Joint Program Executive Officer (PEO) – VAE and PEO with scientific and acquisition skills

- Implement an organizational alignment that mirrors the vaccine industry's short chain of command and decision making at the level of the project manager, with requisite technical expertise in the chain of command, project management, and execution level (Figure 6).

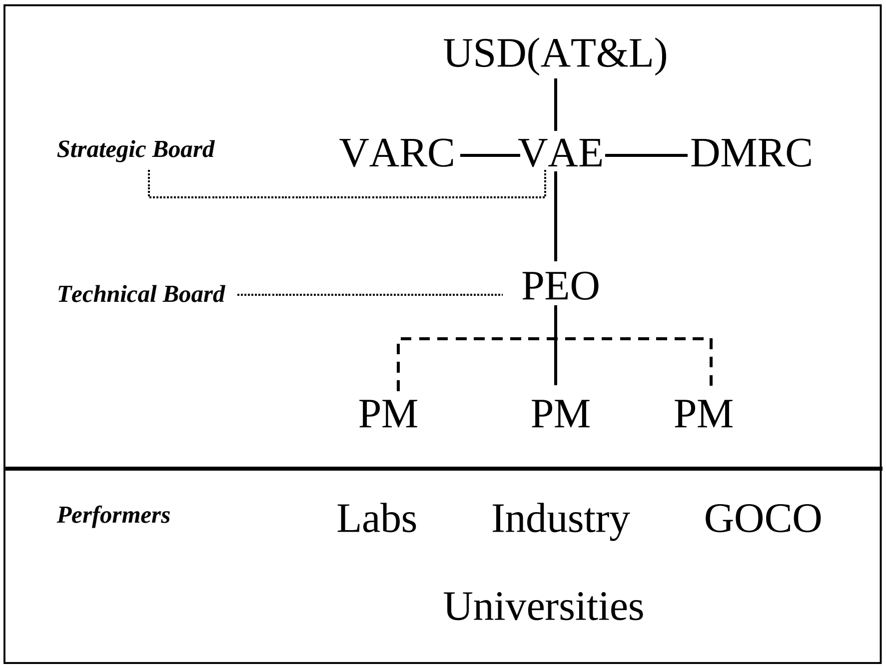


Figure 6. Industry-Based Management Organization for DoD AVP

- Establish a Vaccine Acquisition Executive (VAE) as full life-cycle advocate for all DoD vaccine programs (Table 18, Figure 6).
- Establish a Strategic Board to review the DoD AVP and advise the VAE (Table 18, Figure 6). This Strategic Board staff consists of industry executives and health care professionals having a working expertise in clinical infectious diseases, international health, or vaccine research, development, clinical testing, operations and quality systems. It should review programs strategically at least twice a year.
- Establish a VARC to advise and support milestone decisions by the VAE (Table 18, Figure 6). Members of the VARC should mirror for DoD the capabilities, experience, and technical skills of the Strategic Board; however, the VARC must be empowered to perform inherently government functions.
- Charter a technically qualified Joint PEO for the AVP program that is accountable to the VAE (Table 18, Figure 6). The PEO must have authority over the entire vaccine life cycle from discovery through post-licensure activities.
- Establish a Technical Board to review the DoD AVP program that meets quarterly and advise the PEO. This technical board staff consists of working experts with tactical "hands on" experience in the major elements of vaccine development–discovery, manufacturing, clinical development, regulatory affairs, quality control and assurance, and assay development. It would principally be derived from industry and would meet quarterly to review tactical plans and progress of the program (including the GOCO) and advise the PEO.
- Adopt an industry-based management philosophy for DoD AVP (Table 19).

Table 19. Industry-Based Management Philosophy for DoD AVP

➢ Scientific & technical advisors on tactical operations to PEO – Periodic (scheduled) review – All process/product candidates – Pharmaceutical executives – Senior scientists/physicians
➢ Breaches in approved program baseline reviewed by VAE
➢ PEO responsible for sponsoring ($) S&T/relevant infrastructure and exploits DoD laboratory capability
➢ No dual hats

- *Adopt a tailored life-cycle management model that mirrors that used by the vaccine industry wherein decisions to transition candidates from discovery (S&T) to development and manufacturing only occur when risks have been reduced to an acceptable level [e.g., after Phase 2 clinical trials and development and manufacturing schedules allow for completion within 3 to 6 years]*.
- Estimating that 8 DoD vaccines would reach licensure in 7 to 12 years, the estimated cost of the AVP program is $3.2 billion.
- Develop a sound investment strategy for the DoD AVP portfolio (Tables 13 and 14). A major initial goal of the VAE and PEO should be review of the entire AVP program vaccine candidates for feasibility and status in the vaccine life cycle.
- Use an integrated strategy that includes; GOCO (see Tables 15 and 16), PSC, DoD biomedical laboratories, and DoD partnerships with commercial companies (including appropriate incentives), National Institutes of Health, Public Health Service, and academia.
- Develop an integrated plan, including checks and balances (i.e., QA and QC) for managing the functions and responsibilities associated with the contracts, administration, operation and long-term sustainment of the DoD vaccine program (e.g., partnerships with industry and academia, GOCO vaccine facility, PSC, DoD biomedical laboratories, as well as oversight and management staffs).
- Promote a robust S&T strategic plan with increased emphasis on surrogate markers of immunity (protection) in man.
- Exploit special contract provisions, as well as Other Transaction Authority (OTA), that allow maximum flexibility in meeting vaccine program needs, and special incentives for success.
- Establish a unified process for identifying and prioritizing threats and requirements.
- Establish AVP plans
  - Core personnel incentive, recruitment, retention, and staffing plan (Table 6)
  - Facility infrastructure sustainment and modernization plan
  - Surge capacity plans (including conversion of existing plants)
  - Strategic inventory plan
  - Contract management plan with assistance from Defense Contract Management Agency
  - National public affairs plan that informs the public of DoD's vaccine plan, including rationale and benefits (e.g., combat capability, readiness, deterrence, and national preparedness).

Finally, the current DoD AVP program has extremely limited input from the vaccine industry. Therefore, the major source of invaluable expertise and experience is missing from the Program. The Panel recommends that DoD, at a very senior level, meet with the Chief of Executive Officers or Chief Operating Officers of the principal vaccine manufacturers. (This could be done through the Pharmaceutical Research and Manufacturers Association and BIO). The agenda should be:

- Outline the threat and requirements of the DoD program.
- Seek advice as to whether industry would contribute to development of all required DoD vaccines or to selected DoD vaccines.
- Seek support for the GOCO strategy to develop vaccines of limited interest to industry.
- Seek industry participation as advisors on the strategic advisory board to the VAE and on the technical advisory board to the PEO.

The Panel is confident that such high-level exposure to the DoD AVP program will enhance the possibility of industry involvement in development of certain DoD vaccines and at the very least, obtain industry support for the DoD program and GOCO and for the availability of pharmaceutical executives and industry vaccine development personnel to serve as critical advisors to the program.

The Panel's findings and recommendations are presented below so as to respond to the four specific areas of focus that the DEPSECDEF requested the independent panel of experts to address. A summary of findings and recommendations for each of the DEPSECDEF focus areas is provided in Table 20.

Table 20. Summary of Findings and Recommendations by DEPSECDEF Focus Area

Focus Area	Findings	Recommendation
1 - Vaccines to protect Service members against BW threats as well as infectious diseases.	Vaccines for BW defense and protection against endemic diseases are essential enablers of force projection.	Combine programs from discovery to production.
2 - A comparison of current Department efforts with best business practices in the biologics industry, and if/how the Department can leverage the best aspects of the private sector programs from industry.	Current Department efforts do not meet industry best practices: ➢ Diffuse management and fragmented lines of responsibility ➢ Inadequate scientific oversight ➢ Inadequate program integration from discovery through licensure ➢ Inadequate resources to meet goals	Adopt integrated approach utilizing: ➢ Management and development skills of industry ➢ Accountable, lean DoD management structure ➢ Strong technical guidance and personnel ➢ GOCO
3 - A determination of whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.	Vaccine acquisition processes are different from weapons system acquisition processes and success requires different procedures.	➢ Strong technical input imperative – Workforce – Management ➢ Stable, long-range funding for vaccine life cycle ➢ Reprogramming authority
4 - The development of recommendations for how the Department should best develop and oversee a vaccine acquisition production program.	DoD AVP management practices are generally contrary to industry best practices.	➢ Combined, integrated industry acquisition model ➢ Focused and streamlined organization ➢ Segregated, OSD-sponsored funding ➢ Incentivized industry involvement (with GOCO) ➢ DoD, Executive Branch, and Congressional support to remove impediments and provide necessary incentives

APPENDIX A

Conduct of the Study of Department of Defense Acquisition of Vaccine Production

By memorandum dated July 20, 2000 (Attachment I) the Deputy Secretary of Defense directed the Director, Defense Research and Engineering (DDR&E) and the Assistant Secretary of Defense (Health Affairs) [ASD(HA)] to "…jointly contract with a private organization or panel of experts to conduct a comprehensive study of the Department of Defense's (DoD's) procurement of vaccine production. The experts involved in the study should have expertise in the scientific, regulatory and industrial aspects of vaccine production. The study should focus on review of the following areas:

a. Vaccines to protect Service members against biological warfare threats as well as infectious diseases.

b. A comparison of current Department efforts with best business practices in the biologics industry, and if/how the Department can leverage the best aspects of the private sector programs from industry.

c. A determination whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.

d. The development of recommendations for how the Department should best develop and oversee a vaccine production program."

The DDR&E was directed to fund this study and the Director, Bio Systems, Office of the DUSD (S&T), ODDR&E, assigned the study support task to Science Applications International Corporation (SAIC) using an existing delivery order under SAIC contract N00600-96-D-2109. At that time the DoD was sponsoring or conducting a number of other assessments related to vaccines for force protection. These included:

a. Defense Science Board Summer Study 2000, *Task Force on Defense against Biological Weapons* that considered the vaccine supply chain for Defense needs.

b. Assessment by the Principal Deputy Under Secretary of Defense for Acquisition, Technology and Logistics [PDUSD(AT&L)] of BioPort Corporation production of the Food and Drug Administration (FDA) licensed, anthrax vaccine adsorbed.

c. A cost and operational analysis of a government-owned and contractor-operated (GOCO) vaccine production facility for biological defense vaccines sponsored by the Deputy Assistant to the Secretary of Defense (Chemical/Biological Defense [DATSD(CBD)] through the Joint Program Office for Biological Defense (JPO BD) and executed by the Joint Vaccine Acquisition Program, Project Management Office (JVAP PMO).

d. An assessment of the Military Infectious Diseases Research Programs (MIDRP) by the National Academy of Sciences, Institute of Medicine (IOM) for the Commanding General, U.S. Army Medical Research and Materiel Command (USAMRMC) who executes the Secretary of the Army lead agent responsibility for the military infectious diseases research, development, test and evaluation programs.

Supported by SAIC, the DATSD(CBD) and Director, Bio Systems recommended a Panel (Attachment II with resumes at Attachment III) and study plan to the DDR&E and ASD(HA). These were approved by memorandum on August 17, 2000 signed by the DDR&E and ASD(HA) (Attachment IV). This memorandum jointly requested Defense Components involved in AVP to provide briefings and narrative back-up concerning the topic. The approach the Panel Chair approved was for SAIC staff to review and critique the briefings with the intent to both highlight information for the Panel members' consideration and to identify areas that might require clarification for elaboration in follow-on presentations by Defense Component personnel. SAIC also established a secure web site for Panel members to access DoD Directives, Instructions, and related information concerning DoD acquisition of vaccine procurement. Throughout their deliberations the Panel was supported by the DATSD(CBD), Director, Bio Systems, and SAIC staff who provided information and assisted the Panel members' understanding of DoD organizations, practices and procedures. It should be understood that the Panel Chair was fully responsible for and directed this effort. DoD and SAIC staff provided support and assistance as requested.

The first meeting of the Panel was held September 25 and 26, 2000 (Attachment V). During this meeting the Panel received the Formal Charge from Dr. Mark, DDR&E and Dr. Clinton, ASD(HA) who also discussed background information and their perspectives on the problem with Panel members. During this meeting, SAIC staff presented and supported Panel discussions of briefings received in response to the DDR&E and ASD(HA) request, as well as related background information such as FDA regulatory considerations that directly influence the problem, Defense Acquisition Workforce reform initiatives, and DoD-specific regulatory considerations. Additionally, Mr. Steve McManus provided a briefing on vaccine management by the Defense Support Center Philadelphia, Defense Logistics Agency (DLA). Copies of all presentations are included in Volume II of this report.

The Panel Chair determined that the next step was for the Panel members to conduct interviews with specific DoD personnel involved in Defense AVP. These interviews were conducted during the second meeting conducted October 11, 12 and 13, 2000 (Attachment VI). The morning of the first day focused on Defense procurement with a briefing by the Director, Defense Contract Management Agency followed by a discussion of procurement and contracting support to GOCOs in general and related matters led by Mr. Robert Scott, past Deputy Director, DLA. The second day focused on Defense acquisition practices and procedures and DoD research, development and acquisition matters as they relate to vaccines. The Panel interviewed the following individuals on the second day:

- Lieutenant General Paul Kern, U.S. Army, Military Deputy to the Assistant Secretary of the Army (Acquisition, Logistics and Technology) [ASA(ALT)] and Director, Army Acquisition Career Management.

- Major General John Parker, M.D., U.S. Army, Deputy for Medical Systems, OASA(ALT) and Commanding General, USAMRMC.

- Mrs. Vicky Armbruster, Joint Program Manager for Biological Defense.

- Colonel Charles Hoke, M.D., U.S. Army, Director, MIDRP, Headquarters, USAMRMC.

- Colonel David Danley, Ph.D., U.S. Army, Project Manager, JVAP.

Throughout the second (October 11-13, 2000) and third meeting (November 8 and 9, 2000), the Panel members assessed Defense efforts and acquisition processes against industry best practices. These assessments largely drew on the Panel members' expert opinion and experience of what does and does not work in the private sector. Within the industry considerations, distinctions were made between the large vaccine manufactures and smaller biotechnology firms and how their practices contrasted and compared with the DoD efforts. These assessments served as the basis for recommendations that were initiated during the second meeting and concluded during the third meeting.

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ATTACHMENT I

Review of the Department's Acquisition of Vaccine Production Memorandum

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DEPUTY SECRETARY OF DEFENSE

1010 DEFENSE PENTAGON
WASHINGTON, DC 20301-1010

JUL 2 0 2000

MEMORANDUM FOR DIRECTOR, DEFENSE RESEARCH AND ENGINEERING
ASD (HEALTH AFFAIRS)

THROUGH: USD (ACQUISITION, TECHNOLOGY, AND LOGISTICS)
USD (PERSONNEL AND READINESS)

SUBJECT: Review of the Department's Acquisition of Vaccine Production

I direct that you jointly contract with a private organization or panel of experts to conduct a comprehensive study of the Department of Defense's (DoD's) procurement of vaccine production. The experts involved in the study should have expertise in the scientific, regulatory, and industrial aspects of vaccine production. The study should focus on review of the following areas:

a. Vaccines to protect Service members against biological warfare threats as well as infectious diseases.

b. A comparison of current Department efforts with best business practices in the biologics industry, and if/how the Department can leverage the best aspects of the private sector programs from industry.

c. A determination whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.

d. The development of recommendations for how the Department should best develop and oversee a vaccine production program.

The panel's report of their findings should be completed within four months of the date of this memorandum. Funding for the study should be provided by DDR&E.

Rudy de Leon

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ATTACHMENT II

Deputy Secretary of Defense's Independent Panel of Experts
Acquisition of Vaccine Production

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Franklin H. Top, Jr., M.D.—Panel Chair
Executive Vice President and Medical Director
MedImmune, Inc.
35 West Watkins Mill Road
Gaithersburg, MD 20878
topf@medimmune.com
Phone: 301-527-4251
Fax: 301-527-4201

John J. Dingerdissen
Senior Director, Viral Vaccine Manufacturing
Merck Manufacturing Division
Merck & Co., Inc.
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William H. Habig, Ph.D.
Director
R&D Quality Assurance and Compliance
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355-1307
Phone: 610 889-4405
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Gerald V. Quinnan, Jr., M.D.
Professor
Preventive Medicine, Medicine, and Microbiology
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814
Phone: 301-295-3734
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Email: gquinnan@usuhs.mil

Rita L. Wells, Ph.D.
Deputy Executive Director
Committee for Purchase from People
Who are Blind or Severely Disabled
1421 Jefferson Davis Highway
Jefferson Plaza 2, Suite 10800
Arlington, VA 22202-3259
Phone: 703-603-0657
Fax: 703-603-0655
Email: rwells@jwod.gov

Technical Advisors – Government

Primary:

Anna Johnson-Winegar, Ph.D.
Deputy Assistant to the Secretary of Defense for Chemical/Biological Defense Programs
3050 Defense Pentagon, Room 3C257
Washington DC 20301-3050
Phone: 703-693-9410
Fax: 703-695-0476
Email: johnsoad@acq.osd.mil

Robert E. Foster, Ph.D.
Director, Bio Systems
Office of the Deputy Under Secretary of Defense (Science and Technology)
3080 Defense Pentagon, Room 3D129
Washington, DC 20301-3080
Phone: 703-697-8714
Fax: 703-693-7042
Email: fosterre@acq.osd.mil

Other:

Steve McManus
Director, Pharmaceuticals Group
Defense Supply Center, Philadelphia
Defense Logistics Agency
DSCP-MG (Bldg 6A)
700 Robbins Avenue
Philadelphia, PA 19111
Phone: 215-737-2801
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Thomas C. Fileccia
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Depot, Managed Care, Direct Vendor Delivery Sections
Defense Supply Center, Philadelphia
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700 Robbins Avenue
Philadelphia, PA 19111-5092
Phone: 215-737-2839
Fax: 215-737-3127
Email: tfileccia@dscp.dla.mil

Technical Advisors/Analysts – Contract

Daniel L. Rickett, Ph.D. – Lead Analyst
Vice President and Manager
Biomedical Technology Division
Science Applications International Corporation

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Senior Medical Scientist
Biomedical Technology Division
Science Applications International Corporation

Donna L. Bareis, Ph.D.
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Biomedical Sciences Group
Science Applications International Corporation

Mark R. Brunswick, Ph.D.
Expert Biologist/Senior Regulatory Scientist
Biomedical Technology Division
Science Applications International Corporation

Joseph C. Denniston, V.M.D., Ph.D.
Senior Biomedical Scientist
Biomedical Technology Division
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Science Applications International Corporation

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Senior Program/Policy Analyst
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ATTACHMENT III

Panel Member Resumes

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CURRICULUM VITAE
Franklin H. Top, Jr., M.D.

EDUCATION

University of Minnesota, Pediatric Infectious Disease Fellowship, 1964 -1966
University of Minnesota, Pediatric Residency, 1962 - 1964
University of Minnesota, Pediatric Internship, 1961 - 1962
Yale University, M.D. cum laude, 1961
Yale University, B.S. in Biochemistry, 1957

PROFESSIONAL EXPERIENCE

MEDIMMUNE, INC.
1988 - Present
Executive Vice President, Medical Director, and Director
Responsible for planning and execution of clinical studies of MedImmune products. Member, Board of Directors.

PRAXIS BIOLOGICS
1987 - 1988
Senior Vice President, Clinical Research and Medical and Regulatory Affairs
Responsible for planning and execution of all clinical research involving Praxis' vaccines. Responsible for medical affairs and for corporate liaison with the FDA, Center for Biological Evaluation and Research . As additional duty, served as Executive Vice President and acting Chief Executive Office of the company.

WALTER REED ARMY INSTITUTE OF RESEARCH
1983 - 1987
Director and Commandant
Commander and scientific leader of the Department of Defense's largest medical research laboratory (and five overseas satellite laboratories) with research interests in infectious diseases, drug and vaccine development, military occupational health hazards, military stress and neuropsychiatry. Responsible for staff of over 1,000 employees and an annual budget of $45 million.

UNITED STATES ARMY MEDICAL RESEARCH
INSTITUTE OF CHEMICAL DEFENSE
1981 - 1983
Commander
Commander and scientific leader of the Army's lead laboratory for medical defense against chemical warfare. Developed and implemented new programs in drug development. Responsible for a staff of 200 people, an annual budget of $13 million, and $20 million contract program.

WALTER REED ARMY INSTITUTE OF RESEARCH
1979 - 1981
<u>Deputy Director</u>
Responsible for daily operations of the Department of Defense's largest medical research laboratory.

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
1978 - 1987
<u>Professor of Pediatrics</u>
Participated in Pediatric Infectious Diseases rounds, conferences, and attended on Pediatric Infectious Disease service at Walter Reed Army Medical Center.

WALTER REED ARMY INSTITUTE OF RESEARCH
1976 - 1978
<u>Director, Division of Communicable Diseases and Immunology</u>
Directed and supervised all Walter Reed Army Institute of Research research on vaccines and infectious diseases.

1973 - 1976
<u>Chief, Department of Virus Diseases</u>
Directed and supervised a virus laboratory of 40 employees with research interests in viral respiratory diseases, dengue virus and hepatitis virus. Served as Department of Defense working liaison with other federal agencies - Center for Disease Control, National Institute of Allergy and Infectious Diseases, and the Bureau of Biologics, Food and Drug Administration - in the National Influenza Vaccine Program.

SOUTHEAST ASIA TREATY ORGANIZATION
MEDICAL RESEARCH LABORATORY
1970 - 1973
<u>Chief, Department of Virology</u>
Directed and supervised a virus research laboratory with 40 employees. Coordinated WHO sponsored studies of the immunopathogenesis of dengue hemorrhagic fever with Scripp's Clinic and Research Foundation, Ramathibodi Medical School, and various other hospitals. Supervised the training of the Army's Pediatric Infectious Disease fellows tour at Bangkok Children's Hospital.

WALTER REED ARMY INSTITUTE OF RESEARCH
1966 - 1970
<u>Assistant Chief, Department of Virus Diseases</u>
<u>Internist, Department of Virus Diseases</u>
Internist then Assistant Chief, Department of Virus Diseases. Designed and conducted clinical studies of safety and immunogenicity and later efficacy trials of live oral adenovirus type 4 and 7 vaccines for prevention of Acute Respiratory Disease in military recruits.

MEMBERSHIPS

Alpha Omega Alpha Medical Honor Society, 1960
American Academy of Pediatrics, Fellow
American Medical Association
American Association for the Advancement of Science
American Association of Immunologists
American Board of Pediatrics, 1966
Society for Pediatric Research
American Society of Tropical Medicine and Hygiene
Infectious Disease Society of America
Microbial & Infectious Disease Advisory Committee, National Institute of Allergy and Infectious Diseases, NIH, 1976 - 1980

HONORS

Colonel, U.S. Army (retired)
Legion of Merit with Two Oak Leaf Clusters
Meritorious Service Medal

SELECTED PUBLICATIONS

1. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics,* in press.

2. The PREVENT Study Group. Reduction of RSV hospitalization among premature infants and infants with bronchopulmonary dysplasia using Respiratory Syncytial Virus Immune Globulin. *Pediatrics*, 99: 93-99, 1997.

3. Bancroft, W.H., Top, F.H. Jr., Eckels, K.H., Anderson, J.H. Jr., McCown, J.M. and Russell, P.K. Dengue-2 vaccine: Virological, immunological and clinical responses of six yellow fever-immune recipients. *Inf & Immun* 31: 698-703, 1981.

4. Takafuji, E.T., Gaydos, J.C., Allen, R.G. and Top, F.H. Jr. Simultaneous administration of live enteric-coated adenovirus types 4, 7 and 21 vaccines; Safety and Immunogenicity. *J Inf Dis* 140: 48-53, 1979.

5. Wise, T.G., Dolin, R., Mazur, M.H., Top, F.H. Jr., Edelman, R. and Ennis, F.A. Serological responses and systemic reactions in adults following vaccination with bivalent A/Victoria-A/New Jersey and monovalent B/Hong Kong influenza vaccines. *J Inf Dis* 136: S507-S517, 1977.

6. Top, F.H. Jr., and Russell, P.K. Influenza A/Swine at Fort Dix, New Jersey (January-February 1976). IV. Summary and speculation. *J Inf Dis* 136: S376-S380, 1977.

7. Hodder, R.A., Gaydos, J.C., Allen, R.G., Top, F.H. Jr., Nowosiwksy, T. and Russell, P.K. Influenza A/Swine at Fort Dix, New Jersey (January-February 1976). III. Extent of spread and duration of the outbreak. *J Inf Dis* 136: S363-S368, 1977.

8. Gaydos, J.C., Hodder, R.A., Top, F.H. Jr., Allen, R.G., Soden, V.J., Nowosiwsky, T. and Russell, P.K. Influenza A/Swine at Fort Dix, New Jersey (January-February 1976). II. Transmission and morbidity in units of cases. *J Inf Dis* 136: S363-S368, 1977.

9. Gaydos, J.C., Hodder, R.A., Top, F.H. Jr., Soden, V.J., Allen, R.G., Bartley, J.D., Zabkar, J.H., Nowosiwsky, T. and Russell, P.K. Influenza A/Swine at Fort Dix, New Jersey (January -February 1976). I. Case finding and clinical study of cases. *J Inf Dis* 136: S356-362, 1977.

10. Parkman, P.D., Galasso, G.J., Top, F.H. Jr. and Noble, G.R. Summary of clinical trials of influenza vaccines. *J Inf Dis* 134: 100-107, 1976.

11. Benenson, M.W., Top, F.H. Jr., Gresso, W., Ames, C.W. and Altstatt, L.B. The virulence to humans of Japanese encephalitis virus in Thailand. *Am J Trop Med Hyg* 24: 974-980, 1975.

12. Top, F.H. Jr. Control of adenovirus acute respiratory disease in U.S. Army trainees. *Yale J Biol Med* 48: 185-195, 1975.

13. Bokisch, V.A., Top, F.H. Jr., Russell, P.K., Dixon, F.J. and Muller-Eberhard, H.J. The potential pathogenetic role of complement in dengue hemorrhagic shock syndrome. NEJM 289: 996-1001, 1973.

14. Pathogenetic mechanisms in dengue hemorrhagic fever: Report of an international collaborative study. Bull. *WHO* 48: 117-133, 1973.

15. Dudding, B.A., Top, F.H. Jr. , Scott, R.M., Russell, P.K. and Buescher, E.L. An analysis of hospitalizations for acute respiratory disease in recruits immunized with adenovirus type 4 and 7 vaccines. *Am J Epidem* 95: 140-147, 1972.

16. Top, F.H. Jr., Dudding, B.A., Russell, P.K. and Buescher, E.L. Control of respiratory disease in recruits with type 4 and 7 adenovirus vaccines. *Am J Epid* 94: 142-146, 1971.

17. Top, F.H. Jr., Buescher, E.L., Bancroft, W.H. and Russell, P.K. Immunization with live types 7 and 4 adenovirus vaccines: II. Antibody response and protective effect against acute respiratory disease due to adenovirus Type 7. *J Inf Dis* 124: 155-160, 1971.

18. Top, F.H. Jr., Grossman, R.A., Bartelloni, P.J., Segal, H.G., Dudding, B.A., Russell, P.K., and Buescher, E.L. Immunization by selective intestinal infection with adenovirus type 7: Tests for safety, infectivity, antigenicity and potency in volunteers. *J Inf Dis* 124: 239-248, 1970.

19. Top, F.H. Jr. and Wannamaker, L.W. The serum opacity reaction of Streptococcus pyogenes: The demonstration of multiple, strain-specific lipoproteinase antigens. *J Exp Med* 127: 1013-1034, 1968.

20. Top, F.H. Jr., Wannamaker, L.W., Maxted, W.R. and Anthony, B.F. M antigens among group A streptococci isolated from skin lesions. *J Exp Med* 126: 667-635, 1967.

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JOHN J. DINGERDISSEN
825 Bainbridge Drive
West Chester, PA 19382
(215) 652-4460 (W) (610) 399-3772 (H)

PERSONAL HISTORY

Birth Date: November 10, 1949
Citizenship: USA
Marital Status: Married, three children

PROFESSIONAL EXPERIENCE

Merck Manufacturing Division
Viral Vaccine Manufacturing, Senior Director: 1997-Present

- Responsible for a staff of ~45 professionals and ~160 union employees involved in the manufacture of Varivax®, M-M-R® II, Vaqta®.
- Responsible for the strategic capacity planning for the Poultry Area, Rotavirus and Varivax®.
- Responsible for the start-up of the new Rotavirus manufacturing facility.
- Responsible for Vaccine Operations' representation on the Company negotiation committee with the PACE union.
- Directs the organization in establishing production, cGMP, safety and environmental initiatives.
- Responsible for a budget of ~$40 MM, producing ~$600 MM worth of bulk vaccine product.

Merck Manufacturing Division
Biological Manufacturing, Senior Director: 1994-1997

- Responsible for a staff of ~75 professionals and 250 union employees involved in the manufacture of M-M-R® II, RECOMBIVAX HB®, Elspar®, Varivax® and Vaqta™.
- Responsible for the supply of launch materials for three new products: Varivax®, Vaqta® and COMVAX®.
- Responsible for Vaccine Operations' representation on the Company negotiation committee with the OCAW union.
- Responsible as point person for all major labor relations issues.
- Directs the organization in establishing production, cGMP, safety and environmental initiatives.
- Responsible for a budget of ~$40-50 MM.

Merck Manufacturing Division
Biotechnology, Director: 1990-1994

- Responsible for the Biological Technical Services and Biological Process Engineering departments. The focus of these groups is to provide for technical implementation of new processes as well as process improvement and technology enhancement in Biological Manufacturing. In addition, a third area of responsibility includes the design and implementation of the Biotechnology Manufacturing Complex, a $170 MM production facility.

- Direct the development and organization of ~50 staff scientists including cell biologists, microbiologists, virologists, biochemists, chemical engineers, biochemical engineers, and mechanical engineers.
- Manage a $5.5+ MM budget.
- Direct the strategic objectives for the Biotechnology organization. Develop and lead the implementation of the vision for the Biotechnology area.
- Establish the objectives, productivity initiatives, and direction for each of the technical departments.
- Direct the cohesive partnership with Merck Research Laboratories on the process optimization and implementation of new products and processes.
- Responsible for creating an environment of risk-taking and empowerment to help the scientists/engineers to solve taxing and extremely difficult technical production problems.

E. I. DuPont de Nemours & Company
Biotechnology Development Group, Senior Research Supervisor: 1988-1990

- Responsible for the fermentation/Protein Purification Process Development, GMP Scale-Up groups and the Analytical and Fermentation research support groups. Group included 32 scientists and support personnel.
- Chaired the 1L-1 Development Subcommittee.
- Primary responsibility for the preparation of recombinant proteins and polypeptides to support all phases of clinical development through product licensing for therapeutic and diagnostic business groups.
- Responsible for the production for bulk antigen for support of commercial European sales of an AIDS test kit.
- Responsible for the development of a raw materials management system for the production of GMP clinical supplies.
- Responsible for the process development and production of multigram quantities of PAI for research studies in animals.
- Managed the development and supervision of 3 Ph.D. scientists, 5 M.S./B.S. scientists, and 24 B.S. technicians.
- Responsible for the development of state-of-the-art capability in cell harvesting using UF.

SmithKline & French Laboratories
Biopharmaceutical R&D
Scientific Coordination Biotechnology Research, Senior Investigator: 1987-1988

- Coordinate and facilitate scientific and technical aspects of research programs and feasibility studies in Biopharmaceutical R&D.
- Reporting directly to the V.P. of Biopharmaceutical R&D, manage interactions and serve as scientific liaison between Biopharmaceutical R&D and other areas of SK&F and SKB regarding coordination of research efforts.
- Coordinate AIDS diagnostic and vaccine development programs in collaboration with SK-Bioscience and SK-Biologicals.
- Associate Project Leader for the Malaria Vaccine Development Project.

- Scientific Program Coordinator for the AIDS Antiviral Research Program and the Third Generation Fibrinolytics Research Program.
- Coordinate and facilitate research efforts in collaboration with outside academic and industrial partners.
- Recommend priorities for research programs and feasibility studies within Biopharmaceutical R&D.
- Represent V.P. of Biopharmaceutical R&D on safety, facilities, and GMP committees internally and I.B.A. and P.M.A. committees externally.

SmithKline & French Laboratories
Protein Biochemistry/Natural Products
Pharmacology Depts., Associate Investigator: 1984-1986

- Completed formal management training at the Wharton School of Business, University of Pennsylvania.
- Implemented the use of Project Scheduling Network software for planning clinical production campaigns.
- Responsible for the institution of GMP procedures and compliance testing for large scale protein purification.
- Interacted with appropriate scientists (molecular genetics, fermentation, cell culture, and pharmaceutics) and support functions (site services, regulatory compliance, engineering, etc.) in order to assure quality of clinical batches.
- Responsible for the supervision of the isolation/purification of clinical supplies of protein from rDNA sources.
- Responsible for writing the Manufacturing Control Instructions and Standard Operating Procedures according to GLP/GMP guidelines.
- Contributed to the design and completion of the purification scheme used to produce 75 grams of tissue plasminogen activator for pre-clinical Path/Tox studies, Phase I and II clinical trials.
- Responsible for the development of a raw materials management system for GMP production supplies.
- Assumed a major role in the successful completion of the preparation of two bulk malaria vaccines for clinical trials by planning and directing the actual process runs.
- Contributed to the preparation of three INDs.
- Increased the scientific capability of the group with personnel changes and equipment acquisitions.
- Proposed and implemented the acquisitions of high-tech robotics equipment for automation of tedious assays.
- Contributed to the design and completion of the purification scheme used in the production of Hepatitis B antigen and malaria antigen.
- Developed new rapid approaches to antibiotic discrimination.
- Participated on the R&D Chemical Health and Safety Committee as a member representing the Vice President of Biological R&D.
- Contributed to the design of the downstream protein purification facility in a Biopharmaceutical GMP Pilot Plant.

SmithKline & French Laboratories
Natural Products Pharmacology Dept., Senior Scientist: 1982-1983

- Assumed responsibility for the Recovery Group in Natural Products Pharmacology.
- Responsibilities included planning, scheduling, and reporting all experiments: interacted with four research program heads in the establishment and completion of objectives; supervision of five technicians; chairman of the Lead Evaluation Subcommittee.
- Designed the downstream processing facilities in a temporary pilot plant.
- Member of the Career Development Study Group.
- Developed straight forward approaches to antibiotic discrimination with a technological breakthrough.
- Introduced HPLC technology into the research group.
- Implemented the use of a computer data file for research data.

SmithKline & French Laboratories
Medicinal Chemistry Dept., Senior Medicinal Chemist: 1980-1982

- Responsible for the planning and scheduling of research in the antibiotic recovery area.
- Developed new techniques to aid in t he early research stages of current AHP development project.
- Managed the development and supervision of 25 technicians/associates.

SmithKline & French Laboratories
Medicinal Chemistry Dept., Medicinal Chemist: 1977-1980

- Responsible for research in antibiotic discovery, purification and structure determination.
- Developed mini-resin screen for methods development: saves time and money.
- Supervision and development of two technicians.

SmithKline & French Laboratories
Medicinal Chemistry Dept., Associate Medicinal Chemist: 1973-1977

- Responsible for research in antibiotic discovery, purification and structure determination.

Purdue University
School of Pharmacy
Dept. of Medicinal Chemistry & Pharmacognosy, Research Assistant: 1972-1973

- Responsible for independent laboratory experimentation.

Purdue University
Graduate Teaching Assistant: 1971-1972

- Responsible for setting up and teaching laboratory classes in medicinal chemistry and pharmacognosy.

Schering Corporation
Antibiotic Isolation Dept., Laboratory Assistant: 1970-1971

- Responsible for carrying out independent laboratory experiments in the antibiotic isolation/ recovery group.

EDUCATION

Certificate in Business Administration (MBA Core Courses)	University of Pennsylvania Wharton Management Program Philadelphia, PA 1983-1985
Advanced Graduate Courses (Organic, analytical, and biochemistry)	Villanova University Villanova, PA 1979-1980
Business Management Courses	Temple University Philadelphia, PA 1976-1977
M.S.	Purdue University West Lafayette, IN Medicinal Chemistry & Pharmacognosy Thesis: "Alkaloids of the Cactus Genus Dolichothele" 1971-9173
B.S.	Jersey City State College Jersey City, NJ Biology (Major) and Chemistry 1967-1971

TRAINING

Harvard University Executive Business Program, 2000
Diversity Training, 1998
Covey Leadership Training, 1994
Seven Habits of Highly Effective People, 1993
Principle Centered Leadership, 1993
Advanced Management Seminar I, 1991
MPMD Management Meeting, 1990
Leadership Conference, DuPont Pharmaceuticals, 1990
Anatomy of Persuasion, Aubuchon & Associates, 1989
How to Supervise Better, Padgett/Thompson, 1988
Multimate Word Processing Course, SK&F, 1987
Lewis Allen Management Course, Lewis Allen Association, 1987
IBM PC Course, SK&F, 1986
Lotus 1-2-3 Course, SK&F, 1986
Good Manufacturing Practice for the Pharmaceutical & Allied Health Industries, Center for Professional Advancement, 1986
Zymark Robotics Training Course, Zymark Corp., 1985
Burger Writing Course, SK&F, 1978
Supervisory Training Course, SK&F, 1977
High Pressure Liquid Chromatography, American Chemical Society, 1977

SOCIETIES & AFFILIATIONS

American Chemical Society (General and Microbial & Biochemical Technology Division)
Sigma Xi
Delaware Valley Chromatography Forum
Delaware Valley Robotics Interest Group (Vice Chairman, 1985-1986)
Pharmaceutical Manufacturers Association, Biological Section, Biotechnology Division
  Committee on Product Isolation and Purification - Vice Chairman (1987-1989)
  Committee on Process Development and Manufacturing - Vice Chairman (1989-1990)
  Biological and Biotechnology Section - Steering Committee (1990-Present)
Pennsylvania Biotechnology Association
  Board of Directors (1992-1993)
  President (1994-1995)
Governor Ridge's Network 21 - Biotechnology Task Force (1996)
PhRMA Adhoc Committee on Biological Weapons Convention (1996-Present)
International Society for Vaccines (1997)
Bioprocessing Resource Center, Inc., Board of Directors, (1997)

AWARDS

Cum laude graduate, Jersey City State College, 1971
Who's Who in American Colleges and Universities, 1971
Graduate Teaching Assistantship, Purdue University, 1971
Research Assistantship, Purdue University, 1972

SYMPOSIA CHAIRED/ORGANIZED

PMA Biological Section Spring Meeting, "Problems in Bioprocessing," Amelia Island, FL, May 1-3, 1989.
Biotech USA, "Production Scale Protein Purification," San Francisco, CA, October 2-4, 1989.
PMA Biological Section Fall Meeting, "Microheterogeneity of Recombinant Protein Products," Baltimore, MD, September 23-26, 1990.
PMA Biological and Biotechnology Section Spring Meeting, San Francisco, CA, May 5-8, 1991.
PMA Biological and Biotechnology Section Fall Meeting, "Regulation of Recombinant Products," Washington, DC, September 15-18, 1991.
PMA Biological and Biotechnology Section Spring Meeting, "Experiences with the EEC Approval Process," Orlando, FL, May 3-6, 1992.
PMA PERI Course Instructor, Biotechnology Quality Control, "Principles of Protein Isolation and Purification," 1992-1993.
PMA Biological and Biotechnology Section Spring Meeting, "Workshop on Multiproduct Facility Drugs," May 10, 1994.
BIO '96 Biotechnology Industry Organization International Meeting, "Planning for Biotech Manufacturing," June, 1996.

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Dingerdissen, J. J. 1983. Preparative large scale liquid chromatography. Gordon Conference on Separation and Purification.

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1987 - J. J. Dingerdissen, R. Mehta, M. C. Shearer, G. F. Wasserman. Kibdelosporangium aridum SKF AAD-609. No. 4, 694,069.

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CURRICULUM VITAE

NAME: William H. Habig

PLACE OF BIRTH: Newark, New Jersey

MARITAL STATUS: Married, three children

EDUCATION: 1964 - B.S. - Rutgers University, New Brunswick, New Jersey in "Preparation for Research" curriculum

1968 - Ph.D. (Biochemistry) – University of Vermont, Burlington, Vermont.

EXPERIENCE:

Jul. 1995 – present Director, R&D Quality Assurance, Centocor, Inc., Malvern, PA – responsible for GCP, GLP, environmental, and health compliance programs

Nov. 1988-Jun.1995: - Deputy Director, Division of Bacterial Products, Center for Biologics Evaluation and Research, FDA.

Jul. 1984-Jun. 1995: - Chief, Laboratory of Bacterial Toxins, Center for Biologics Evaluation and Research, FDA. Research and Regulation

Nov. 1975-Jun 1984: - Research Chemist, Laboratory of Bacterial Toxins, Center for Biologics Evaluation and Research, FDA. Research on bacterial vaccines, toxins, and adjuvants. Extensive involvement in regulatory affairs, including IND and license evaluation and inspections.

Sept. 1972-Oct. 1975: - Staff Fellow, Laboratory of Biochemistry and Metabolism, NIAMDD, NIH. Advisor: Dr. W.B. Jakoby. Research on glutathione transferases, liver detoxification enzymes.

Feb. 1971-July 1972: - Postdoctoral Fellow, Division of Laboratories and Research, New York State Dept. of Health, Albany, NY 12201. Dr. Donald S. Berns. Studied biliproteins from blue-green algae. Joint appointment as Research Associate, Dept. of Biochemistry, Albany Medical College.

Sept. 1968-Jan. 1971: - Biochemist (as Captain, U.S. Army) at Walter Reed Army Medical Center, Microbiology Division, Washington, D.C. Studied several antigens of *Yersinia pestis*, particularly the capsular antigen and cytochromes.

1964-1968 - Graduate Research Assistant, Dept. of Microbiology and Biochemistry, University of Vermont. Advisor: Dr. David Racusen. Thesis title: A High Molecular Weight Malate Dehydrogenase in Leaves.

AWARDS:

1995: FDA Distinguished Career Service Award
1995: Certificate of Appreciation (for significant contributions to training at CBER)
1994: Certificate of Appreciation (US-Egypt Cooperative Health Program)
1993: FDA Group Recognition Award (Childhood Vaccine Group)
1993: FDA Superior Service Award (for exemplary leadership in fulfilling scientific and regulatory missions of CBER)
1992: FDA Group Recognition Award (Desert Shield/Storm Task Force)
1991: FDA Award of Merit (Group Award)
1988: Ref. No. 9 in Publications list identified as "Citation Classic" (cited more than 1,000 times) by Current Contents
1988: FDA Commendable Service Award (critical and effective reviews of diverse and complex applications)
1988: FDA Commendable Service Award (Group Award)
1986 and 1982: Employee Suggestion Awards
1982 - 1991: Analytical Biochemistry Editorial Board
1968: Distinguished Honor Graduate, Medical Field Service School, Fort Sam Houston, Texas

MEMBERSHIPS (CURRENT):

American Association for the Advancement of Science
Parenteral Drug Association

OTHER ACTIVITIES:

Member of Analytical Biochemistry Editorial Board (1982-1991; 2000 - 2006)

PUBLICATIONS

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2. Habig, W.H. and D. Racusen. 1969. The effect of light on ribulose diphosphate carboxylase in albino corn leaves. Can. J. Bot. 47:1051.

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61. Habig, W.H. 1988. Biological Detoxification in 1988 Yearbook of Science and Technolgy (S.P. Parker, ed.). McGraw Hill, New York, pp. 453-456.

62. Habig, W.H., T. Holohan and T. Phillips. 1988. Circulating Immune Complexes after DTP Immunization (Letter to the Editor). J. Pediatrics 112:162-163.

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CURRICULUM VITAE

June 10, 1999

Name: Gerald V. Quinnan, Jr., M.D.
Birth: September 7, 1947; Boston, Massachusetts
Spouse and Children: Married to Leigh A. Sawyer; five children
Date of Birth: September 7, 1947

Education:

1965 - 1969	Bachelor of Arts, Chemistry, College of Holy Cross, Worcester, MA
1969 - 1973	M.D., Cum Laude, Saint Louis University, School of Medicine, Saint Louis, MO

Graduate Training:

1973 - 1974	Internship, Straight Medicine, University Hospital, Boston University Medical Center, Boston, MA
1974 - 1975	Residency, Internal Medicine, Boston University Medical Center, Boston, MA
1975 - 1977	Fellowship, Adult Infectious Diseases, Boston University Medical Center, Boston, MA
1977 - 1978	Research Associate, Division of Virology, Bureau of Biologics, Food and Drug Administration (FDA),USPHS, Bethesda, MD

APPOINTMENTS:
Academic

1975 - 1977	Teaching Fellow in Medicine, Boston University Medical Center, Boston, MA
1978 - 1980	Medical Officer, Division of Virology, Bureau of Biologics, FDA
1978 - 1982	Senior Attending Physician, Infectious Disease Service, Clinical Center, National Institutes of Health (NIH), Bethesda, MD
1978 - 1979	Lecturer, Second Year Course on Infectious Diseases, George Washington University Medical Center, Washington, DC
1979 - 1985	Lecturer, FAES Course in Internal Medicine, NIH, Bethesda, MD
1980 - 1981	Director, Herpesvirus Branch, Division of Virology, Bureau of Biologics, FDA
1980 - 1981	Deputy Director (Acting), Division of Virology, Bureau of Biologics, FDA
1981 - 1988	Director, Division of Virology, Office of Biologics Research and Review, Center for Drugs and Biologics, FDA
1988 - 1993	Deputy Director, Center for Biologics Evaluation and Research (CBER), FDA
1990 - 1992	Acting Director, CBER, FDA
1993	Acting Director, Office of Blood Research and Review, CBER, FDA
1993 -present	Professor of Preventive Medicine, Medicine and Microbiology, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences

Certification and Licensure:

Medical License: Massachusetts, Maryland, Virginia (inactive)
National Board of Medical Examiners, 1974
American Board of Internal Medicine, 1976

Scientific Societies: Alpha Omega Alpha, 1972
American Association for the Advancement of Science
American Federation for Medical Research
American Society for Clinical Investigation (1985; 37 years of age)
American Society for Microbiology
Infectious Diseases Society of America (Fellow)
Sigma Xi, 1992

Editorial Activities:

Editorial Board: Journal of Biological Standardization (1992-1997)
AIDS Research and Human Retroviruses (1985-1998)

Reviewer: New England Journal of Medicine
Annals of Internal Medicine
Journal of the American Medical Association
Journal of Clinical Investigation
The Journal of Infectious Diseases
Clinical Infectious Diseases
Journal of Virology
Journal of Immunology
Journal of AIDS

Uniformed Service:

1977 - 1980	Lieutenant Commander (0-4), USPHS
1980 - 1982	Commander(0-5), USPHS
1982 - 1992	Captain(0-6), USPHS
1992 - 1993	Rear Admiral(0-7), USPHS
1993 -present	Captain(0-6), USPHS

Other Professional Activities:

1974 - 1977	Emergency Medicine, Needham Emergency Medical Corporation, Glover Memorial Hospital, Needham, MA
1974 - 1976	Emergency Medicine, Waltham Hospital, Waltham, MA
1974 - 1977	Consultant, Massachusetts Department of Public Health
1977 - 1978	FDA Influenza A/USSR Virus Vaccine Task Force,
1979	Panel Member US-USSR Agreement on Vaccine Research and Development
1980 - 1983	President, Parish Council, Saint Patrick's Church, Rockville, MD
1980 - 1993	Temporary Advisor, World Health Organization
1980 - 1993	USPHS Interagency Group on Vaccine Development and Availability
1981 - 1982	FDA Reye Syndrome Working Group
1981 - 1983	Consultant, Infectious Disease Associates, Fairfax, VA
1982 - 1985	USPHS Reye Syndrome Task Force,
1981 - 1984	USPHS AIDS Executive Committee
1982 - 1988	Director, Athletic Program, Saint Patrick's Church, Rockville, MD
1984 - 1992	USPHS Executive Task Force on AIDS, Vaccine Development Subcommittee
1988 - 1993	USPHS Executive Task Force on AIDS, Blood Subcommittee
1992 - 1993	USPHS Interagency Group on Blood Safety, Chair

1993 - 1994 Chair, USAID Technical Advisory Group on Rinderpest Vaccine Development
1994 - Consultant, FDA Vaccines and Related Biologics Advisory Committee
1995 - Member Scientific Advisory Board, Aviron Corporation
1995- Ad Hoc Member, AIDS Related Research Study Section, NIH, 1995
Previous Ad Hoc Consultations for the U. S. Public Health Service Advisory Committee on Immunization Practices, Pan American Health Organization, Infectious Diseases Committee of the American Academy of Pediatrics, and for special study sections of the National Institute of Allergy and Infectious Diseases, National Cancer Institute, National Institute of Neurological and Communicative Disorders and Stroke, and National Institute on Drug Abuse
Participated on steering committees, program committees, and organizing committees of numerous national and international meetings.

Study Sections (recent):

AIDS Related Research-A, ad hoc reviewer, 1996-present.
National Cooperative Vaccine Development for AIDS, 1997
AIDS Related Research-VACC, member, 1998-present

Awards, Honors:

Elected to Alpha Omega Alpha, 1973
M.D. Degree, Cum Laude
Diplomate, American Board of Internal Medicine, 1976
Eligible, Infectious Disease Subspecialty Board, 1977
FDA Commendable Service Award, 1979
USPHS Unit Commendation, 1983
USPHS Meritorious Service Medal, 1984
Elected to American Society for Clinical Investigation, 1985
Elected to Fellow in the Infectious Disease Society of America, 1986
USPHS Outstanding Unit Citation, 1987
USPHS Unit Commendation, 1989
USPHS Citation, 1989
USPHS Distinguished Service Medal, 1990
USPHS Commendation Medal, 1991
Elected to Membership, Sigma Xi, 1992
Surgeon General's Medal for Exemplary Service, 1993
USPHS Unit Commendation, 1993
USPHS Outstanding Unit Citation, 1993
USPHS Commendation Medal, 1993
Distinguished Career Service Award, Center for Biologics Evaluation and Research, 1993

Funded Grants:

1994 - present: Uniformed Services University of the Health Sciences grant #RO87EZ, "Mechanisms of Neutralization Resistance of HIV-1," Principal Investigator
1995 - present: National Institutes of Health grant RO1 AI37438-01A1, "Neutralization Resistance of HIV-1," Principal Investigator
1997 - present: National Institutes of Health/Fogarty International Center Grant, #D43TW-96001, "International Training in Emerging Infectious Diseases,"

CoDirector

1998 - present: National Institutes of Health grant R21 AI42645, “Broad Neutralizing Response to HIV/VEE Replicons,” Principal Investigator

1998 - present: USUHS Grant #87JZ01, ”Cohort Study of HTLV-1 and Strongyloides Pathogenesis,” Coinvestigator.

Patent Applications:

1. Quinnan, GV and Zhang PF: Expression and characterization of HIV-1 envelope protein associated with a broadly reactive neutralizing antibody response. Submitted. 1998.

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3. Quinnan G, Manischewitz J and Ennis F: Cytotoxic T lymphocyte response to murine cytomegalovirus infection. Nature 273:541-543, 1978.
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5. Wise T, Manischewitz J, Quinnan G, Aulakh G and Ennis F: Latent cytomegalovirus infection of BALB/c mouse spleens detected by an explant culture technique. J Gen Virol 44:551-556, 1979.
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8. McLaren C, Grubbs GE, Staton E, Barthlow W, Quinnan G and Ennis FA: Comparative antigenicity and immunogenicity of A/USSR/77 influenza vaccines in normal and primed mice. Infect Immun 28:171-177, 1980.
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14. Kirmani N, Ginn RK, Mittal KK, Manischewitz JF and Quinnan GV: Cytomegalovirus specific cytotoxicity mediated by non-T lymphocytes from peripheral blood of normal volunteers. Infect Immun 34:441-447, 1981.
15. Quinnan GV, Manischewitz JF and Kirmani N: Involvement of natural killer cells in the pathogenesis of murine cytomegalovirus interstitial pneumonitis and the immune reponse to infection. J Gen Virol 58:173-180, 1982.
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Dr. Wells is the Deputy Executive Director and Chief Operating Officer of the Committee for Purchase from People Who Are Blind or Severely Disabled. The Committee is an independent Federal agency responsible for managing the Javits-Wagner-O'Day (JWOD) Program, through which Federal activities purchase goods and services from nonprofit agencies associated with the National Industries for the Blind (NIB) and NISH, serving people with other severe disabilities. JWOD Program procurements provide high quality goods and services needed for the operation of the federal government, and also provide employment and job skills training for more than 34,000 people who are blind or have other severe disabilities.

Dr. Wells has an extensive background in Federal acquisition and management. She began her career in a contracting intern program with the Department of Defense (DoD) and went on to hold various acquisition related positions including as the program manager of a joint DoD-wide program, a Procuring Contracting Officer (TOMAHAWK Cruise missile program), an Administrative Contracting Officer for the Defense Logistics Agency, and a contract price analyst with the Pacific Command of the Air Force. She also was a member of the acquisition management faculty at both the Industrial College of the Armed Forces (ICAF), and the Air Force Institute of Technology (AFIT).

In addition, Dr. Wells teaches business administration and contract management courses for the University of Virginia. She also is a Faculty Associate at Johns Hopkins University for graduate courses in leadership and global strategic management.

She holds a doctorate from The Ohio State University, an MBA from Southern Illinois University, and a BA from the University of Illinois. Dr. Wells is a graduate of the Industrial College of the Armed Forces and the Department of Defense Senior Executive Leadership Course.

She is the recipient of many awards including the Hammer Award, the Commander's Award for Public Service, and the Meritorious Civilian Service award. Dr. Wells is a National Contract Management Association (NCMA) Fellow and a Certified Professional Contracts Manager (CPCM).

Dr. Wells resides in Falls Church, Virginia with her husband, John H. Wells, Ed.D., and their children, Martha and David.

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ATTACHMENT IV

Review of the Department of Defense's (DoD) Acquisition of Vaccine Production Memorandum

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OFFICE OF THE SECRETARY OF DEFENSE

1000 DEFENSE PENTAGON
WASHINGTON, DC 20301-1000

AUG 17 2000

MEMORANDUM FOR SECRETARIES OF THE MILITARY DEPARTMENTS
CHAIRMAN OF THE JOINT CHIEFS OF STAFF
DUSD, INDUSTRIAL AFFAIRS
DUSD, ACQUISITION REFORM
DUSD, LOGISTICS
DIRECTOR, DIA
DIRECTOR, DLA
DIRECTOR, DTRA
DIRECTOR, DARPA
DIRECTOR, ACQUISITION RESOURCES AND ANALYSIS
DIRECTOR, DEFENSE PROCUREMENT
PRESIDENT, NDU
COMMANDANT, DSMC

SUBJECT: Review of the Department of Defense's (DoD) Acquisition of Vaccine Production

On August 20, 2000, the Deputy Secretary of Defense tasked the Director, Defense Research and Engineering (DDR&E) and the Assistant Secretary of Defense for Health Affairs (ASD(HA)) to jointly contract with a private organization or panel of experts to conduct a comprehensive study of the DoD's procurement of vaccine production (Enclosure 1). The panel's report of their findings is to be completed by November 20, 2000.

In response to this tasking, the DDR&E contracted with Science Applications International Corporation (SAIC) to support this effort. SAIC participated with DDR&E and ASD(HA) in drafting the approach to be followed (Enclosure 2) and a list of recommended topics and key points to be presented to the panel assembled in response to the subject (Enclosure 3). We request that your organization provide us a point of contact by August 23, 2000, to help expand upon the key points to be addressed and recommend and justify any special policies or procedures they believe are required to facilitate DoD oversight of successful vaccine acquisition.

Please provide the name of your organization's point of contact to Mr. Tom Bibby at 703-697-5561 or e-mail: bibbytm@acq.osd.mil. Your inputs for the study will be needed by September 6, 2000, and should be in briefing format with narrative back-up and source references.

Hans Mark
Director
Defense Research & Engineering

J. Jarrett Clinton, MD, MPH
Acting Assistant Secretary of Defense
(Health Affairs)

Enclosures:
1. DEPSECDEF Memorandum, 20 Jul 00
2. Study Approach to be Followed
3. List of Recommended Topics & Key Points

DEPSECDEF Review of the Department's Acquisition of Vaccine Production Approach to be Followed

1. Tasks (from DEPSECDEF memo dated July 20, 2000)

   a. Consider vaccines—for which DoD is a major customer—to protect service members from biological warfare threats as well as infectious diseases.
   b. Compare DoD status quo with best business practices and identify if/how DoD can leverage best aspects of private sector programs from industry.
   c. Determine whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.[1]
   d. Develop recommendations for how the Department should best develop and oversee a vaccine production program.

2. Participants

   a. DoD personnel may serve as technical advisors to the panel; not as panel members.
   b. Panel chair with widely recognized expertise in the commercial vaccine industry is the preferred choice; however, this is not essential if a creditable one is not available.
   c. Execute both a disclosure statement of related activities and plans, as well as non-disclosure statements.

3. Approach

   a. SAIC prepares read-ahead material for panel members.
   b. SAIC identifies candidate presenters from DoD and from industry and defines the scope of their presentations to include "must address" items.
   c. SAIC conducts a critique of all read-ahead documents, and identifies potential issues and questions for panel consideration.
   d. Panel receives read-ahead presentations from DoD with SAIC critiques, then members meet to discuss, identify issues and additional questions, and arrange schedules for interviews.
   e. Panel members interview "presenters" in a question and answer format.
   f. Slip the meeting schedule start until September and adhere to November 20 due date in the DEPSECDEF memo.
   g. Final product is DEPSECDEF briefing and back-up material.
   h. Read-ahead material and proceedings will be organized and catalogued for future reference.

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[1] Operationally defined as DoD Agency and Component augmentation to and implementation of the DoDD 5000 series policies and Goldwater-Nichols Act.

DEPSECDEF Review of the Department's Acquisition of Vaccine Production
Recommended Presentations

The following table contains recommended topics and points to be presented to the panel assembled in response to the subject. The respondent organizations are offered the opportunity to expand upon the mandatory key points to be addressed. Additionally, they are requested to recommend and justify any special policies or procedures they believe are required to facilitate DoD oversight of successful vaccine procurement. Responses should be in briefing format with narrative back-up and source references. These should be due to SAIC to initiate a critique not later than September 6, 2000.

Topic and Key Points to Address
• *US Vaccine Policy*
• *Roles and Responsibilities: RDA from Milestone I to Procurement*
• *Vaccine Procurement and Logistics* [1]
• *Vaccine Adverse Event Reporting and Product Recall*
• *Post-marketing Surveillance*
• *Clinical Record Keeping*
• *Industrial Base Experience—capacity (surge), stockpile, diversity*
• *Federal Regulatory Issues*
• *Vaccine Product Life Cycle Management* [2]
• *Industrial Base Experience*
• *DoD and Service-unique (if any) Requirements Definition*
• *Operational Requirements Definition*
• *Threat Assessments*
• *Planning, Programming and Budgeting—Resource Management*
• *Vaccine Acquisition Strategy and Plans—Rationale*
• *Intellectual Property Management—DoD and Commercial*
• *Contracting and CRADA Mechanisms*
• *Product and Operational Liabilities and Indemnification*
• *Security*
• *Geopolitical Issues*

[1] Supplemented by DSPC Representative
[2] Supplemented by DSMC Representative

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ATTACHMENT V

Deputy Secretary of Defense Vaccine Acquisition and Procurement Study Panel Meeting Agenda, September 25 and 26, 2000

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DEPUTY SECRETARY OF DEFENSE
VACCINE ACQUISITION AND PROCUREMENT STUDY PANEL MEETING
September 25 and 26, 2000
Crystal Gateway 4
Sign-In Suite 1500
Conference Room on 12th floor

AGENDA

September 25, 2000

8:00 – 8:15	Administrative announcements	Dr. Rickett
8:15 – 8:30	Introductions	Members and staff
8:30 – 9:30	Background and related studies	Dr. Johnson-Winegar
9:30 – 10:00	Discuss approach	Dr. Top
10:00 – 10:15	*Break*	
10:15 – 11:00	Threat Assessment	Dr. Bancroft
11:00 – 12:00	Requirements & Acquisition Mgmt	Dr. Denniston
12:00 – 13:00	Working Lunch – Discussion	Panel
13:00 – 13:30	Formal Charge to the Panel	Drs. Mark & Clinton
13:30 – 14:30	Acquisition Life Cycle	Dr. Rickett
14:30 – 15:30	DoD Vaccine Acquisition	Dr. Bancroft
15:30 – 15:45	*Break*	
15:45 – 16:30	DSCP Vaccine Management	Mr. McManus
16:30 – 17:00	Discussion of Next Steps	Panel
17:00	Recess until 8:00 a.m., September 26th	

September 26, 2000

8:00 – 8:15	Administrative announcements	Dr. Rickett
8:15 – 9:15	Discuss DoD Vaccine Acquisition	Panel
9:15 – 10:15	Industry Best Practices	Mr. Gardner
10:15 – 10:30	*Break*	
10:30 – 11:00	DoD Specific Regulatory Issues	Mr. Miller
11:00 – 11:30	FDA Regulatory Considerations	Dr. Brunswick
11:30 – 13:00	Working Lunch – Clarification Discussions	Panel
13:00 – 15:00	Identify Missing Elements	Panel
15:00 – 15:30	*Break*	
15:30 – 17:00	Develop Agenda for next meeting	Panel
17:00	Recess until next meeting (October 10th?)	

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ATTACHMENT VI

Deputy Secretary of Defense Vaccine Acquisition and Procurement Study Panel Meeting Agenda, October 11, 12, and 13, 2000

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DEPUTY SECRETARY OF DEFENSE
VACCINE ACQUISITION AND PROCUREMENT STUDY PANEL MEETING

October 11, 12 and 13, 2000
Epicenter 4A
SAIC Towers
1710 SAIC Drive
McLean, Virginia 22102
Phone: 703-821-4300
Fax: 703-676-4050

AGENDA

October 11, 2000

8:00 – 8:15	Administrative Announcements	Dr. Rickett
8:15 – 9:45	Recap and Discussion	Panel
9:45 – 10:00	*Break*	
10:00 – 11:00	Defense Contract Management Agency	Maj Gen Malishenko, USAF
11:00 – 12:00	Program Office/Contracting Interactions	Mr. Scott
12:00 – 13:00	Working Lunch – Discussion	Panel
13:00 – 15:00	Develop Approach and Questions for Day 2	Panel
15:00 – 15:15	*Break*	
15:15 – 17:00	Develop Approach and Questions for Day 2	Panel

October 12, 2000

8:00 – 9:00	Interview LTG Kern, U.S. Army	Panel
9:00 – 10:00	Interview MG Parker, U.S. Army and Ms. Armbruster, JPO BD	Panel
10:00 – 10:15	*Break*	
10:15 – 11:15	Interview COL Hoke, U.S. Army and COL Danley, U.S. Army	Panel
11:15 – 12:00	Discussions	Panel
12:00 – 13:00	Working Lunch – Discuss Way Forward	Panel
13:00 – 15:00	Discussions and Report Development	Panel
15:00 – 15:15	*Break*	
15:15 – 17:00	Report Preparation	Panel

October 13, 2000

8:00 – 10:00	Report Preparation	Panel
10:00 – 10:15	*Break*	
10:15 – 12:00	Report Preparation	Panel
12:00 – 13:00	Working Lunch – Discussions	Panel
13:00 – 15:00	Report Preparation	Panel
15:00 – 15:15	*Break*	
15:15 – 17:00	Report Preparation	Panel

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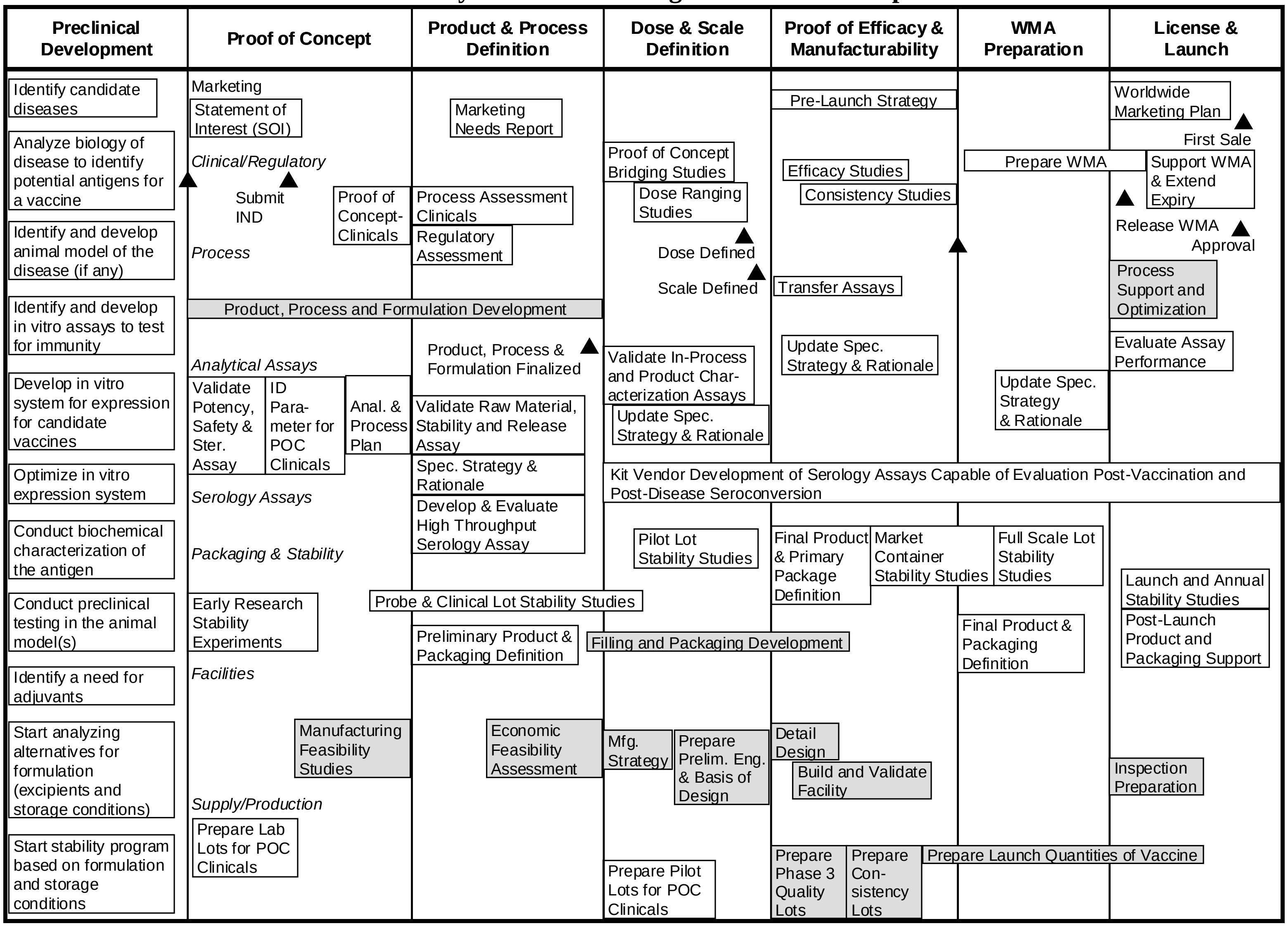
APPENDIX B

Generic Industry Process for Biologics Product Development



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APPENDIX C

Several Categories of Consideration for Vaccine Discovery through the Manufacturing Process

- Technologies
  - Conventional – live attenuated or inactivated organisms
  - DNA
  - Recombinant proteins
  - Viral or bacterial vector delivery
  - Immune stimulators
  - Synthetic peptides
  - Fermentation
  - Cell culture
  - Inactivation
  - Protein purification
  - Polysaccharide purification
  - Protein-polysaccharide conjugation
  - Adjuvant adsorption
  - Lyophilization
- Source Materials
  - Vendor audits
  - Source identifiers
  - Lot traceability
  - Process control
  - Quality control
  - Material specifications
  - Inspection
  - Container testing
- Specialized Equipment
  - Fermenters
  - Robots
  - Centrifuges
  - Filtration Systems
  - Chromatography systems
  - Lyophilizers
  - Filling systems
  - Inspection systems
  - Packaging systems
  - Automation
- Product Characterization
  - Capillary zone electrophoresis
  - DNA and protein sequencing
  - Enzyme immunoassay and radioimmunoassays
  - HPLC
  - NMR
  - Immunochemical rate nephelometry
  - Size exclusion chromatography

Several Categories of Consideration for Vaccine Discovery through the Manufacturing Process (cont.)

- Personnel Qualifications and Training
  - 30%–40% Advanced Degrees in area directly related to job
    - Technology (e.g., immunology and virology)
    - Process engineering and manufacturing (e.g., biologicals)
    - Regulatory (e.g., FDA, Environmental Protection Agency, and Occupational Safety and Health Administration)
    - Business (e.g., management, processes, and cost analysis)
  - Training (2–3 weeks per year)
    - Cutting edge technology, technology transfer, and analytical methodologies
    - Process specifics and manufacturing support
    - current Good Manufacturing Practice, current Good Clinical Practice, and current Good Laboratory Practice
    - Project planning (cost, schedule, and performance)
- Quality
  - Assurance (e.g., internal audits, regulatory updates, and agency inspections)
  - Testing
  - Validation (e.g., equipment cleaning, sterilization, and performance)
  - Product release [sequential and repeated testing (e.g., raw materials → test → culture media → test → bulk intermediates → test → final formulated bulk → test & CBER release → filled containers → test → packaged items → test → release to market) throughout process with detailed documentation to support release by CBER]. Note: With regard to product release, it typically takes 7 to 12 months to get bulk material released and 6 to 12 weeks for release approval following filling.
  - Licensing
  - Environmental monitoring

APPENDIX D

Briefing – DoD Acquisition of Vaccine Production (Report to the Deputy Secretary of Defense by the Independent Panel of Experts), November 29, 2000

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DoD Acquisition of Vaccine Production

Report to the Deputy Secretary of Defense by the Independent Panel of Experts

November 29, 2000

Panel

- Franklin H. Top, Jr., M.D. – Chair
  Executive Vice President and Medical Director
  MedImmune, Inc.
- John J. Dingerdissen
  Senior Director, Viral Vaccine Manufacturing
  Merck & Co., Inc.
- William H. Habig, Ph.D.
  Director, R&D Quality Assurance
  Centocor, Inc.
- Gerald V. Quinnan, Jr., M.D.
  Professor, Preventive Medicine, Medicine and Microbiology
  Uniformed Services University of the Health Sciences
- Rita L. Wells, Ph.D.
  Deputy Executive Director
  Committee for Purchase from People Who are Blind or Severely Disabled

Terms of Reference

The Deputy Secretary of Defense requested that the study by the independent panel of experts focus on the following areas:

- Vaccines to protect Service members against biological warfare threats as well as infectious diseases.
- A comparison of current Department efforts with best business practices in the biologics industry, and if/how the Department can leverage the best aspects of the private sector programs from industry.
- A determination of whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.
- The development of recommendations for how the Department should best develop and oversee a vaccine acquisition production program.

Facts Bearing on the Problem

- BW and endemic diseases are proven, high consequence threats to military operational effectiveness
- Vaccines are lowest risk, most effective protection
  - Better than antibiotics or other treatments
  - Enable force projection
- Current approach is insufficient and will fail
- **A NEW APPROACH CAN MAKE THIS PROGRAM WORK**

Why Will Current Program Fail?

- Approach is contrary to business success model
  - No one in charge
  - Diffuse management
  - Fragmented program
- Lack of integration from discovery through licensure
- Lack of essential scientific oversight and talent
- Insufficient capture of industrial base
- Goals and dollars do not match

Industry Best Practices

Successful Vaccine Acquisition

Industry Best Practices effectively integrate:

- Policy
- Product life cycle
  - Research
  - Development
  - Production
  - Licensure
  - Sustainment
- Resources
- Management

Resources
Industry Benchmark

- Funding stability
- Up-front multiyear commitment
- Flexible "reprogramming" authority ($ and type)
- Product focus, not budget focus

Baseline Schedule Fully Funded

Resources (cont.)
Industry Benchmark

- R&D $300M - $400M/product
- Facility capital investment estimate
  - Production, labs, and support - $75M - $115M/product
- Operations and Maintenance Estimate
  - Manufacturing $30M - $35M/product/year

DoD Products Underresourced

Human Investment
Industry Benchmark at 8 Product Scale

- 2,500 people
- Exceptional and specialized skills
- Scarce national pool
- Competitive compensation
- Special HR programs necessary
  - Recruit, train, and retain

People + Process → Vaccines

Management
Industry Benchmark

- Goal is quality product
- Scientific expertise at every level
- Problem focus for continuing improvement
  - Rapid assessment and decisions
  - Mitigate risk at every stage
- Empowered and accountable management teams

DoD Practices

Best Business Assessment

Industry Best Practices	Assessment of DoD	Rationale for Assessment
Integrated Discovery Through Licensure	R	Piecemeal process
Scientific Talent	Y	Good S&T, inadequate development and production
Technical Qualifications of Management	R/Y	Vaccine Acquisition ≠ Weapons System Acquisition
Management Focus and Accountability	R/Y	Fragmented and Multilayered below DEPSECDEF
Funding Stability	R	Annual allocation and frequent decrement drills
Funding Commitment	R	Development/Acquisition not funded following discovery
Flexible Reprogramming	R/Y	Limited by Congress
Focus on Product Quality	Y	Goal G; Execution R

G = Full Compliance

Y = Moderate Compliance

R/Y = Low Compliance

R = No Compliance (High Risk)

Strategic Options

- Industry
- Government
- Combined integrated approach

Industry Option: Impediments

- Size & scope of program
- Industrial base at full capacity
- Idle manufacturing
- Risk to industry
  - Efficacy risk
  - Program stability
  - Perceptions
  - Political
- Defense procurement practices

Government Option: Impediments

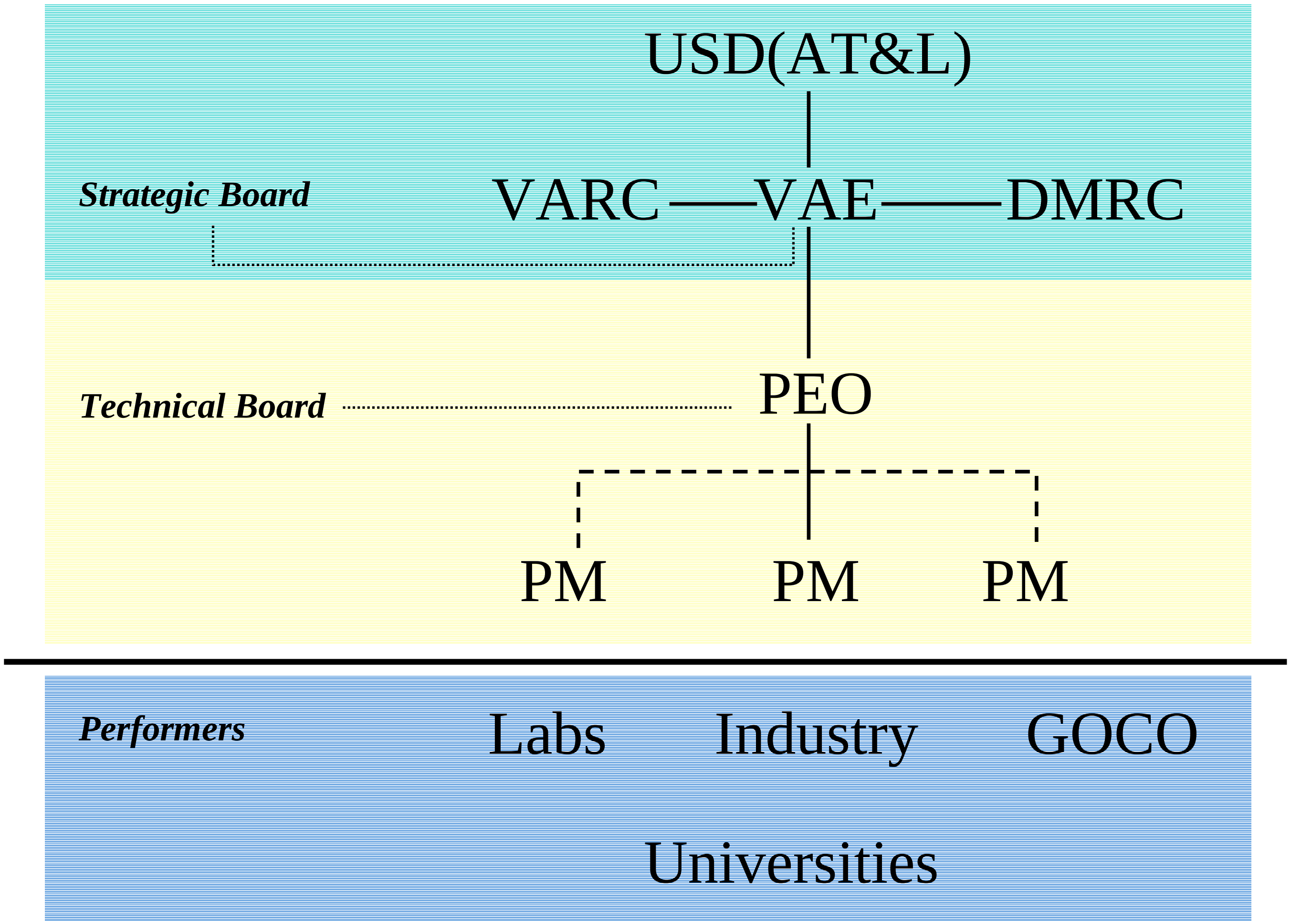
- Size - 2,500 personnel
- Lack of personnel experienced in vaccine development processes
- Noncompetitive recruitment

Preferred Option: Integrated Approach

- Combines:
  - Management/development skills of industry
  - Acquisition skills of DoD
  - Scientists from Federal, academic/industry labs
  - Exploit industry development/manufacture where possible
  - GOCO for development/manufacture of remaining products

Incentivize Industry

Proposed Management Organization



GOCO Facilities

- Shell/buildout to process and manufacturing scale
- Expandable
- 3 to 4 product/process capacity
- Pilot production/scale-up
  - 2 products at one time
- Inherent clinical, regulatory, QC & QA elements, applied research lab capability
- University/industry corridor location is essential--Northeast coast lowest risk

Resource Estimates

(8 Vaccines*)

- R&D Funds -- $3.2B
- Initial Capital Funding ≥ $370M
  - $75M - $115M for each additional vaccine after first 4
  - 5% - 10% infrastructure improvement/year
- Operations and Maintenance ~ $300M/year
- 2,500 people

* BD and MIDRP require >8 vaccines total; study scale was 8 vaccines

Industry Incentives

- Overture to industry
- Encourage industry development of vaccines
  - Longest multiyear contracts possible
  - Incentive-based contracts
  - Government-provided facility

Findings and Recommendations

1. Vaccines to protect Service members against biological warfare threats as well as infectious diseases.
   – Combine programs from discovery to production

Findings and Recommendations (cont.)

2. A comparison of current Department efforts with best business practices in the biologics industry, and if/how the Department can leverage the best aspects of the private sector programs from industry.
   a. Current Department efforts do not meet industry best practices:
      - Diffuse management and fragmented lines of responsibility
      - Inadequate scientific oversight
      - Inadequate program integration from discovery through licensure
      - Inadequate resources to meet goals
   b. Adopt integrated approach utilizing:
      - Management/development skills of industry
      - Accountable, lean DoD management structure
      - Strong technical guidance and personnel
      - GOCO

Findings and Recommendations (cont.)

3. A determination of whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.
   - Yes, vaccine acquisition is different from weapons acquisition and success requires different procedures
     - Strong technical input imperative
       - Workforce
       - Management
     - Stable, long-range funding for vaccine life cycle
     - Reprogramming authority

Findings and Recommendations (cont.)

4. The development of recommendations for how the Department should best develop and oversee a vaccine acquisition production program.
   a. Combined, integrated model
   b. Focused and streamlined organization
   c. Segregated, OSD-sponsored funding
   d. Incentivized industry involvement (with GOCO)
   e. DoD, Executive Branch, and Congressional support to remove impediments and provide necessary incentives

Backup Slides

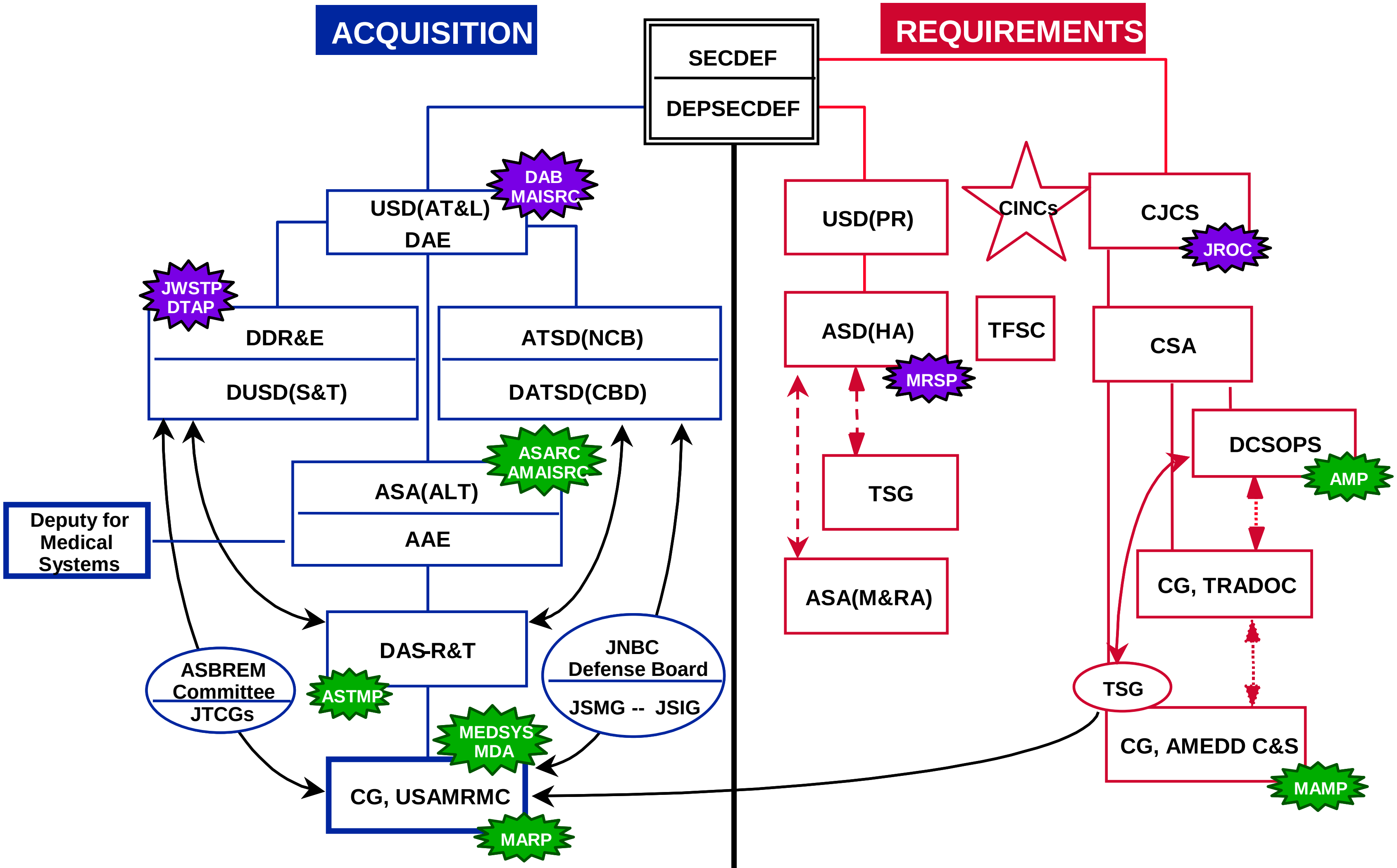
Product Life Cycle Integration

Component	Example
Research	Follow-on candidates
Development	Optimal shot regimen
Production	Validated process
Licensure	FDA compliance
Sustainment	Reliable supply

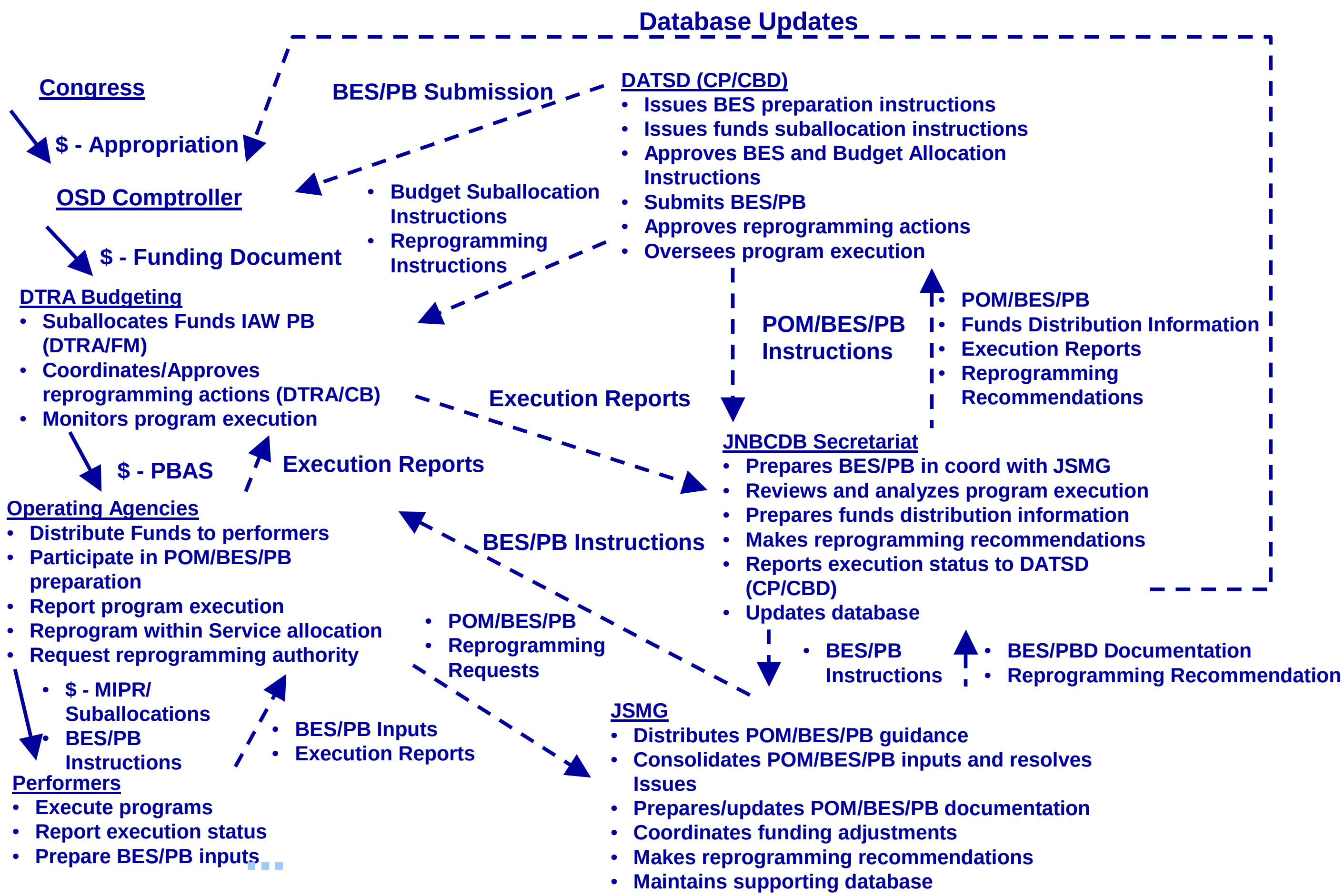
Success

- Scientifically competent, empowered management
- Must integrate
  - Science & technology
    - Discovery
    - Applied activities
  - Product development
  - Manufacturing
  - Product licensure
  - Postlicensure sustainment

Management Organization



Chemical and Biological Defense Program Funds Management Process



JSMG Hand Book of Standard Operating Procedures, Fig IV-I, Page 19

Proposed Management Structure

- Tailored Acquisition Model
  - OSD Vaccine Acquisition Executive (VAE)
  - Oversight (ACAT I)--technically qualified
  - Strategic Board advises VAE
- Vaccine Acquisition Review Council (VARC) and Defense Medical Requirements Council (DMRC)

Proposed Management Structure

- Joint Program Executive Officer (PEO)
  - VAE and PEO with scientific and acquisition skills
- Scientific & technical advisors on tactical operations to PEO
  - Periodic (scheduled) review
- PEO responsible for sponsoring ($) S&T/relevant infrastructure and exploits DoD lab capability
- No dual hats

Resource Estimates

- R&D Funds -- $3.2B
  - ~ 8 successful vaccines (7-12 years each)*
  - ~ $300 - $400M/product R&D to licensure
    - ~ 2 products/year to start
    - ~ 4 products/year at year 4
    - ~ 8 products/year when mature

* BD and MIDRP require >8 vaccines total; study scale was 8 vaccines

Resource Estimates (cont.)

- Capital funds ≥$370M
  - ~ $300M construction for manufacturing
  - ~ $70M construction for labs
  - ~ $75-$115M for each additional vaccine after the initial 4
  - ~ 5%-10% infrastructure improvements/year at year 8
- Operations and Maintenance funds
  - ~ $300M/year for 8 vaccines

Human Investment Estimate

- 2,500 people–exceptional and specialized skills
  - Scarce national pool
- Competitive compensation
- Special programs necessary
  - Train to expand the pool
  - Recruit
  - Retain
  - Compensate

People + Process → Vaccine

Vaccine Study Panel

Panel Sponsors

- Hans Mark, Ph.D.

  Director, Defense Research and Engineering

- J. Jarrett Clinton, M.D., M.P.H.

  Acting Assistant Secretary of Defense (Health Affairs)

Panel Support

Department of Defense

- Anna Johnson-Winegar, Ph.D.
  Deputy Assistant to the Secretary of Defense (Chemical/Biological Defense)
- Robert E. Foster, Ph.D.
  Director, Bio Systems, Office of the Deputy Under Secretary of Defense (S&T)
- Steve McManus
  Director, Pharmaceuticals Group, Defense Supply Center, Philadelphia

Contract

- Science Applications International Corporation

Daniel L. Rickett, Ph.D.	Joseph C. Denniston, V.M.D., Ph.D.
William H. Bancroft, M.D.	Mark. R. Brunswick, Ph.D.
Donna. L. Bareis, Ph.D.	James M. Miller, Esq.
Thurman D. Gardner, C.C.E/A.	Joseph F. Soukup, Ph.D.

- Hicks Associates, Inc.
  George T. Singley, III

Briefings

- DATSD(CBD): Background and Related Issues
- SAIC: U.S. and International Vaccine Industrial Base
- SAIC: Vaccine Manufacturing Industry Best Practices
- SAIC: Food and Drug Administration Considerations
- SAIC: Overview of DoD Requirements Related to Vaccine Production
- SAIC: Selected Examples of DoD Experience with Acquisition of Licensed Vaccines
- DIA: Worldwide Biological Warfare Threat
- DSMC: Requirements Generation Process and Acquisition Life Cycle
- DSMC: Defense Acquisition Process Milestones and Phases: A Summary of the Revised 5000 Series

Briefings (cont.)

- SAIC: Defense Acquisition Workforce
- Joint Vaccine Acquisition Program: Acquisition of Biological Defense Vaccines
- U.S. Army Medical Research and Materiel Command: Vaccine Development and Production Process & Issues
- Defense Supply Center Philadelphia: Vaccine Management
- Defense Advanced Research Projects Agency: Vaccine Program Overview
- Headquarters, U.S. Navy: Review of DoD Acquisition and Production of Vaccines

Interviews

- Lieutenant General Paul Kern, USA, Military Deputy to the Assistant Secretary of the Army (AL&T) and Director, Acquisition Career Management
- Major General Timothy Malishenko, USAF, Director, Defense Contract Management Agency
- Mr. Robert Scott, Senior Principal, American Management Systems
- Major General John Parker, M.D., USA, Commanding General, U.S. Army Medical Research and Materiel Command (USAMRMC)
- Mrs. Vicky Armbruster, Joint Program Manager for Biological Defense
- Colonel David Danley, Ph.D., USA, Project Manager, Joint Vaccine Acquisition Program
- Colonel Charles Hoke, M.D., USA, Director, Military Infectious Diseases Research Program, HQ, USAMRMC

Acronyms

ACAT	Acquisition Category
AAE	Army Acquisition Executive
AMEDD C&S	Army Medical Department Center and School
AMP	Army Modernization Plan
ASA(ALT)	Assistant Secretary of the Army for Acquisition, Logistics and Technology
ASA(M&RA)	Assistant Secretary of the Army for Manpower and Reserve Affairs
ASARC	Army Systems Acquisition Review Council
ASD(HA)	Assistant Secretary Defense for Health Affairs
ASTMP	Army Science and Technology Master Plan
ATSD(NCB)	Assistant to the Secretary of Defense (Nuclear, Chemical, Biological)
BD	Biological Defense
BES	Budget Estimate Submission
BW	Biological Warfare
CG	Commanding General
CINC	Commander in Chief
CJCS	Chairman, Joint Chiefs of Staff
CSA	Chief of Staff, Army
DAB	Defense Acquisition Board
DAE	Defense Acquisition Executive
DATSD(CBD)	Deputy Assistant to the Secretary of Defense (Chemical/Biological Defense)
DCSOPS	Deputy Chief of Staff for Operations (U.S. Army)
DDR&E	Director, Defense Research and Engineering
DEPSECDEF	Deputy Secretary of Defense
DIA	Defense Intelligence Agency
DMRC	Defense Medical Requirements Council
DoD	Department of Defense
DTAP	Defense Technology Area Plan
DTRA	Defense Threat Reduction Agency
DUSD(S&T)	Deputy Under Secretary of Defense (Science and Technology)
FDA	Food and Drug Administration
GOCO	Government-Owned, Contractor-Operated

Acronyms (cont.)

JNBC	Joint Nuclear, Biological, Chemical
JNBCDB	Joint Nuclear, Biological, and Chemical Defense Board
JROC	Joint Requirements Oversight Council
JSIG	Joint Services Integration Group
JSMG	Joint Services Materiel Group
JTCG	Joint Technology Coordinating Group
JWSTP	Joint Warfighting Science and Technology Plan
MAISRC	Major Automated Information System Review Council
MAMP	Mission Area Materiel Plan
MARP	Management Assessment Review Plan
MDA	Milestone Decision Authority
MIDRP	Military Infectious Diseases Research Program
MIPR	Military Interagency Purchase Request
MRSP	Medical Readiness Strategic Plan
OSD	Office of Secretary of Defense
PB	President's Budget
PBAS	Program Budget Accounting System
PEO	Program Executive Officer
PM	Program Manager
QA	Quality Assurance
QC	Quality Control
R&D	Research and Development
RDA	Research, Development, and Acquisition
S&T	Science & Technology
SAIC	Science Applications International Corporation
SECDEF	Secretary of Defense
TFSC	Theater Functional Steering Committee
TRADOC	Training and Doctrine Command
TSG	The Surgeon General
USAMRMC	U.S. Army Medical Research and Materiel Command
USD(AT&L)	Under Secretary of Defense for Acquisition, Technology and Logistics
USD(PR)	Under Secretary of Defense for Personnel and Readiness
VAE	Vaccine Acquisition Executive
VARC	Vaccine Acquisition Review Council

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APPENDIX E

Acronyms

ACAT	Acquisition Category
AAE	Army Acquisition Executive
ACIP	Advisory Committee on Immunization Practices
AMAISRC	Army Major Automated Information System Review Council
AMEDD C&S	Army Medical Department Center and School
AMP	Army Modernization Plan
ASA(ALT)	Assistant Secretary of the Army for Acquisition, Logistics and Technology
ASA(M&RA)	Assistant Secretary of the Army for Manpower and Reserve Affairs
ASARC	Army Systems Acquisition Review Council
ASBREM	Armed Services Biomedical Research Evaluation and Management (Committee)
ASD(HA)	Assistant Secretary Defense for Health Affairs
ASTMP	Army Science and Technology Master Plan
ATSD(NCB)	Assistant to the Secretary of Defense (Nuclear, Chemical, Biological)
AVA	Anthrax Vaccine, Adsorbed
AVP	Acquisition of Vaccine Production
BDP	Biological Defense Program
BES	Budget Estimate Submission
BW	Biological Warfare
CBER	Center for Biologics Evaluation and Research
CG	Commanding General
CINC	Commander in Chief
CJCS	Chairman, Joint Chiefs of Staff
CSA	Chief of Staff, Army
DAB	Defense Acquisition Board
DAE	Defense Acquisition Executive
DAS-R&T	Deputy Assistant Secretary of the Army for Research and Technology
DATSD(CBD)	Deputy Assistant to the Secretary of Defense (Chemical/Biological Defense)
DCSOPS	Deputy Chief of Staff for Operations (U.S. Army)
DDR&E	Director, Defense Research and Engineering
DEPSECDEF	Deputy Secretary of Defense
DIA	Defense Intelligence Agency
DLA	Defense Logistics Agency
DMRC	Defense Medical Requirements Council
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DTAP	Defense Technology Area Plan

DTRA	Defense Threat Reduction Agency
DUSD(S&T)	Deputy Under Secretary of Defense (Science and Technology)
EEE	Eastern Equine Encephalitis
FDA	Food and Drug Administration
FTE	Full-time Equivalent
GOCO	Government-Owned, Contractor-Operated
HIV	Human Immunodeficiency Virus
IAW	In Accordance With
IDP	Infectious Disease Program
IND	Investigational New Drug
IOM	Institute of Medicine
JNBC	Joint Nuclear, Biological, Chemical
JNBCDB	Joint Nuclear, Biological, and Chemical Defense Board
JPO BD	Joint Program Office for Biological Defense
JROC	Joint Requirements Oversight Council
JSIG	Joint Services Integration Group
JSMG	Joint Services Materiel Group
JTCG	Joint Technology Coordinating Group
JVAP	Joint Vaccine Acquisition Program
JVAP PMO	Joint Vaccine Acquisition Program, Project Management Office
JWSTP	Joint Warfighting Science and Technology Plan
MACOMs	Major Commands
MAISRC	Major Automated Information System Review Council
MAMP	Mission Area Materiel Plan
MARP	Management Assessment Review Plan
MDA	Milestone Decision Authority
MIDRP	Military Infectious Diseases Research Program
MIPR	Military Interagency Purchase Request
MRSP	Medical Readiness Strategic Plan
NCI	National Cancer Institute
NEPA	National Environmental Policy Act
NIAID	National Institute of Allergy and Infectious Diseases
O&M	Operations and Maintenance
ODDR&E	Office of the Director, Defense Research and Engineering
OMA	Operations and Maintenance, Army
OSD	Office of Secretary of Defense
OTA	Other Transaction Authority
PB	President's Budget
PBAS	Program Budget Accounting System
PBD	Program Budget Decision
PEO	Program Executive Officer

PMs	Program Managers
PPB	Planning, Programming, and Budgeting
PSC	Prime Systems Contractor
QA	Quality Assurance
QC	Quality Control
R&D	Research and Development
RDA	Research, Development, and Acquisition
RDT&E	Research, Development, Test, and Evaluation
RFPs	Request for Proposals
S&E	Scientists & Engineers
S&T	Science & Technology
SAIC	Science Applications International Corporation
SEB	Staphylococcal Enterotoxin B
SECDEF	Secretary of Defense
TFSC	Theater Functional Steering Committee
TRADOC	Training and Doctrine Command
TSG	The Surgeon General
UNICEF	United Nations International Children's Emergency Fund
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USAMRMC	U.S. Army Medical Research and Materiel Command
USD(AT&L)	Under Secretary of Defense for Acquisition, Technology and Logistics
USD(PR)	Under Secretary of Defense for Personnel and Readiness
VAE	Vaccine Acquisition Executive
VARC	Vaccine Acquisition Review Council
VEE	Venezuelan Equine Encephalitis
WEE	Western Equine Encephalitis
WMA	Worldwide Marketing Assessment
WRAIR	Walter Reed Army Institute of Research

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APPENDIX C

Surgeon General's Letter
to the
Secretary of Defense

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Assistant Secretary for Health
Surgeon General
Washington, D.C. 20201

JAN 31 2001

The Honorable Donald H. Rumsfeld
Secretary of Defense
Washington, D.C. 20301

Dear Mr. Secretary:

In fulfillment of the requirement in Section 218 of the National Defense Authorization Act for FY 2001, I am pleased to offer the following observations regarding the utility for the civilian sector of a government-owned, contractor-operated (GOCO) vaccine production facility, particularly for vaccines relevant to defense against the release of biological warfare agents.

Biological agents, even if adversaries intend them solely for use against military targets, could have the potential for causing severe, primary or collateral civilian casualties. Therefore, HHS has a substantial interest in the availability of vaccines that can be used, in sufficient quantity, to offer protection for civilian populations. For many reasons, a GOCO vaccine production facility, under the proper conditions, could assure the availability of these vaccines for military, as well as eventual civilian use should the need arise. Therefore, we want to encourage DOD to proceed with plans to develop a GOCO vaccine production capability and offer our technical assistance within the resources available to HHS. We believe that civilian participation can strengthen GOCO's operation and contribute to its success. Joint planning could avoid the eventual consideration of separate government-owned production of orphan and other vaccine products required mainly by the civilian population.

Should civilian use of the products of a GOCO be incorporated into your plans, we would welcome the opportunity to discuss means to participate in facility design and eventual product planning and production financing. The list of biological weapon threats facing civilian populations is very similar to that under consideration in DOD's initial planning, but the total production requirements may be substantially different. In addition, there may eventually be vaccines that need to be produced in a GOCO facility for which civilian needs dominate total demand (e.g., malaria, viral hemorrhagic fevers) but for which there is also a substantial requirement for force protection, even though the diseases against which they are protective are not considered bio-weapons.

In designing a GOCO and determining its requirements, we hope that product and production flexibility would be an important consideration. In the projected eight years to completion of the facility, disease and other threat profiles may evolve with a commensurate change in production needs. The introduction of West Nile encephalitis to the United States is just one example of how rapidly threats from infectious agents may change without warning, producing new challenges for protection of our armed forces as well as of our civilian population. New production technologies are also on the horizon, and what now may be considered an Aorphan@ vaccine may take on new significance in the future.

We believe that a GOCO vaccine production facility can yield many benefits for meeting defense as well as civilian vaccine needs. We look forward to working with you in addressing such questions as how joint investment and production management might be achieved, how vaccine requirements for extended age groups might be accommodated, and how a variety of legal questions such as vaccine licensing and liability might be addressed.

I look forward to our continued discussions about this important step in further assuring the protection of our country from the effects of the unleashing of biological agents against our armed forces and civilian population.

Sincerely yours,

David Satcher, M.D., Ph.D.
Surgeon General, USPHS

cc: Dr. Anna Johnson-Winegar