

**THE DEPARTMENT OF DEFENSE
ANTHRAX VACCINE IMMUNIZATION PROGRAM:**

UNPROVEN FORCE PROTECTION

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This report was prepared by the majority staff of the Subcommittee on National Security, Veterans Affairs and International Relations, House Committee on Government Reform. By request of the Subcommittee Chairman, Vice Chairman and Ranking Member, the report has been proposed for consideration and adoption by the full Government Reform Committee.

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Summary

Responding to service members' complaints of program insensitivity to adverse health effects, inadequate medical record keeping and heavy-handed program operation, the Subcommittee initiated an oversight investigation into the design and implementation of the Department of Defense (DOD) force-wide, mandatory Anthrax Vaccine Immunization Program (AVIP). Because the anthrax vaccine is still being studied as a potential causative or contributing factor in Gulf War veterans' illnesses¹, the Subcommittee measured the program against this standard: Any expanded use of the same vaccine should be undertaken only with the greatest care and only to the extent necessary.

As currently designed and implemented, the anthrax vaccine program fails on both counts. The AVIP lacks a consistent standard of care and is designed to reach far beyond those at risk.

Based on the testimonial and documentary record², the Subcommittee finds the AVIP a well-intentioned but overwrought response to the threat of anthrax as a biological weapon. Against the so-called Asymmetric threats to U.S. conventional military superiority posed by a growing range of chemical and biological weapons, the anthrax vaccine program represents a medical Maginot Line, a fixed fortification protecting against attack from only one direction.

¹ P.L. 105-277, Title XVI, sec. 1603(d).

² In response to the Subcommittee's investigative requests, DOD provided more than 100,000 pages of documentary and electronic records on the anthrax vaccine program from 1991 to the present. Five Subcommittee hearings were held in 1999, encompassing 20 hours of testimony from 46 witnesses. The full Committee on Government Reform also heard testimony on the subject of vaccines for military defense on October 12, 1999.

Unrealistic Program

As a mandatory, force-wide countermeasure to the real threat of weaponized anthrax on the battlefield, the vaccine effort is unrealistic. It expands and distorts the use of invasive, dated medical technology to address perceived weaknesses in detection technology and external physical protection against biological attack. Born of a post-Gulf War panic over apparent weaknesses in chemical and biological (CB) warfare defenses, the AVIP is an unmanageably broad military undertaking built on a dangerously narrow scientific and medical foundation.

At best, the vaccine provides some measure of protection to most who receive it. Just how much protection is acquired, by whom, for how long and against what level of challenge are questions DOD answers with an excess of faith but a paucity of science.

Many members of the armed forces do not share that faith. They do not believe merely suggestive evidence of vaccine efficacy outweighs their concerns over the lack of evidence of long term vaccine safety. Nor do they trust DOD has learned the lessons of past military medical mistakes: atomic testing, Agent Orange, Persian Gulf War drugs and vaccines. Heavy handed, one-sided informational materials only fuel suspicions the program understates adverse reaction risks in order to magnify the relative, admittedly marginal, benefits of the vaccine.

As a military operation, the AVIP rests on weak conceptual and logistical footing. It suffers from poor planning, inflexible execution and over-extended supply lines. As a health care effort, the AVIP compromises the practice of medicine to achieve military objectives.

The decision to use the 1950's era vaccine, which requires an elaborate inoculation regime of six shots over 18 months, presents daunting, perhaps insurmountable, logistical challenges to reach a force of 2.4 million active duty and reserve component members. Research to support a shorter, more manageable inoculation regimen was not completed before the AVIP was launched. Development of a purer, potentially less reactogenic anthrax vaccine using recombinant technologies was not pursued aggressively.

Unstable Supply

The sole-source procurement strategy leaves the program vulnerable to supply shortages and price increases. Because Food and Drug Administration (FDA) regulations require a dedicated production facility for spore-based biologics, other pharmaceutical firms will not commit the time and capital needed to manufacture an old vaccine for a very limited market. As a result DOD and the sole vaccine maker are locked in a mutually dependent relationship.

The manufacturer, struggling to reopen a plant with a checkered regulatory history, clings to a captive customer. Threats to stop production render DOD unable to resist demands for extraordinary financial relief and pressure to permit the use of publicly funded improvements to monopolize the private domestic and foreign markets as well.

Uncertain Safety

Incurious reliance on FDA approval of the vaccine as Asafe≡ for occupational exposure blinds the program to potential adverse reaction trends in a vastly expanded, demographically diverse population of vaccine recipients. Adverse events following vaccination are reported by women at twice the rate among men. The vaccine may be as safe as many other approved products, but valid data to support, or refute, that proposition will not come from the AVIP. Preposterously low adverse report rates generated by DOD point to a program far more concerned with public relations than effective force protection or the practice of medicine.

The AVIP raises an ominous question: Who protects the force from ill-conceived force protection? The anthrax vaccine effort is designated a Acommander=s program≡ not a medical program, so DOD doctors appear unable to act as advocates for individual patients in the face of command pressure to meet force-wide inoculation levels. FDA regulations reach only the vaccine producer, the BioPort Corporation, not the activities of the vaccine purveyor, the Pentagon, although for purposes of the AVIP the distinction is meaningless.

Untested Efficacy

Administration of the anthrax vaccine for mass prophylaxis against biological warfare should be considered an off-label use of the product to treat an indication for which it is not explicitly licensed. DOD=s operational use of a standard of Afunctional protection≡ after three inoculations constitutes a *de facto* alteration of the approved six shot regimen. Both the new indication and the new schedule should be undertaken only pursuant to FDA regulations governing clinical trials of investigational new drugs (IND).

Under supervision of the FDA and an Institutional Review Board (IRB), DOD would be required to inform vaccine recipients adequately, obtain informed consent and gather data on vaccine safety consistently. If necessary, DOD could request the president waive the informed consent requirement for certain deployed personnel under the statute, regulation and Executive Order that provide far greater protections to service members than the process used for similar waivers during the Gulf War.³

³ 10 U.S.C. 1107(f); 21 CFR Part 50; Executive Order of September 30, 1999 (No. 13139).

Findings in Brief

1. **The AVIP is a well-intentioned but over-broad response to the anthrax threat.** It represents a doctrinal departure overemphasizing the role of medical intervention in force protection.
2. **The AVIP is vulnerable to supply shortages and price increases.** The sole-source procurement of a vaccine that requires a dedicated production facility leaves DOD captive to old technology and a single, untested company. Research and development on a second-generation, recombinant vaccine would allow others to compete.
3. **The AVIP is logistically too complex to succeed.** Adherence to the rigid schedule of six inoculations over 18 months for 2.4 million members of a mobile force is unlikely, particularly in reserve components. Using an artificial standard that counts only shots more than 30 days overdue, DOD tolerates serious deviations from the Food and Drug Administration (FDA) approved schedule.
4. **Safety of the vaccine is not being monitored adequately.** The program is predisposed to ignore or understate potential safety problems due to reliance on a passive adverse event surveillance system and DOD institutional resistance to associating health effects with the vaccine.
5. **Efficacy of the vaccine against biological warfare is uncertain.** The vaccine was approved for protection against cutaneous (under the skin) infection in an occupational setting, not for use as mass protection against weaponized, aerosolized anthrax.

Recommendations in Brief

- 1. The force-wide, mandatory AVIP should be suspended until DOD obtains approval for use of an improved vaccine. To accomplish this:**
 - 2. DOD should accelerate research and testing on a second-generation, recombinant anthrax vaccine; and,**
 - 3. DOD should pursue testing of the safety and efficacy of a shorter anthrax inoculation regimen; and,**
 - 4. DOD should enroll all anthrax vaccine recipients in a comprehensive clinical evaluation and treatment program for long term study.**
- 5. While an improved vaccine is being developed, use of the current anthrax vaccine for force protection against biological warfare should be considered experimental and undertaken only pursuant to FDA regulations governing investigational testing for a new indication.**

Background

The Program

On December 15, 1997, after what DOD described as a detailed, deliberative process[≡] spanning almost four years⁴, Secretary of Defense William S. Cohen announced a program to immunize all active duty personnel against anthrax, a bacterial disease that in spore form can be used as a biological weapon. The effort is called the Anthrax Vaccine Immunization Program (AVIP).⁵

The program was designed to be implemented in three phases⁶:

Phase I(3/98 - 1/00)	Forces assigned or rotating to high threat areas	400,000
Phase II (1/00 - 1/04)	Early deploying forces into high threat areas	1,000,000
Phase III (10/02 - 9/06)	Remainder of the total force, boosters, etc.	1,000,000

The AVIP is a medical force protection effort undertaken by DOD pursuant to a 1993 policy calling for immunizations against validated biological warfare threat agents, for which suitable vaccines are available, in sufficient time to develop immunity before deployment to high-threat areas...⁷

⁴ *Anthrax Immunization Program*, 106th Cong., 1st sess., p. 8 (1999) (Subcommittee on National Security, Veterans Affairs, and International Relations hearing of Mar. 24, 1999, No. 106-17) [hereinafter ANSVAIR Anthrax Hearing (I)] (prepared statement of Dr. Sue Bailey).

⁵ DOD Media Release, ADefense Department to Start Immunizing Troops Against Anthrax, No. 679-97, December 15, 1997.

⁶ AVIP briefing slides (in subcommittee files).

⁷ Department of Defense, DOD Directive 6205.3, ADOD Immunization Program for Biological Warfare Defense, November 26, 1993. Other elements of force protection include

intelligence about threats, detection capability, physical protection (suits, masks, etc.), post-exposure treatment with antisera and antibiotics, and strategic deterrence. In the Gulf War, up to 150,000 U.S. service personnel received one or two doses of the anthrax vaccine along with other immunizations and medications. Due to poor or non-existent record keeping, however, DOD is unable to conduct a systematic follow-up on the health effects, if any, of the Gulf War vaccines.

According to the DOD news release announcing the vaccine program, AAfter a three year study, Secretary of Defense William S. Cohen concluded that the vaccination is the safest way to protect highly mobile U.S. military forces against a potential threat that is 99 percent lethal to unprotected individuals.⁸ Cohen added, ATo be effective, medical force protection must be comprehensive, well documented and consistent. I have instructed the military to put such a program in place.⁹

Accordingly, Secretary Cohen set four conditions on the start of vaccinations:

- 1) supplemental testing to assure sterility, safety, potency and purity of the vaccine stockpile;
- 2) implementation of a system for fully tracking anthrax immunizations;
- 3) approval of operational plans to administer the vaccine and communications plans to inform military personnel;
- 4) review of medical aspects of the program by an independent expert.¹⁰

In 1998, supplemental testing of the anthrax vaccine stockpile began.¹¹ An elaborate interim record keeping and tracking system was designed to combine vaccination data from the three military services into an existing central data base, the Defense Enrollment Eligibility Reporting System (DEERS).¹² A more efficient, centralized immunization records system is under development.¹³ Communication plans were approved centered around a tri-fold brochure to be given to service personnel.¹⁴ An anthrax vaccine web site was also created.¹⁵ A physician reviewed the AVIP program plans.¹⁶

In March 1998, at the request of the regional commander, 48,000 troops assigned to the Persian Gulf area began the vaccination series. On May 18, 1998, Secretary Cohen pronounced

⁸ See *supra* note 5, p.1.

⁹ *Ibid.*

¹⁰ *Ibid.*

¹¹ Letter from Anthony M. Lutrell, Vice President - Quality Assurance, BioPort Corp. to Dr. Michael Gilbreath, Joint Program Office for Biological Defense, DOD, January 8, 1999 (in subcommittee files).

¹² Major William Terry, ATracking Troops= Anthrax Shots, (with charts), *ArmyLINK News*, March 1999.

¹³ *Ibid.*

¹⁴ Department of Defense, AVIP tri-fold brochure, AWhat Every Service Member Should Know About Anthrax (undated) (in subcommittee files).

¹⁵ Department of Defense web site on Anthrax Vaccination Immunization Program, <http://www.anthrax.osd.mil>.

¹⁶ Letter from Dr. Gerard N. Burrow, Special Advisor to the President for Health Affairs, David Page Smith Professor of Medicine, Professor of Obstetrics and Gynecology, Yale University School of Medicine, to DOD Undersecretary Rudy de Leon, Feb. 19, 1998 (in subcommittee files).

the four conditions fulfilled and approved the total force program, which began in September with troops in Korea.¹⁷

DOD cited several factors to support the conclusion the anthrax vaccine is both safe for widespread use and effective against the most likely anthrax threat:

- 1) FDA approval and monitoring of the vaccine;
- 2) vaccine usage since approval;
- 3) assured production capacity;
- 4) independent medical review;
- 5) supplemental vaccine testing; and

¹⁷ Steve Bowman, *Department of Defense Anthrax Vaccination Program (98-873F)*, Congressional Research Service Report (updated), October 28, 1998, p. 2.

6) vaccine tests in animals.¹⁸

FDA Approval of the Vaccine

The AVIP uses the only anthrax vaccine licensed for manufacture in the United States. Anthrax Vaccine Absorbed (AVA) was approved as safe in 1970 based on animal studies and one study of wool workers exposed to indeterminate levels of cutaneous (through skin) and airborne anthrax spores. The disease primarily infects grazing animals and the vaccine has been used since 1970 by some veterinarians, livestock workers and researchers at risk from exposure. The approved immunization process requires a fixed schedule of six injections over 18 months and an annual booster. The vaccine does not contain live anthrax bacteria, but challenges the immune system to mount a response to filtered elements of the killed bacteria absorbed into an adjuvant.¹⁹

Subsequent FDA review of the studies in 1985 concluded the vaccine was safe, A fairly well tolerated,≡ and effective against cutaneous anthrax, but that data from both human and animal tests was insufficient to support a finding of efficacy with regard to airborne exposure.²⁰ In analyzing the benefit/risk ratio of classifying the old vaccine as compliant under new FDA standards, the expert panel concluded, A This vaccine is recommended for a *limited, high-risk of exposure population* along with other industrial safety measures designed to minimize contact with potentially contaminated material. The benefit-to-risk assessment is satisfactory *under the prevailing circumstances of use.*≡²¹ (emphasis added)

The sole producer of the vaccine is the Michigan Biologics Products Institute (MBPI), formerly the Michigan Public Health Department. Since licensure in 1970, FDA monitoring of the vaccine consisted of collecting adverse reaction data and conducting intermittent manufacturing plant inspections.

¹⁸ Prepared statement of Dr. Sue Bailey, Assistant Secretary for Health Affairs, DOD, NSVAIR Anthrax Hearing (I), p. 9 .

¹⁹ The FDA-approved immunization schedule: Day 1, 2 weeks, 4 weeks, 6 weeks, 6 months, 12 months and 18 months. An adjuvant is an ingredient that modifies or enhances the effectiveness of the drug or treatment.

²⁰ Federal Register, 21 CFR Part 610, December 13, 1985, p. 51058.

²¹ *Ibid.*

While detailed information on inspection activities prior to 1990 is not readily available, FDA regulatory scrutiny of the manufacturer has been increasing since then. The Lansing, Michigan facility has been cited repeatedly by the FDA for quality control deficiencies and Anumerous significant deviations from the Federal Food, Drug and Cosmetic Act, FDA=s regulations and the standards in MBPI=s license.²² In March 1997, the FDA warned MBPI that steps would be taken to revoke production licenses, including anthrax vaccine, unless immediate actions were taken to correct longstanding deficiencies.²³ In March 1998 the plant was closed for \$1.8 million in renovations and a \$15 million expansion funded by DOD.²⁴ Vaccine production resumed in May 1999, but neither the renovated facility nor any newly produced vaccine lots have been approved by the FDA.²⁵

²² *Safety and Efficacy of the Mandatory Vaccine*, 106th Cong., 1st sess., p. 58 (1999) (Subcommittee on National Security, Veterans Affairs, and International Relations hearing of Apr. 29, 1999, No. 106- 26) [hereinafter ANSVAIR Anthrax Hearing (II)] (testimony of Dr. Kathryn Zoon, Director, FDA Center for Biologics Evaluation and Research).

²³ Center for Biologics Evaluation and Research, FDA, AFDA Warns Michigan Biological Products Institute of Intention to Revoke Licenses, No. D0382, March 11, 1997.

²⁴ *Department of Defense=s Sole-Source Anthrax Vaccine Procurement*, 106th Cong., 1st sess., p. 8 (1999) (ANational Security, Veterans Affairs, and International Relations Subcommittee hearing of June 30, 1999) [hereinafter ANSVAIR Anthrax Hearing (III)] (testimony of Louis J. Rodrigues, Director, Defense Acquisitions Issues, National Security and International Affairs Division, U.S. General Accounting Office).

²⁵ DOD News Briefing, Monday, December 13, 1999 (available at

Deviations from good manufacturing practices can effect vaccine safety and effectiveness. FDA will not permit the release of vaccines not documented to meet approved potency, sterility and stability levels. Based on concerns over the impact of production process errors on vaccine quality, BioPort quarantined 11 lots of anthrax vaccine. Additional lots are being held pending resolution of questions about potency testing that arose during the supplemental review.²⁶

http://www.defenselink.mil and in subcommittee files).

²⁶ A Medical Readiness: DOD Faces Challenges in Implementing Its Anthrax Vaccine Immunization Program, ≡ (GAO/NSIAD-00-36) U.S. General Accounting Office, October 22, 1999, p. 13. See also, Department of Defense Joint Program Office - Biological Defense, A Investigation of Supplemental Potency Testing ≡ JPO-0855 (undated) (in subcommittee files). See also, prepared statement of BG Eddie Cain, Joint Program Manager, Joint Program Office for Biological Defense, NSVAIR Hearing (II), p. 68.

Under FDA regulations, stockpiled lots must be tested for potency at predetermined intervals. Potency test are done using guinea pigs by comparing the survival rates of animals vaccinated with the test lot(s) against those vaccinated with a previously manufactured control or Areference≡ lot. Potency test failures during the DOD supplemental testing program have raised questions regarding the validity of test procedures and the selection of reference lots.²⁷

Assured Production Capacity

MPBI was purchased in September 1998 by the BioPort Corporation, a new company formed by private investors, including former Joint Chiefs Chairman Adm. William J. Crowe. The next month BioPort was awarded a DOD contract valued at \$29 million to produce anthrax vaccine for the AVIP.²⁸ The contract (DAMD17-98-C 8052) provides for a one year Base Period and two option years. The contract provides for a full-term, fixed price, fixed annual quantity because Athe Government currently requires all the AVA [anthrax vaccine absorbed] that BioPort can produce.≡ Under the agreement, BioPort will receive progress payments at various stages of the anthrax vaccine production process.

On August 5, 1999, DOD announced the contract had been Arestructured≡ to increase the price by \$24.1 million, including \$18.7 million of advance payments.²⁹

This contract, and earlier contracts with MPBI and MDPH, were accompanied by a justification and authorization for other than full and open competition (sole source). The sole source procurement was authorized because AMichigan Biologics Products Institute (MBPI) is the only organization in the U.S. with a Food and Drug Administration (FDA) License to

²⁷ Letter from Joseph S. Little, Contracting Officer, Department of the Army to Fuad El-Hibri, BioPort Corporation, Sept. 23, 19989 (in subcommittee files).

²⁸ Department of Defense (1998) Award/Contract: U.S. Army Medical Research ACQ Activity - BioPort Corporation, DAMD17-98-C-8052, Sept. 17, 1998.

²⁹ Department of Defense, Media Release, ADOD Announces Contract Restructuring,≡ August 5, 1999 (in subcommittee files).

manufacture AVA≡ and A[d]ue to the time and expense required to produce a licenced product, investing in alternate manufacturers is not considered to be an effective way of meeting the Government=s requirements.≡³⁰ DOD also indemnified MBPI/BioPort against liability arising from Athe risks of adverse reactions, or the failure to confer immunity against anthrax....≡³¹

³⁰ Joseph S. Little AJustification and Approval for Other than Full and Open Competition,≡ Anthrax Vaccine Absorbed, DAMD17-97-0014 (JPO 0836) May 20, 1997 (in subcommittee files).

³¹ Memorandum of Decision, Secretary of the Army Louis Caldera, Authority Under Public Law 85-804 to include an Indemnification clause in Contract DAMD 17-91-C-1139 With Michigan Biologic Products Institute, September 3, 1998 (in subcommittee files).

Potential liability resulting from adverse events was a major issue for the anthrax vaccine manufacturer even when the vaccine was used by a only few hundred people each year. In 1986, Secretary of the Army John Marsh, Jr. authorized indemnification of the State of Michigan Department of Public Health, which would not provide the vaccine without indemnification due to the possibility that persons vaccinated may develop anaphylaxis or some unforeseen reaction of serious consequences, including death.³²

In 1992, Secretary of the Army Togo West, Jr. approved a request to indemnify the anthrax vaccine manufacturer, the Michigan Biologics Product Institute (MBPI), against all liability arising from:

The unusually hazardous risks associated with potentially severe adverse reactions and the potential lack of efficacy of the AVA. These concerns stem from: a) the *limited use of the vaccine to date*, i.e., tests prior to approval of the vaccine by the Food and Drug Administration are on *too small a scale to permit accurate assessment of types and severity of adverse reactions (only widespread use can provide this assessment)*; and b) insufficient experience in mass immunization programs to truly evaluate the efficacy of the vaccine. Moreover, there is no way to predict whether the pathogen against which the vaccine may be used will be sufficiently similar to the pathogen used in tests to ensure vaccine efficacy.³³ [emphasis added]

In 1998, Secretary of the Army Louis Caldera again authorized indemnification of MBPI because the size of the proposed vaccination program may reveal unforwarned idiosyncratic

³² Memorandum of Decision Secretary of the Army John O. Marsh, Authority under 50 U.S.C. 1431-1435 (P.L. 85-804) to Include an Indemnification Clause in Contracts or Purchase Orders with the State of Michigan, February 27, 1986 (in subcommittee files).

³³ Memorandum of Decision, Secretary of the Army Togo West, Jr., Authority under P.L. 85-804 to Include an Indemnification Clause in Contract DAMD17-91-C-1139 with the Michigan Biologic Products Institute [undated] (in subcommittee files).

adverse reactions.³⁴ The contracting officer justified the later indemnification request, in part, because, ASince 1990, approximately 600,000 doses have been issued from MBPI=s stockpile. The limited use of AVA to date versus the large number of doses that are being stockpiled and subject to use may expand the data base to a point where the statistical significance of a predicted adverse reaction may become a reality.³⁵

³⁴ See *supra* note 31.

³⁵ Joseph S. Little, Contracting Officer, AContracting Officer=s Request for Authorization for Indemnification Under Authority of Public Law 85-804,≡ Oct. 8, 1997, p. 3 (in subcommittee files).

Following the Gulf War, and prior to adoption of the DOD immunization policy in 1993, and the mandated AVIP in 1998, Pentagon officials considered and rejected alternative anthrax vaccine production sites.³⁶ Instead, an acquisition strategy was adopted focusing solely on the MBPI/BioPort vaccine.³⁷

Vaccine Usage and Safety

DOD literature says the anthrax vaccine has been safely and routinely administered in the United States to veterinarians, laboratory workers, and livestock handlers for more than twenty-five years.³⁸ Testimony at the March 24 hearing indicated between 100 and 300 civilians may receive the vaccine each year. Since approval, and prior to the AVIP, fewer than 68,000 doses had been distributed apart from stocks used in Operation Desert Storm.³⁹

As with any vaccine, anthrax inoculation can cause adverse health events in some individuals, ranging from soreness or swelling at the injection site (local reactions) to fevers, chills, muscle aches and anaphylaxis⁴⁰ (systemic reactions). Local reaction may be mild,

³⁶ BG Eddie Cain, AProcurement of the Anthrax Vaccine-Single Source Versus Additional Site, DOD Information Paper, JPO 0920, October 19, 1998 (in subcommittee files).

³⁷ BG John C. Doesberg, AAcquisition Strategy for the Procurement of Anthrax Vaccine Adsorbed, Joint Program Office for Biological Defense, JPO 0120, February 1, 1997 (in subcommittee files).

³⁸ See *supra* note 14.

³⁹ Prepared statement of Dr. Kathryn Zoon, Director, FDA Center for Biologics Evaluation and Research, NSVAIR Anthrax Hearing (II), p. 52-53.

⁴⁰ Anaphylaxis is one form of hypersensitivity to a drug or antigen. Anaphylactic shock is an often severe, sometimes fatal, physical reaction characterized by respiratory symptoms,

moderate or severe enough to require medical attention. Systemic reactions are generally considered clinically more significant. Reactions may increase in severity after successive injections.⁴¹

fainting, swelling and itching.

⁴¹ Michigan Biologic Products Institute, A Anthrax Vaccine Absorbed: How Supplied, References, Description, Clinical Pharmacology, Indications and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Dosage and Administration, ≡ FDA License No. 99, Rev. Feb. 1998 (in subcommittee files).

The AVA has been described as a relatively crude, imprecisely characterized vaccine, and estimates of reaction rates vary widely.⁴² According to the FDA-approved AVA product labeling, 30 percent of vaccine recipients can be expected to suffer mild local reactions, 4 percent will incur moderate local reactions and less than .2 percent will experience systemic reactions.⁴³

In 1994 and 1995, DOD considered the need for a new anthrax vaccine based on the reactogenicity of the current vaccine.⁴⁴

To avoid adverse reactions, the vaccine should not be given to those who experienced a severe reaction to a previous dose or to those with acute respiratory disease or an active infection. Immune compromised persons (i.e. HIV infected) may not respond to the vaccine. It is not recommended for pregnant women or for those under 18 or over 65 years of age.⁴⁵

The Army Anthrax Vaccine Immunization Plan directs medical personnel to report severe adverse reactions (resulting in hospitalization or more than 24 hours lost from duty) through the Vaccine Adverse Events Reporting System (VAERS) administered by the Department of Health and Human Services (HHS).⁴⁶ Within HHS, VAERS is a joint project of the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA).⁴⁷ VAERS guidance recommends recording any clinically significant symptoms occurring subsequent to vaccine administration, whether or not a causal relationship has been established between the vaccine and the adverse reaction.⁴⁸

The Army Medical Surveillance Activity also receives copies of VAERS forms from all the uniformed Services and produces a quarterly report for the U.S. Army Medical Command.⁴⁹ The Army Surgeon General has requested the assistance of the HHS Vaccine Injury Compensation Program in evaluating all anthrax-related VAERS data.⁵⁰

⁴² Phillip Brachman and Arthur Friedlander, *Vaccines*, 2d ed., pp. 729-739, Philadelphia, WB Saunders (1994).

⁴³ See *supra* note 41.

⁴⁴ LTC George W. Anderson, Jr., Memorandum AMinutes of the FDA meeting of May 5, 1994 Concerning Production and Purification of PA from Delta Stern-1 (pPa102) CR4, ≡ U.S. Army Medical Research Institute on Infectious Diseases, May 19, 1994 (in subcommittee files).

⁴⁵ See *supra* note 41.

⁴⁶ Gen. William W. Crouch, U.S. Army Vice Chief of Staff, MEMORANDUM AArmy Anthrax Vaccine Immunization Program Plan, Apr. 29, 1998, p. 3 and Annex C (in subcommittee files).

⁴⁷ FDA Center for Biologics Evaluation and Research, AVaccine Adverse Events Reporting System (VAERS) ≡ available at <http://www.fda.gov.cber/vaers/faq.htm>.

⁴⁸ *Ibid.*

⁴⁹ See *supra* note 46, p. C-7.

⁵⁰ *Anthrax Vaccine Adverse Reactions* 106th Cong. 1st sess. (1999) (subcommittee on

National Security, Veterans Affairs, and International Relations hearing of July 21, 1999)
[hereinafter ANSVAIR Anthrax Hearing (IV)≡] [The Subcommittee hearing has not yet been
printed. Page numbers in this and subsequent references to statements at this hearing refer to
individual prepared written statements or the unofficial transcript, held in subcommittee files.]
(prepared statement of Gen. Robert Claypool, p. 13-14).

The AVIP convened a clinical conference in May 1999 to discuss anthrax issues, including adverse events. Col. Renata Engler, M.D., Chief, Allergy-Immunology Department, Walter Reed Army Medical Center, presented data from ongoing research and case studies showing higher adverse reaction rates in women.⁵¹ Also discussed at the conference was the Army Surgeon General's proposed longitudinal cohort study to assess near-term and long-term health effects of the anthrax vaccine.⁵²

To convey important information about medical exemptions and adverse reactions, the Army implementation plan directs commanders and medical staff to provide recipients Adequate information on the vaccine, its safety, its benefits, and the need for adherence to the immunization schedule prior to the first anthrax vaccination.⁵³ The other Service implementation plans contain identical or similar requirements.

On April 1, 1999, VAERS data (1990 to 1999) contained 101 reports of adverse events associated with anthrax inoculation, 14 of which were considered serious.⁵⁴ In May 1999, DOD reported a total of 123 VAERS filings with FDA, but included only 65 of those in the calculation of an adverse reaction rate of .007 percent of 890,888 vaccinations given to date. According to DOD, only 11 VAERS reports met strict reporting requirements.⁵⁵

⁵¹ COL Renata Engler, MD., USA, Chief, Allergy and Immunology Department, Walter Reed Army Medical Center, *APresentation-Anthrax Immunization: Challenges for the Future*, *Department of Defense Conference for Biological Warfare Defense Immunizations*, Fort Detrick, Maryland, May 25-27, 1999 (in subcommittee files).

⁵² Department of the Army, Office of the Surgeon General, *AMemorandum for Conference Participants*, Apr. 16, 1999, p. 2 (in subcommittee files).

⁵³ See *supra* note 46 p. C-5.

⁵⁴ Testimony of Dr. Kathryn Zoon, Director, FDA Center for Biologics Evaluation and Research, NSVAIR Anthrax Hearing (II), p. 55.

⁵⁵ Department of Defense, *Briefing Slide: Anthrax Vaccine Adverse Events-Vaccine Adverse Event Reporting System (VAERS) Military - Week Ending May 21, 1999*" May 28,

Independent Medical Review

1999 (in subcommittee files).

A review of the AVIP plans, and of basic literature on the anthrax vaccine, was conducted by Dr. Gerard N. Burrow, of the Yale University School of Medicine.⁵⁶ According to Dr. Burrow⁵⁷, he conducted his review over three months, read materials provided by DOD and interviewed Pentagon officials responsible for designing and implementing the program. On February 19, 1998, in a four page letter, he concluded, AThe anthrax vaccine appears to be safe and offers the best available protection against wild-type anthrax as a biological warfare agent.≡ The letter contains two paragraphs on safety and efficacy. Regarding the safety of the vaccine stockpile, all of which was manufactured under conditions cited by FDA as deficient, Dr. Burrow pointed to the DOD supplemental testing program, and the fact that AFDA directed MBPI to do a comprehensive review to demonstrate that deviations in biologic product lines did not impact anthrax vaccine quality and integrity. The results of this review should be available in the near future.≡⁵⁸ Regarding efficacy of the vaccine, the letter recites usage figures since approval in 1970 and cites the conclusion of an unpublished DOD study that Aunit effectiveness could best be preserved through the use of pre-deployment vaccination.≡⁵⁹

In a letter to the Subcommittee in response to a request to testify on his review of the program, Dr. Burrow wrote:

Unfortunately, I do not believe I can make a significant contribution to the work of your Committee. I chaired the Institute of Medicine Committee that reviewed the Defense Department program for clinical care of Gulf War veterans in active service and interacted with personnel in the Office of Health Affairs. The Defense Department was looking for someone to review the program in general and make suggestions, and I accepted out of patriotism. I was very clear that ***I had no expertise in Anthrax*** and they were clear that they were looking for a general oversight of the vaccination program.

I visited the Pentagon on a number of occasions, talked with a variety of people in and out of government and presented my report which you have to the Secretary on March 2, 1998. ***I had no access to classified information.*** ...≡⁶⁰
(emphasis added)

Supplemental Testing

⁵⁶ See *supra* note 16.

⁵⁷ In an April 16, 1999 telephone conversation with Subcommittee staff, Dr. Burrow said his charge was a general review of the program, and that as an internist, he has little experience with vaccines. His primary recommendation was the use of focus groups of military personnel to determine appropriate communication strategies.

⁵⁸ See *supra* note 16.

⁵⁹ *Ibid.*

⁶⁰ Letter from Dr. Gerard N. Burrow, Yale University School of Medicine, to Rep. Christopher Shays, April 26, 1999 (in subcommittee files).

To address concerns over the age and quality of stockpiled vaccine, DOD undertook an effort to re-test the product before use. A contractor was retained to conduct supplemental testing of vaccine lots, all of which had been manufactured in an aging production facility, and some of which had been approved by the FDA for use beyond the initial expiration date.

Mitretek Systems Inc. reviewed vaccine production records and observed additional testing conducted by BioPort personnel.⁶¹ Of the 31 vaccine lots⁶² subjected by DOD to supplemental testing, 18 remained unavailable as of July, 1999 due to unresolved purity, potency or sterility issues.⁶³

Some involved in the program opposed supplemental testing as redundant and likely to cause more problems than it solved by establishing a self-imposed vaccine safety standard in addition to FDA lot-release criteria.⁶⁴ Their concerns were validated when the supplemental testing program appears to have overwhelmed the MBPI/BioPort testing capabilities, producing anomalous results and delaying the program.⁶⁵ Once the testing problems became apparent, vaccine lots not technically in the stockpile when the AVIP was announced were not subjected to the supplemental assays under the rationale the FDA was requiring the same tests for lot release.⁶⁶ All the lots submitted for supplemental testing had also undergone the same FDA lot

⁶¹ See *supra* note 17, p. 3.

⁶² Each lot contains approximately 200,000 doses of vaccine.

⁶³ See *supra* note 26, p. 13.

⁶⁴ Dr. Michael Gilbreath, Information Paper, JPO 0364, Feb. 4, 1998 (in subcommittee files); prepared statement of Dr. Robert C. Myers, Chief Operating Officer, BioPort Corporation, NSVAIR Anthrax Hearing (II), p. 83-84.

⁶⁵ *Ibid.* (Gilbreath Information Paper)

⁶⁶ Letter from Sec. of Defense William Cohen to Reps. Shays (CT), Gilman (NY), Kelly (NY), Souder (IN), Ose (CA), and Talent (MO), September 30, 1999, Attachment p. 1 (in subcommittee files).

release protocols.

Animal Data on Efficacy

DOD=s determination the vaccine affords protection against virtually all strains of airborne anthrax spores rests primarily on studies of vaccinated animals (guinea pigs, rabbits and monkeys) challenged with various strains of the disease.⁶⁷ But widely varied results within and between animal species suggest variable modes of protection not necessarily correlated to antibody levels stimulated by the vaccine.⁶⁸ Without a proven model in animals that is known to correlate to protection in humans, animal data remains only suggestive.

⁶⁷ Testimony of Dr. Sue Bailey, DOD Assistant Secretary for Health Affairs, NSVAIR Anthrax Hearing (I), p. 11.

⁶⁸ Prepared statement of Dr. Meryl Nass, NSVAIR Anthrax Hearing (II) p. 108-111.

Vaccine-acquired anthrax immunity may also be limited or overwhelmed when the subject is challenged with variant anthrax strains.⁶⁹ A report by the Senate Committee on Veterans= Affairs concluded that:

Adata suggests that the vaccine can protect humans against inhaled anthrax but to date there is inadequate information to judge how well it works, particularly against weaponized anthrax, which could cause exposure to greater concentrations of anthrax than has occurred among workers exposed on the job.⁷⁰

In response to questions regarding the efficacy of the vaccine against antibiotic resistant or genetically altered anthrax strains, DOD said

AThe current US-licensed anthrax vaccine is considered to be highly effective against naturally occurring strains of anthrax, including antibiotic resistant strains. The development of genetically engineered organisms using anthrax or any other biological warfare agent is a potential threat that must be evaluated carefully. We are not aware, however, of any information to suggest that these modified strains have been used in any context other than the research laboratory.⁷¹

When one U.S. laboratory studying the release of anthrax at Sverdlovsk implied the Russian mixtures of anthrax strains might overcome the protection afforded by the anthrax vaccine, DOD persuaded the author Ato correct the press release to make it more accurate. The modification stated, in part, Athere is no experimental data or evidence to suggest that such a mixture is resistant to the FDA-licensed anthrax vaccine used by the US military.⁷²

Opposition to the AVIP

Some have refused the vaccine. Active duty personnel have been disciplined under service-specific policies for refusing a lawful order. Reservists and National Guard members have resigned or transferred to units or Anon-mobility[≡] positions which do not require the vaccine. The DOD does not collect uniform records on refusals, but media reports indicate more than 300

⁶⁹ *Ibid.*

⁷⁰ *Report of the Special Investigation Unit on Gulf War Illnesses*, Senate Committee on Veterans= Affairs, 105th Congress, 2nd Session, September 1998, S. Rpt. 105-39, p. 122. See also, *As Military Research Hazardous to Veteran=s Health? - Lessons Spanning Half a Century*,[≡] Staff report prepared for the Committee on Veterans Affairs, United States Senate, p. 11, 103d Congress, 2d Session, S. Prt. 103-97, December 8, 1994.

⁷¹ See *supra* note 66.

⁷² *Ibid.* Nor is there data demonstrating the vaccine is effective against altered or mixed anthrax strains.

service men and women have refused to take the shot.⁷³

⁷³ AVaccine Refused by 23 Aircraft Carrier Sailors,≡ *Associated Press*, March 11, 1999 (in subcommittee files). The reported number of vaccine refusers has remained fairly stable in public reports, between 200 and 300, for some months.

Hearing testimony and correspondence from Reservists and National Guard members suggests up to 30 percent of some units would resign or seek to transfer due to the anthrax program.⁷⁴ Their concerns focus on the lack of systematic, long-term studies on anthrax vaccine health effects.⁷⁵

Safety is also an issue for some because the anthrax vaccine is one of the exposures under study by the National Academy of Science=s Institute of Medicine (IOM) pursuant to the Persian

⁷⁴ *Impact of the Anthrax Vaccine Program on Reserve and National Guard Units*, 106th Cong., 1st sess., p. 57 (Subcommittee on National Security, Veterans Affairs and International Relations hearing, Sept. 29, 1999) [hereinafter ANSVAIR Anthrax Hearing (V)] [The Subcommittee hearing has not yet been printed. Page numbers in this and subsequent references to statements at this hearing refer to individual prepared written statements or the unofficial transcript, held in subcommittee files.] (testimony of Capt. David Panzera; testimony of Tech. Sgt. William Mangieri, NSVAIR (V), p. 58) See also, testimony of Capt. Thomas Rempfer, NSVAIR Anthrax Hearing (I), p.110; testimony of Maj. Redmond Handy, NSVAIR Anthrax Hearing (I), pp. 102-102. DOD does not collect data on refusals or resignations attributable to the vaccine. An informal survey of Reserve and Guard units shows more than 700 current or likely departures due to the AVIP. The survey can be found at: http://www.dallasnw.quik.com/cyberella/Anthrax/Chron_Info.html, p. 12-13.

⁷⁵ Testimony of Col. Redmond Handy, NSVAIR Anthrax Hearing (I), p. 91; prepared statement of Ms. Randi Martin-Allaire, NSVAIR Anthrax Hearing (II), p. 171; prepared statement of Sgt. Michael Shepard, NSVAIR Anthrax Hearing (II), p. 193; testimony of Major Cheryl Hansen, NSVAIR Anthrax Hearing (V), p. 31.

Gulf War Veterans Act of 1998, enacted as Title XVI of the 1998 Omnibus Appropriations Act, P.L. 105-277. The law directs IOM to review associations between illnesses and wartime exposures that warrant a presumption of service-connection for sick Gulf War veterans.⁷⁶ That study is ongoing.

Efforts to meet Secretary Cohen=s four preconditions to AVIP implementation, intended to address likely reservations about the program, have only served to intensify concerns:⁷⁷

1. Problems with supplemental testing underscore vaccine safety and production issues. The failure to test all lots produced before the plant closed suggests to some the promise of supplemental testing was not fulfilled.

⁷⁶ P.L. 105-277, title XVI.

⁷⁷ Letter from Reps. Benjamin Gilman (NY), et. al. to Defense Secretary William Cohen, July 20, 1999, p. 1 (in subcommittee files).

2. The prerequisite communication effort engenders resentment and mistrust as simplistic DOD attempts at education and risk communication portray very limited vaccine use as Aoutine⁷⁸ and attack those with legitimate questions as Aparanoics⁷⁹ and simple-minded victims of Internet propaganda.⁸⁰

3. Delays in posting data to the tracking system reduce its value as a real time indicator of medical readiness and increases tolerance of deviations in the FDA approved inoculation regimen.⁸¹

4. Contrary to subsequent DOD characterizations, the promised outside, expert, scientific review of the program was only very general in nature.⁸²

Others question the necessity of the program, asking whether it betrays a lack of confidence in deterrence and other force protection elements, and suggesting a vaccine program makes anthrax attack more, not less, likely.⁸³

⁷⁸ See *supra* note 14.

⁷⁹ Lt. Gen. Ronald Blanck, AIgnore the Paranoics: The Vaccine is Safe, *Army Times*, Feb. 2, 1999, p. 12.

⁸⁰ Douglas J. Gilbert, American Forces Press Service, AAnthrax Vaccine Called Effective Force Protection, *DefenseLink*, Nov. 5, 1998 (in subcommittee files); *Washington Times*, AAnthrax Shots Drive Air Force Veteran From Service, *Oct. 13, 1999*, p. 18; *PBS New Hour*, AAnthrax Vaccine, *Oct. 21, 1999* (comments of Gen. Blanck) (transcript in subcommittee files); Col. Guy Strawder, AAVIP Director=s Newsletter (in subcommittee files).

⁸¹ Bradley Graham, AAnthrax Shots Missing Targets? *Washington Post*, Sept. 29, 1999, p. A27.

⁸² See *supra* note 60 and accompanying text.

⁸³ Testimony of Capt. Thomas Rempfer, NSVAIR Anthrax Hearing (I), p. 40-41; testimony of Maj. Russell Dingle, NSVAIR Anthrax Hearing (I), p.49.

Hearings and Legislative Proposals

On March 24, 1999 the Subcommittee on National Security, Veterans Affairs and International Relations held the first of five hearings on the Department of Defense (DOD) Anthrax Vaccination Immunization Program (AVIP). Entitled, *Oversight of the Anthrax Vaccine Inoculation Program*, the hearing examined the effectiveness and efficiency of the AVIP as a medical force protection measure, a record keeping initiative and long term procurement. The Subcommittee heard testimony from Dr. Sue Bailey, Assistant Secretary for Health Affairs, U.S. Department of Defense, accompanied by, Lt. Gen. Ronald R. Blanck, U.S. Army; Rear Admiral Todd Fisher, Deputy Surgeon General U.S. Navy; and Lt. Gen. Charles H. Roadman, II, U.S. Air Force; Capt. Thomas Rempfer, Connecticut Air National Guard; Maj. Russell Dingle, Connecticut Air National Guard; Pfc. Stephen M. Lundbom, U.S. Marine Corps; Attorney Mark Zaid; Col. Redmond Handy, Member Reserve Officer Association; and Lorene K. Greenleaf.

On April 29, 1999, the Subcommittee held a hearing on the AVIP entitled, *Anthrax (II): Safety and Efficacy of the Mandatory Vaccine*. The purpose of this hearing was to examine the vaccine's safety and effectiveness against an aerosolized biological weapons attack. Individuals who testified disputed the Department of Defense claim the vaccine is unquestionably safe for force wide use. Some who testified are experiencing serious illnesses they associate with the anthrax vaccine. Testimony was received from Kwai-Cheung Chan, Director, Special Studies and Evaluations Section, National Security and International Affairs Division, General Accounting Office; Dr. Katherine Zoon, Director, Center for Biologics Evaluation and Research, Food and Drug Administration; Dr. Michael Gilbreath, Medical Project Manager, Joint Program Office for Biological Defense; Dr. Robert Myers, Chief Operating Officer, BioPort Corporation; Dr. Meryl Nass; David Churchill; Randi Martin-Allaire; Roberta Groll; and Michael Shepard.

On June 30, 1999 the Subcommittee held a hearing entitled, *Oversight of DOD Sole Source Anthrax Vaccine Procurement*. The primary focus was to examine AVIP acquisition strategies and procurement activities pursued by the Department of Defense to purchase the vaccine. Issues examined included the technical and financial ability of BioPort to supply the vaccine at the contracted price, and the effect of management problems on the safety and the quality of the vaccine produced. Testimony was given by Louis J. Rodrigues, Director, Defense Acquisition Issues, National Security and International Affairs Division, General Accounting Office; David Oliver, Jr., Principal Deputy Under Secretary of Defense for Acquisition and Technology, Department of Defense; and Fuad El-Hibri, Chief Executive Officer, BioPort Corporation.

On July 21, 1999, the National Security Subcommittee held its fourth hearing on the AVIP. Entitled, *Anthrax Vaccine Adverse Reactions*, the hearing focused on the program's willingness to recognize and ability to treat adverse reactions to the vaccine in military personnel. Issues discussed included the extent the main adverse event surveillance system used by DOD,

the joint FDA/CDC Vaccine Adverse Event Reporting System (VAERS), under-reports adverse events and adverse vaccine reactions. Testifying at this hearing were CPT Michelle Piel, USAF; LT Richard Rovet, USAF; SGT Robert Soska, USA; CPT Jon Richter, USA; Kwai-Cheung Chan, Director, Special Studies and Evaluations Section, National Security and International Affairs Division, General Accounting Office; MG Robert Claypool, Deputy Assistant Secretary for Health Operations Policy, Department of Defense accompanied by, RADM Michael Cowen, Deputy Director for Medical Readiness, Joint Staff, Department of Defense; and COL Renata Engler, Chief, Allergy-Immunology Department, Walter Reed Army Medical Center; and Dr. Susan Ellenberg, Director, Division of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration.

The Subcommittee held its fifth hearing on the AVIP on September 29, 1999 entitled, AImpact of the Anthrax Vaccine Program on Reserve and National Guard Units.≡ The hearing examined the implementation of the AVIP in reserve component units and the impact of the program on retention, readiness and morale. Testifying at the hearing were Lt. Col. Thomas Heemstra, Indiana Air National Guard; Maj. Cheryl Hansen, Air Force Reserves; Capt. David Panzera, New York Air National Guard; Tech. Sgt. William Mangiere, New York Air National Guard; Charles Cragin, Acting Assistant Secretary for Reserve Affairs, Department of Defense, accompanied by, Maj. Gen. Paul Weaver, Jr., Director, Air National Guard, Department of Defense; Col. Frederick Gerber, Director, Health Care Operations, Office of the Army Surgeon General, Department of Defense; and Col. James Dougherty, Air Surgeon, National Guard Bureau, Department of Defense.

In the first session of the 106 Congress, two bills were introduced regarding the anthrax vaccine program:

Rep. Walter Jones (NC) introduced HR 2543 on July 16, 1999. Entitled AThe American Military Health Protection Act,≡ the bill would instruct the Department of Defense to make the anthrax vaccination immunization program voluntary for all members of the Armed Forces until the FDA has approved a new anthrax vaccine for humans or the FDA has approved a new, reduced course of shots for the current anthrax vaccine. This bill was referred to the Committee on Armed Services.

Rep. Benjamin Gilman (NY), introduced HR 2548 on July 19, 1999, cosponsored by Reps. Sue Kelly (NY) and Bob Filner (CA). HR 2548 would suspend further implementation of the Department of Defense anthrax vaccination program until the vaccine is determined to be safe and effective through a study by the National Institutes of Health. The Department of Defense Anthrax Vaccination Moratorium Act was referred to the Committee on Armed Services and to the Committee on Commerce.

The FY2000 Defense Appropriations Act (HR 2561) contained a provision directing the Comptroller General to report on: effects on morale, retention and recruiting; the civilian costs and burdens associated with adverse reactions for members of the reserve components; adequacy of long and short term health monitoring; assessment of the anthrax threat, including but not

limited to foreign doctrine, weaponization, quality of intelligence, and other biological threats. DOD was directed to contract with the National Research Council to conduct studies on: vaccine adverse events and adverse reactions, particularly among women; vaccine efficacy against inhalation anthrax; correlation of animal models to safety and efficacy in humans; research gaps; and other matters.

Discussion

Findings

1. The AVIP is a well-intentioned but over-broad response to the anthrax threat. It represents a doctrinal departure overemphasizing the role of pre-exposure medical intervention in force protection.

DOD bases the scope of AVIP on the scope of the threat, and the perceived need for additional, individual force protection to meet that threat. Threat assessment requires objective and subjective analyses of U.S. vulnerability, enemy capacity, and enemy intentions. AA threat analysis, the first step in determining risk, identifies and evaluates each threat on the basis of various factors, such as its capability and intent to attack an asset, the likelihood of a successful attack, and its lethality.⁸⁴

Since the King of Athens poisoned his enemy's wells in 600 BC and Alexander the Great hurled diseased animal corpses over the walls of a besieged city, ground forces have been vulnerable to casualties caused by natural or pernicious exposure to chemical and biological pathogens.⁸⁵ But in the absence of proven capability and intent to use biological weapons, vulnerability alone does not constitute a validated threat for purposes of determining appropriate and effective countermeasures.

Appropriately, much of the information regarding the BW capabilities and intentions of potential adversaries, and even allies, is classified. As a result, most public descriptions of the anthrax threat focus on the general vulnerability of unprotected forces to anthrax attack, the general ease and availability of anthrax production and the likely lethality of a successful anthrax attack.

⁸⁴ *Combating Terrorism - Threat and Risk Assessments Can Help Prioritize and Target Program Investments*, U. S. General Accounting Office, GAO/NSIAD-98-74, April 1998 p. 3.

⁸⁵ Dr. Stephen C. Joseph, Assistant Secretary of Defense for Health Affairs, ABiological Warfare - INFORMATION MEMORANDUM (undated) p.2 (in subcommittee files).

According to various unclassified DOD statements, more than ten countries have, or are developing, a biological warfare capability.⁸⁶ Those nations are: China, Iran, Iraq, Israel, Libya, North Korea, South Korea, Syria, Taiwan and Russia. Other public lists also include Egypt, Cuba, Japan, and the former Soviet states in Eastern Europe that may have inherited bio-warfare capabilities.⁸⁷ For purposes of the AVIP, the high threat areas validated by our intelligence community for the potential use of anthrax as a biological weapon of mass destruction includes [sic] Korea, Israel, Jordan, Kuwait, Saudi Arabia, Bahrain, Qatar, Oman, UAE and Yemen.⁸⁸ Anthrax is not seen as a threat in the Balkans.⁸⁹

Other descriptions of the anthrax threat focus on the relative ease of acquisition, mass production and weaponization of the stable, long-lasting anthrax microbe. According to DOD, production of biological warfare agents does not require specialized equipment or advanced technology. Biological agents are more potent and efficient than chemical weapons, and can be delivered through a variety of means. Legitimate uses (i.e. vaccine manufacture) for actual use production technologies make counter-proliferation strategies difficult to implement

⁸⁶ DOD Information Paper, ADOD Biological Warfare Threat Analysis, 12/15/97, p. 1. See also, *Proliferation: Threat and Response*, Department of Defense, November 1997.

⁸⁷ Office of Technology Assessment, U.S. Congress, *Proliferation of Weapons of Mass Destruction: Assessing the Risks*, p. 65, OTA-15C-559, August, 1993 (in subcommittee files). Notably included among those nations are U.S. allies who, it must be presumed, pose less danger to U.S. forces than nations currently opposing U.S. policy goals.

⁸⁸ See *supra* note 66, Attachment p. 13.

⁸⁹ *Ibid.*

successfully.⁹⁰

Secretary Cohen told Members, "Anthrax poses a clear and present danger to our armed forces. It is the weapon of choice for germ warfare because it is easy to weaponize and is as lethal as the Ebola virus. At least seven potential adversaries have worked to develop the offensive use of anthrax."⁹¹

In testimony before a subcommittee of the House Armed Services Committee, Deputy Secretary of Defense John Hamre said, "Currently, at least ten nation states and two terrorist groups are known to possess, or have in development, a biological warfare capability."⁹²

⁹⁰See *supra* note 86. The release of deadly chemical sarin gas in Tokyo by the Aum Shinrikyo cult highlighted the terrorist, and by implication, the military threat posed by chemical and biological weapons. But subsequently acquired information regarding the cult's unsuccessful attempts to use biological agents is seen by some as a counter to the argument those agents are not technically challenging to produce and deploy.

⁹¹See *supra* note 66.

⁹²Prepared statement of Hon. John J. Hamre, Deputy Secretary of Defense, submitted to the Subcommittee on Military Personnel, House Committee on Armed Services, p. 2, September 30, 1999.

DOD testimony to the Subcommittee portrayed the threat similarly: AAs identified by the Chairman of the Joint Chiefs of Staff, anthrax is a major threat to our troops. Anthrax is the primary biological warfare threat faced by U.S. forces. More than 10 countries, including Iraq, have or are suspected of developing this biological warfare capability. Anthrax is the biological weapon most likely to be encountered because it is highly lethal, easy to produce in large quantities, and relatively easy to develop as a weapon.⁹³

The AVIP tri-fold brochure describes the threat as follows:

ABiological weapons are maintained by several countries around the world. Use of these weapons could cause widespread illness among unprotected military forces.

Anthrax is the biological weapon most likely to be encountered because it is:

- X Highly lethal
- X Easy to produce in large quantities
- X Relatively easy to develop as a weapon
- X Easily spread over a large area
- X Easily stored and dangerous for a long time⁹⁴

Clearly, DOD has determined the threat is real and imminent, and has concluded it would be irresponsible not to deploy an available countermeasure to protect the lives and fighting capability of U.S. forces.⁹⁵

But similar statements on the threat have been made by DOD for many years. According to GAO testimony, AThe nature and magnitude of the military threat of biological warfare (BW) has not changed since 1990, both in terms of the number of countries suspected of developing BW capability, the types of BW agents they possess, and their ability to weaponize and deliver those BW agents. Inhalation anthrax is considered by DOD to be the primary BW threat because

⁹³ Prepared statement of Dr. Sue Bailey, DOD Assistant Secretary for Health Affairs, NSVAIR Anthrax Hearing (I), p. 8.

⁹⁴ See *supra* note 14.

⁹⁵ Prepared statement of Dr. Sue Bailey, DOD Assistant Secretary for Health Affairs, NSVAIR Anthrax Hearing (I), p. 13.

of its lethality, ease of production, and weaponization.⁹⁶

⁹⁶ Prepared statement of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Affairs Division, U.S. General Accounting Office, NSVAIR Anthrax Hearing (II), p. 12.

According to unclassified briefing materials assessing the anthrax threat, anthrax stocks and weaponized anthrax have been confirmed only in Southwest Asia. A stock of anthrax has been confirmed in Northeast Asia. Capacity to produce and weaponize anthrax elsewhere (South Asia or transnational) is suspected but unconfirmed.⁹⁷

Assessment of the Iraqi threat concludes that substantial anthrax production capacity exists but exceeds the ability to weaponize. While Iraq appears likely to be able to launch a BW attack using AL HUSSEIN ballistic missiles, aircraft delivery is seen as less likely due to U.S. and Coalition air superiority.⁹⁸ So Saddam would be unlikely to use WMD unless he perceives regime's survival at stake.⁹⁹

So the threat remains tactically limited and regional. The AVIP is universal.

Several factors appear to have fueled the 1997 decision to launch a mandatory, force-wide program to address a long acknowledged, regionally-based threat.

After the Gulf War, the Department of Defense undertook what is now characterized as a detailed, deliberative process¹⁰⁰ over more than three years that culminated in the conditional decision to implement a mandatory, force-wide anthrax immunization program. After a three year study, the Department has concluded that the vaccination is the only safe way to protect highly mobile U.S. military forces against a potential threat that is 99 percent lethal to

⁹⁷ DOD, Briefing Slide entitled "Anthrax Threat," April 20, 1998 (in subcommittee files).

⁹⁸ DOD, Briefing Slide entitled "Assessment," April 20, 1998 (in subcommittee files).

⁹⁹ *Ibid.*

¹⁰⁰ Prepared statement of Dr. Sue Bailey, Assistant Secretary of Defense for Health Affairs, NSVAIR Anthrax Hearing (I), p. 8.

unprotected individuals.¹⁰¹

That study was conducted, for the most part, behind closed doors. However, the documentation provided to the subcommittee by DOD¹⁰² describes a process more predetermined than deliberative, as the obvious operational benefits of passive, pre-exposure protection (versus cumbersome protective masks and suits), and the Iraqi threat, drove the decision to use the only vaccine currently available.¹⁰³

¹⁰¹ Letter from Sandra K. Stuart, Assistant Secretary of Defense (Legislative Affairs) to The Honorable Christopher Shays (CT), p.1, December 15, 1997.

¹⁰² Letter from Rep.Christopher Shays, Chairman, Subcommittee on National Security, Veterans Affairs and International Relations, House Committee on Government Reform to Secretary of Defense William Cohen, May 12, 1999 (in subcommittee files)

¹⁰³ Department of Defense, Information Paper ADOD Biological Warfare Force Protection, December 15, 1997, p. 2 (in subcommittee files).

In November 1993, DOD Directive 6205.3 set out a broad policy supporting immunization research, development, testing, acquisition and stockpiling of vaccines against current and emerging biological warfare threats. The directive required immunization only of A designated or A programmed personnel against agents A for which suitable vaccines are available, in sufficient time to develop immunity before deployment to high threat areas....¹⁰⁴

With regard to anthrax, DOD conducted research and program planning to develop an A improved anthrax vaccine (IAV) that would generate immunity against the known threat in a reasonable time. According to a DOD Operational Requirements Document (ORD), the need for an improved vaccine was identified in the MNS (Mission Needs Statement) for Medical Defense Against Chemical and Biological Warfare Agents in August 1994 and in the MNS for Department of Defense Biological Defense in August 1992.¹⁰⁵

The mission profile for the improved vaccine called only for inoculation of deployed and rapid deployment units A based on intelligence estimates of the potential for use of specific BW agents against U.S. forces. ... Other military personnel will be vaccinated prior to departure to BW threat areas. An accelerated immunization program will be conducted under certain alert or mobilization conditions.¹⁰⁶

Shortcomings of the currently licensed vaccine were seen as the A serious logistical obstacles, especially for reserve forces posed by the approved six-shot schedule and reports that suggest A this vaccine may not provide universal protection against all anthrax strains.¹⁰⁷ Minimum standards for the improved vaccine included generation of a protective immune response within 14 days of administering three inoculations.

Briefing materials produced by the U.S. Army Medical Research Institute of Infectious Disease (USAMRIID) in 1994 listed the following problems with the current vaccine:

Prolonged immunization schedule

Reactogenicity:

¹⁰⁴ See *supra* note 7, p. 2.

¹⁰⁵ Department of Defense, A Operational Requirements Document (ORD) for Improved Anthrax Vaccine, Oct. 2, 1995, p. 1 (in subcommittee files).

¹⁰⁶ *Ibid.*, p. B-1.

¹⁰⁷ *Ibid.*, p. 2.

Systemic reactions: .7 - 1.3%
Significant local reactions: 2.4 -3.9% (5.9%)

Vaccine components completely undefined in terms of characterization and quantitation of the PA, and other bacterial products and constituents present

Significant lot-to-lot variation in the PA immunogen content
Human trials with similar but not identical vaccine showed protection against cutaneous anthrax but insufficient data to show efficacy against inhalation anthrax

Made from spore-forming strain requiring dedicated production facility¹⁰⁸

Minutes of a May 1994 USAMRIID meeting addressed the Army's need for a new Anthrax vaccine. This need is based on reactogenicity of the current vaccine, the desire to make a vaccine with defined and well characterized components, and the need to produce a vaccine which does not require a BL-3¹⁰⁹ containment for production or a dedicated production facility, since *B. anthracis* is a spore former.¹¹⁰

Iraq's 1995 declarations to the United Nations Special Commission (UNSCOM) described a substantial BW program¹¹¹ including 8,000 liters of anthrax, 6,000 of which Iraq claimed to have weaponized in missile warheads, aerial bombs, rockets, remote-control aircraft and agricultural sprayers mounted on planes and helicopters.¹¹² At the same time, DOD interest in an improved anthrax vaccine diminished sharply. Reservations about the suitability of the old vaccine were put aside once it was made the centerpiece of the proposed immunization effort.

The vaccine program is just one element of the Joint Biological Warfare Defense concept encompassing:

- X detection and warning
- X individual (masks, suits) and collective protection (sealed command and control facilities)
- X medical (vaccines) countermeasures to prevent disease
- X contamination avoidance

¹⁰⁸ U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Briefing Slide A Problems with Current MDPH Vaccine, (undated) (in subcommittee files).

¹⁰⁹ Bio-Safety Level 3, the second most stringent of the four levels of controls to protect persons handling infectious agents. For a description of current bio-safety standards see: <http://www.cdc.gov/od/ohs/biosfty/bmb14/bmb14s3t.htm>

¹¹⁰ See *supra* note 44, p. 1.

¹¹¹ See *supra* note 85, p. 5.

¹¹² *Ibid.*

X decontamination¹¹³

Treaties, anti-proliferation regimes, as well as the prospect of tactical and nuclear retaliation, are also meant to deter use of chemical and biological weapons.

¹¹³ *Ibid.*, p. 7.

These are meant to be parts of an Aintegrated and overlapping systems approach to BW defense¹¹⁴ in which both military and medical considerations dictate a hierarchy of force protection measures emphasizing contamination avoidance and physical protection over medical intervention and decontamination. One statement of chem/bio defense doctrine ranks force protection strategies as follows:

A... The most effective and singularly most important prophylaxis in defense against biological warfare agents is physical protection. Preventing exposure of the respiratory tract and mucous membranes ... to infectious and/or toxic aerosols through use of a full-face respirator will prevent exposure, and should, theoretically, obviate the need for additional measures. Chemical protective masks effectively filter biological hazards.

... All medical prophylactic modalities described should be viewed only as **secondary** (i.e. backup), and are not be relied upon as primary protective measures. Agent exposures near the source of dissemination will be high, and likely to overwhelm any medical protective measure.¹¹⁵

The AVIP makes medical prophylaxis a primary aspect of force protection and CBW deterrence. In testimony, the DOD Assistant Secretary for Health Affairs put the proposition quite directly: AOur greatest and prime biological enemy today is anthrax. And our strongest weapon against anthrax is vaccination.¹¹⁶ The Navy=s Deputy Surgeon General added:

AWe are fortunate to have a time tested, safe and effective vaccine to provide an

¹¹⁴DOD, *Medical Defense Against Biological Material*, (undated) p. 1.

¹¹⁵*Ibid.* The section on Prophylaxis and Therapy continues: AThe precise efficacy of available medical countermeasures has, of course, never been evaluated in actual field circumstances, but is largely inferred from laboratory studies on nonhuman primates. While these extrapolations may be inexact, the strongly support the efficacy of vaccines and drugs at some agent dose.[≡] (emphasis original)

¹¹⁶Testimony of Lt. Gen. Charles H. Roadman, Surgeon General, USAF, NSVAIR Anthrax Hearing (I), p.17.

important element of the body armor needed to defend our personnel against weaponized anthrax. Anthrax has now joined other immunizations received by our Service men and women to protect against disease threats just as important as wearing a gas mask or carrying a rifle when on the battlefield.¹¹⁷

¹¹⁷Testimony of R.Adm. Todd Fisher, Deputy Surgeon General, USN, NSVAIR Anthrax Hearing (I), p17.

The Air Force Surgeon General expressed a similar rationale: AIn addition to the potential human cost, mass casualties would degrade our military mission, military capability and mission accomplishment. We would not send people into battle without helmets and weapons. So we should also provide the best armor against biological dangers that we can. That armor is immunization.¹¹⁸

But some service members see an important difference between the physical body armor worn in battle, which can be removed, and medical prophylaxis, which cannot. AThe body armor that our Department of Defense refers to is perceived by many service members as >tin foil armor=¹¹⁹

Primary reliance on medical intervention may also undermine confidence in other elements of the force protection hierarchy. One hearing witnesses asked if the vaccine might not Acreate a facade of force protection≡ provoking an adversary to even more lethal chem/bio or conventional attack.¹²⁰ He noted:

AThese foundations of force protection rely on a credible willingness to use force. This resolve won the Cold War and it won the Gulf War. Abandoning this time tested doctrine and emphasizing the inevitability of biological attack to advocate a defensive anthrax vaccination policy may inadvertently result in legitimizing biological warfare.¹²¹

The vaccine policy also reflects a lack of confidence in current force protection equipment. Physical barriers, effective against all toxins and microbes if used properly and in time, are now viewed as Alikely to remain only partially effective for the foreseeable future.¹²² Protective suits and masks Adegrade individual operating capabilities and force effectiveness ...¹²³ The

¹¹⁸ Testimony of Lt. Gen. Charles H. Roadman, II, Surgeon General, USAF, NSVAIR Anthrax Hearing (I), p. 18.

¹¹⁹ Testimony of Captain Thomas Rempfer, NSVAIR Anthrax Hearing (I), p. 40.

¹²⁰ *Ibid.*

¹²¹ *Ibid.*

¹²² See *supra* note 85, p. 11.

¹²³ *Ibid.*

purpose of the current doctrine on bio/chemical defense is to maintain combat operations unencumbered by contamination and the wearing of the protective gear.¹²⁴

¹²⁴See *supra* note 103.

Even this doctrinal reliance on the primacy of medical protection does not necessarily demand the universal, pre-deployment inoculation that characterizes the AVIP. Throughout the policy deliberation process, the option was considered to hold vaccines in stockpiles and defer actual immunization until mobilization to a threat area.¹²⁵ As late as September 1997, decision memoranda to the Under Secretary of Defense contained a recommendation to: AMaintain the planning guidance for total force immunization as a contingency plan, ready for finalizing, coordination, and approval at the appropriate time based on: (a) resolution, in conjunction with the FDA, of facility production issues; and/or (b) changes in the validated anthrax biological warfare threat.¹²⁶

The decision to launch the force-wide, mandatory immunization program, despite well documented misgivings about the vaccine and the capacity of the vaccine manufacturer, seems to have been driven by a genuine concern to avoid casualties, a military requirement for theoretically uniform protection within deployed units, an expansive view of demands on U.S. troop mobility, and the daunting logistics of the chosen vaccine.

AWhy is it essential that the anthrax immunization be mandatory? Military commanders have the responsibility to ensure the health and safety of their troops and to carry out their mission responsibilities. Anthrax is a serious threat. We have a safe and efficacious vaccine. To not use the vaccine constitutes a failure to protect our troops and a risk to carrying out military missions.¹²⁷ According to DOD, AWe are morally obligated to provide the best protection we are capable of providing to our troops -- in the case of protection against anthrax, there is a vaccine to provide individual immunity to this biological warfare agent.¹²⁸ According to Dr

¹²⁵ Dr. Edward D. Martin, et. al., Acting Assistant Secretary of Defense (Health Affairs), Department of Defense, AMemorandum for Deputy Secretary of Defense - Anthrax Vaccination Implementation Plan - ACTION MEMORANDUM,≡ p. 1, Sept. 19, 1997 (in subcommittee files).

¹²⁶ *Ibid.*, p. 2.

¹²⁷ Prepared statement of Dr. Sue Bailey, Assistant Secretary of Defense for Health Affairs, NSVAIR Anthrax Hearing (I), p. 10.

¹²⁸ DOD, *Public Affairs Talking Points*, p. 1, December 15, 1997.

Bailey, A Like other vaccines that are required to prepare military personnel for deployment, the anthrax vaccine is mandatory.¹²⁹

¹²⁹ Prepared statement of Dr. Sue Bailey, Assistant Secretary of Defense for Health Affairs, NSVAIR Anthrax Hearing (I), p. 10.

But the anthrax vaccine requirement differs from general military immunization and chemoprophylaxis policy in two significant respects. Other inoculations are required pursuant to medical, not military command authority,¹³⁰ and they are required primarily to maintain and protect the health of personnel from naturally occurring diseases or pathogens endemic to specific duty or deployment areas. Although the threat of natural anthrax remains a significant problem in numerous countries throughout Africa, the Middle East, Europe and Asia,¹³¹ the general military immunization policy contains no reference to the anthrax vaccine.

When asked how the U.S. program compared to the approach of allied forces, such as Great Britain which began a voluntary program, or Israel which appears to rely primarily on antibiotic treatments, the Pentagon responded, "DOD does not base its policies on those of our allies or coalition partners."¹³² Because our Armed Forces must be prepared to conduct successful military operations worldwide at a moment's notice,¹³³ DOD believes the mandatory AVIP is clearly in our best interests and strongly supports our national security and military strategies.¹³³

But there will be exceptions. A July 1999 Defense Threat Reduction Agency policy on anthrax immunization says:

Deploying civilian employees who decline to participate in the DTRA-AVIP will be required to execute a Statement of Informed Declination¹³⁴ attesting to the Agency's offer of anthrax immunization and the individual's decision to decline. By signing this statement, the employee acknowledges and willingly assumes the enhanced medical risk associated with travel to affected regions without receiving the recommended vaccinations. Hence, his/her deployment to these regions in support or mission requirements will not necessarily be precluded. This statement will become a part of the individual's permanent Occupational Health Record.¹³⁴

One of the primary reasons for the mandatory AVIP is the perceived need for consistent levels of force protection within and between deployed units to guarantee military effectiveness. Field commanders need to know the capabilities of their members. But even the force-wide, mandatory anthrax vaccine program is unlikely to meet that need. DOD concluded, but cannot

¹³⁰ Department of Defense, *Medical Services - Immunizations and Chemoprophylaxis*, Army Regulation 40-562, NAVMEDCOMINST 6230.3, AFR 161-13, CG COMDTINST M6230.4D, October 7, 1988.

¹³¹ See supra note 105, p. 1.

¹³² See supra note 66, p. 14.

¹³³ *Ibid.*

¹³⁴ Defense Threat Reduction Agency, *Policy Memorandum 99-22*, July 23, 1999, p. 2 (in subcommittee files).

prove, that individual antibody response to the vaccine equals protection from anthrax attack. That is, DOD believes the more anthrax-fighting antibodies produced, the more medical Abody armor≅ has been acquired. Animal studies suggest this may be the case for some species, but no correlate has been found in humans to permit extrapolation of this conclusion.¹³⁵

¹³⁵ Prepared statement of Kwai-Cheung Chan, NSVAIR Anthrax Hearing (II), p.17.

In any event, DOD does not test military personnel for antibody levels to determine the extent to which members of a unit may have acquired protection against anthrax. Uniform protection is also unlikely because individual immunological response to the vaccine can vary substantially due to a variety of factors, including gender, and contemporaneous administration of other vaccines or medicines.¹³⁶ Nevertheless, DOD concludes enrollment in the AVIP equals protection for purposes of satisfying the need for uniform force protection.¹³⁷

And, the very factors cited by DOD as necessitating universal AVIP coverage may actually work against that goal. Rapid mobility and the mixture of active and reserve forces mean individuals bring variable levels of protection to their assignments, depending on the number of shots taken to date and their individual immune system response. Some people don't respond to the vaccine at all.¹³⁸ So, beyond the general proposition that vaccinated individuals are likely to have some protection against some level of attack, the AVIP will not assure a commander that a unit is uniformly or even substantially protected. In tactical terms, the protection afforded by vaccination would be needed only during the time between detection and the order to deploy individual and collective physical protective measures (suits, masks, tents, etc.). Better detection capability, improved masks and a battlefield doctrine to deploy protective measures earlier could limit or eliminate the need even for that small window of protection provided by the vaccine.

¹³⁶ Testimony of Col. Renata Engler, Chief, Allergy-Immunology Service, Walter Reed Army Medical Center, NSVAIR Anthrax Hearing (IV), p. 173.

¹³⁷ See *supra* note 46, p. 1.

¹³⁸ Investigational New Drug (IND) application for Anthrax Vaccine Adsorbed (AVA) submitted by Michigan Biologic Products Institute, Lansing, Michigan, September 20, 1996, pp. 28 -29 (in subcommittee files).

2. The AVIP is vulnerable to supply shortages and price increases. The sole-source procurement of a vaccine that requires a dedicated production facility leaves DOD captive to old technology and a single, untested company. Research and development on a second-generation, recombinant vaccine would allow others to compete.

DOD has built a force-wide program on the narrowest possible industrial base.

According to GAO, the most critical component of the program, an adequate supply of vaccine, is threatened by testing delays and possible loss of production capability.¹³⁹ Moreover, GAO found ADOD's plans for maintaining an adequate supply of vaccine are optimistic ... and assume that FDA will grant approval of tested lots in less time than in the past.¹⁴⁰ Despite the possibility of further delays or a recurrence of financial problems at BioPort, ADOD does not have a formal contingency plan to deal with such possibilities.¹⁴¹

When DOD launched the AVIP, subject to the Secretary's four conditions including supplemental testing, MBPI/BioPort held 40 lots of vaccine, roughly the equivalent of 8 million doses, or enough vaccine to provide 1.3 million people the full six-shot regimen (assuming all lots were used before the expiration of original or extended label dating). But problems in the supplemental testing program delayed or precluded release of 18 lots.¹⁴² GAO found:

In summary, as of June 23, 1999, only 713,000 doses in the stockpile were available for use, and more than half of them - about 416,000 doses - will expire in February and April 2000. On the basis of DOD's estimates of doses required per month, the 713,000 doses would sustain phase 1 of the program through December 1999.¹⁴³

¹³⁹ See *supra* note 26, p. 12

¹⁴⁰ *Ibid.*, p. 5.

¹⁴¹ *Ibid.*

¹⁴² *Ibid.*, p. 13.

¹⁴³ *Ibid.*, p. 15; Including an estimated three-month supply already delivered to the field at

the time of this estimate, GAO concluded the program could be sustained at best through March 2000.

But even that delayed schedule may be optimistic. FDA inspectional findings on the renovated facility contain a number of observations repeated from the February 1998 inspection.¹⁴⁴ FDA considered those earlier findings as significant and took issue with DOD officials characterizing cGMP matters as mere bookkeeping difficulties in public statements.¹⁴⁵ If problems with the renovated facility are determined to be significant enough to bar release of vaccine lots produced since May 1999,¹⁴⁶ DOD could face severe shortages.

Because resumption of vaccine production has been delayed longer than anticipated by plant renovations and efforts to meet FDA compliance requirements, implementation of Phase II of the AVIP, scheduled to begin in early 2000, has been delayed in the range of six to 12 months.¹⁴⁷

¹⁴⁴ FDA Form 483, November 15-23, 1999 (in subcommittee files). See also, *Stars and Stripes*, Cohen Defends Mandatory Anthrax Shots After Ordering FDA-Related Suspension, p. 1, Dec. 20, 1999.

¹⁴⁵ E-mails between Food and Drug Administration and Department of Defense dated August 31 - September 1, 1999 (in subcommittee files).

¹⁴⁶ Production of consistency lots began in the renovated and expanded BioPort facility in May 1999. Data on consistency lots is submitted to FDA to validate the production process. Other lots have also been produced by BioPort in the expanded facility, but use of those at risk lots depends on FDA approval of the facility license supplement, an amendment to the license regarding the potency test and approval of test data on each lot.

¹⁴⁷ Dr. Sue Bailey, Department of Defense News Briefing, December 13, 1999, p.

In addition to production problems and delays, BioPort may not be a reliable financial partner in the vaccine enterprise. At the Subcommittee's request, the General Accounting Office (GAO) examined the structure and status of the financial relationship between DOD and BioPort.¹⁴⁸ They reviewed the contract documents, proposals and analyses done in connection with DOD procurement of the anthrax vaccine.¹⁴⁹

2 (available at: <http://www.defenselink.mil>) (in subcommittee files).

¹⁴⁸Letter to David Walker, Comptroller General, U.S. General Accounting Office from Rep. Christopher Shays, Chairman, Subcommittee on National Security, Veterans Affairs and International Relations, House Committee on Government Reform, May 13, 1999 (in subcommittee files).

¹⁴⁹*Contract Management - Observations on DOD's Financial Relationship with the Anthrax Vaccine Manufacturer*, Prepared statement of Louis J. Rodrigues, Director, Defense Acquisition Issues, National Security and International Relations Division, GAO, GAO/T-NSIAD-99-24, June 30, 1999.

Only nine months after entering into the agreement, BioPort's ability to perform under the contract was in doubt.¹⁵⁰ In June 1999, the Defense Contract Audit Agency (DCAA) completed an audit of BioPort's financial condition and reached a similar conclusion.¹⁵¹ According to GAO, estimates contained in BioPort's business plan and contract proposal have proven highly optimistic.¹⁵²

As a result, BioPort had to request emergency assistance from DOD and major modifications to the contract.¹⁵³ In order to remain able to produce vaccine for the AVIP, BioPort sought and received an advance payment of \$10 million, a significant per-dose price increase and DOD

¹⁵⁰ Testimony of Louis J. Rodrigues, Director, Defense Acquisition Issues, National Security and International Affairs Division, U.S. General Accounting Office, NSVAIR Anthrax Hearing (III), p. 4.

¹⁵¹ Defense Contract Audit Agency, Report No. 2261-97G21000018, Department of Defense, September 24, 1997 (in subcommittee files).

¹⁵² Prepared statement of Louis J. Rodrigues, Director, Defense Acquisition Issues, National Security and International Relations Division, GAO, NSVAIR Anthrax Hearing (III), p. 7.

¹⁵³ DOD Briefing Slides, ABioPort Contract - Anthrax Vaccine, June 2, 1999 (in subcommittee files). See also, BioPort Corporation media release, Anthrax Vaccine Manufacturer Calls for Fair and Reasonable Contract, June 30, 1999 (in subcommittee files).

permission to sell up to 300,000 doses each year on the open market, despite the fact those doses would be produced using government furnished equipment under the DOD contract.¹⁵⁴ DOD also authorized BioPort's sale of up to 70,000 doses from the vaccine produced under the prior contract but either released or deemed never part of the stockpile.¹⁵⁵

This early, extraordinary relief was necessary because production delays reduced estimated income. And, the procurement had to be done by means of a fixed price contract because neither side to the contract knew what it actually cost to produce the vaccine.¹⁵⁶ In its transition from a state-owned facility to a private enterprise, MBPI/BioPort has not fully implemented promised cost control and cost accounting systems to support a more appropriate cost-reimbursement procurement.

¹⁵⁴ Testimony of The Honorable David R. Oliver, Jr., Principal Deputy Under Secretary of Defense for Acquisition and Technology, NSVAIR Anthrax Hearing (III), p. 65.

¹⁵⁵ Testimony of The Honorable David R. Oliver, Jr., Principal Deputy Under Secretary of Defense for Acquisition and Technology, NSVAIR Anthrax Hearing (III), pp. 64-65. See also, DOD Briefing Slides, Anthrax Vaccine Absorbed Information Brief, June 4, 1999 (in subcommittee files). The briefing contained the following points: AMs. Spector advised that doses in the inventory that have been paid for cannot be used by BioPort for Private/Foreign Sales and Release doses from stockpile for private sales - JPO/OSD action (very political).

¹⁵⁶ Testimony of Louis J. Rodrigues, Director, Defense Acquisition Issues, National Security and International Relations Division, GAO, NSVAIR Anthrax Hearing (III), p. 28.

GAO also found the dependent relationship between DOD and BioPort unusual and risky. While sole-source procurements for vaccines may be common, those producers usually have other product lines generating income from other customers. In this case, problems with the production and delivery of the one vaccine put the corporation in an extremely bad financial position.¹⁵⁷

One vaccine producer operating a single production site also points to security risks. GAO observed, "But if we are relying upon this vaccine as part of the backbone of our defensive biological program, the question of vulnerability to a single site becomes an issue. If you made a decision with respect to that vulnerability that led you to want to have an alternative site, then we probably should be looking at establishing a second source."¹⁵⁸

Following the Gulf War, and prior to adoption of the DOD immunization policy (1993) and the mandated AVIP (1998), Pentagon officials considered and rejected alternative anthrax vaccine production sites.¹⁵⁹ Instead, an acquisition strategy was adopted focusing solely on the MBPI/BioPort vaccine.¹⁶⁰

Since 1993, DOD has focused almost exclusively on the older, FDA approved vaccine, to the exclusion of development work on newer, recombinant vaccine formulations. Not surprisingly, DOD market surveys detected little interest by other pharmaceutical or biologics companies in producing the older anthrax vaccine under a licence from MBPI. So it appears DOD's sole source justification may be self-validating, in that there is only one AVA producer because the single largest vaccine customer has decided to deal with only one producer.

Other manufacturers would be more likely to express an interest in recombinant vaccine production because it can be done more safely and efficiently than older vaccine formulation methods involving live bacteria. But DOD decided not to emphasize recombinant anthrax vaccine development due to the lengthy (6 to 8 years) development and approval time, and potential high costs.

Yet, had DOD officials elected to pursue second-generation anthrax vaccine development aggressively six years ago, they would be nearing completion on a newer, purer anthrax vaccine. BioPort's current financial demands, and the company's power to hold the AVIP hostage in the future, appear to undermine DOD's determination the MBPI/BioPort acquisition strategy would

¹⁵⁷ *Ibid.*, p. 16.

¹⁵⁸ *Ibid.*, p. 15.

¹⁵⁹ See *supra* note 36, p. 1.

¹⁶⁰ See *supra* note 37.

prove more affordable than new vaccine development.

One legal review of the BioPort contract sole source justification suggested DOD add a reference to ways competition might be increased by utilizing alternative technologies to produce the anthrax vaccine. The suggestion was not incorporated in the final document.¹⁶¹

It appears the choice of the MBPI vaccine for use in the AVIP may also have been premised on DOD and the manufacturer obtaining FDA approval to reduce the lengthy shot course from 6 shots over 18 months, to just 2 or 3 inoculations over 6 weeks. DOD developed a detailed program to gain approval for a shortened AVA shot course due to problematic levels of systemic (0.7 to 1.3 percent) and significant local reactions (2.4 to 3.9 percent) associated with the prolonged immunization schedule.¹⁶² An Investigational New Drug (IND) application was filed on September 20, 1996 at the FDA to study a reduced anthrax vaccine shot course, but design of a definitive comparison study has never been submitted.¹⁶³

So now, having foregone opportunities to improve or diversify anthrax vaccine production capacity, both DOD and BioPort are in a fiscal squeeze. Having made a substantial investment in MBPI and BioPort, DOD now faces hard, costly choices between sustaining the sole FDA licensed manufacturer of the anthrax vaccine, which may prove inadequate, and/or embarking on the establishment and licensure of another. In future budgets, DOD must consider to fund Adeveloping a second source to BioPort or developing a different approach to solve the anthrax

¹⁶¹ Elizabeth Arwine, Legal Advisor, A Legal Review of Justification and Approval (J&A); Michigan Biologic Products Institute (MBPI), Jun. 3, 1997, p.1 (in subcommittee files). See also, Joseph S. Little, A Response to JAG Comments, Department of Defense Memorandum for Record, June 4, 1997 (in subcommittee files).

¹⁶² See *supra* note 108.

¹⁶³ Letter from Melinda K. Plaisier, Interim Associate Commissioner for Legislative Affairs, Food and Drug Administration to Rep. Christopher Shays, Chairman, Subcommittee on National Security, Veterans Affairs and International Relations, House Committee on Government Reform, Mar. 15, 1999 (in subcommittee files).

problem and don't take that money and put it against solving another bio-threat¹⁶⁴

While these alternatives are being reviewed, the mandatory force-wide program to provide protection against what DOD characterizes as the pre-eminent biological warfare threat is on a very uncertain procurement footing. Without more extraordinary DOD assistance, BioPort appears financially incapable of capitalizing and sustaining a highly technical, heavily regulated manufacturing process. The same financial pressures that hindered MBPI's ability to comply with FDA good manufacturing practices could also continue to affect BioPort's capacity to produce a safe and effective product on schedule.

¹⁶⁴Testimony of The Honorable David R. Oliver, Jr., Principal Deputy Under Secretary of Defense for Acquisition and Technology, NSVAIR Anthrax Hearing (III), p. 69.

3. The AVIP is logistically too complex to succeed. Adherence to the rigid schedule of six inoculations over 18 months for 2.4 million members of a mobile force is unlikely, particularly in reserve components. Using an artificial standard that counts only shots more than 30 days overdue, DOD tolerates serious deviations from the Food and Drug Administration (FDA) approved schedule.

No other vaccine required by DOD for force health or combat protection demands so complex an administration schedule.¹⁶⁵ The FDA approved inoculation regime is six shots over 18 months, with a subcutaneous injection of AVA to be given as follows:

#1 B start of series

#2 B two weeks later

#3 B one month after start of series

#4 B six months after start of series

#5 B one year after start of series

#6 B 18 months after start of series.

Booster B annually after completion of initial series.¹⁶⁶

The ability to track immunizations and meet this schedule was one of Secretary Cohen's four preconditions to the AVIP. But even the Secretary of Defense received his fourth inoculation three weeks before it was due.¹⁶⁷

In an effort to comply with the elaborate timetable, DOD administers a three-tiered record keeping system. Each inoculation should be recorded on the individual service member's shot record.¹⁶⁸ Data recorded should include the date and AVA lot number. The same data is also entered into one of the service branch medical systems.¹⁶⁹ Finally, the service branch systems periodically forward inoculation data to the Defense Enrollment Eligibility Reporting System

¹⁶⁵ See *supra* note 130.

¹⁶⁶ See *supra* note 41.

¹⁶⁷ E-mail from Col. Fred Gerber dated September 1, 1998 (in subcommittee files).

¹⁶⁸ Form #PHS-731, Department of Defense (in subcommittee files).

¹⁶⁹ Service-specific subsystems: the Army MEDPROS, Navy SAMS and R-STARS, Air Force MITS.

(DEERS), a pre-existing facility modified to serve as an interim access point for centralized AVIP data. In the future, DOD plans to centralize AVIP data using an upgrade of the Composite Health Care System now under development.¹⁷⁰

¹⁷⁰ See *supra* note 26, p. 10.

This system was designed to address problems with medical record keeping encountered during Operation Desert Shield, Desert Storm and in Bosnia.¹⁷¹ However, while GAO found some improvements in vaccination records, a sampling of AVIP tracking at four locations discovered varying levels of discrepancies between paper and electronic data. According to GAO:

An inconsistency in dates could lead to vaccinations being given off-schedule and to inaccurate readiness reports. Inconsistent or missing lot information could hinder investigations, should concerns arise over a specific lot. Also, information that is not recorded in paper records makes it difficult to address adverse reactions needing immediate care or determine the validity of subsequent claims for disability compensation.¹⁷²

GAO also found use of DEERS data more limited than anticipated. ADEERS was envisioned as a major source of reports on program implementation. However, concerns about the timeliness and accuracy of data in DEERS have caused service representatives to rely on interim, service-specific tracking systems, and other systems to track and report vaccination information.¹⁷³ Specific concerns centered on duty station data, found in some cases to be updated only six to nine months late.¹⁷⁴ This severely limits the utility of DEERS as a tool to generate unit compliance or readiness reports, since the database often does not reflect current unit membership. Readiness estimates based on AVIP tracking data are still suspect,¹⁷⁵ according to an internal DOD document.

The difficulties of tracking anthrax vaccinations in the active force are compounded in

¹⁷¹ *Ibid.*, p. 20.

¹⁷² *Ibid.*, p. 21.

¹⁷³ *Ibid.*, p. 22.

¹⁷⁴ *Ibid.*

¹⁷⁵ E-mails from Maj. Guy Strawder dated February 17, 1999 (in subcommittee files).

reserve component units,¹⁷⁶ given changing unit memberships and monthly training schedules unlikely to match the inoculation regime. This difficulty was anticipated,¹⁷⁷ but DOD acknowledged in testimony that compliance with the FDA inoculation schedule in reserve component units was lower than in the active force due to less frequent drill schedules and timing of access to military medical facilities for purposes of receiving the vaccine.¹⁷⁸

¹⁷⁶ Reserve components consist of Army, Navy, Air Force and Marine reserve units as well as Army and Air National Guard units. Reserve units are elements of the national military. National Guard units are state militias unless federalized.

¹⁷⁷ See *supra* note 108.

¹⁷⁸ Prepared statement of Charles L. Cragin, Acting Assistant Secretary for Reserve Affairs, DOD, NSVAIR Anthrax Hearing (V), p. 5-7; testimony of Charles L. Cragin, NSVAIR Anthrax Hearing (V), p. 150.

As the logistical challenges of vaccine compliance increase, so do the risks of deviations from the approved schedule. While the effect of schedule deviations is another unknown element of the AVIP, DOD concludes that the greater the deviation the less certain the protective effect in humans.¹⁷⁹ Nevertheless, ADOD set a timeliness goal of vaccinating 90 percent of all service members no more than 30 days after their vaccinations are due....¹⁸⁰ DOD reports meeting that goal.¹⁸¹

On August 4, 1999 the Subcommittee requested data on vaccine regimen compliance in all reserve component units then enrolled in the vaccine program. The DEERS reports provided to the Subcommittee contained shot records on 32,681 individuals who had received one or more inoculations prior to July 31, 1999. Almost half (15,625) the individuals listed were overdue to receive an inoculation. In some cases, entire units had missed the schedule by a month or more. A summary of the data follows:

<u>Branch/Res. Comp</u>	<u># Enrolled</u>	<u># Overdue</u>	<u>%Overdue</u>
AFReserves	8931	2954	33
AIRNG	9246	2482	27
ArmyNG	2441	1443	59
ArmyReserves	5802	3661	63
MCReserves	2730	1967	72
USNReserves	3531	3118	88 ¹⁸²

¹⁷⁹ Memorandum on A Policy Deviation from Anthrax Vaccine Immunization Schedule, from the Department of Defense dated September 11, 1998, p. 1 (in subcommittee files).

¹⁸⁰ See *supra* note 26, p. 24. See also, testimony of Charles L. Cragin, Acting Assistant Secretary for Reserve Affairs, DOD, NSVAIR Anthrax Hearing (V), p. 150.

¹⁸¹ Department of Defense, A Anthrax Vaccine Immunization Program Quarterly Review, Jan. 22, 1999, p. 9 (in subcommittee files).

¹⁸² Letter and accompanying computer diskette from Charles L. Cragin to Rep. Christopher Shays dated August 23, 1999 (in subcommittee files).

The Air Surgeon, Col. James Dougherty, disputed the accuracy of the DEERS data. In an e-mail reacting to a media report of poor compliance in a Connecticut Air National Guard unit, he said All the data are inaccurate because the DEERS system is updated weeks after shots are actually administered.¹⁸³ DOD also said the data showing overdue inoculations was inflated due to the inadvertent inclusion of Individual Ready Reserve forces, service members who are separated from military service but available for call-up.¹⁸⁴ Nevertheless, according to an internal DOD document, readiness estimates based on AVIP tracking data are Astill suspect.¹⁸⁵

If the centralized tracking system cannot provide a real-time picture of the inoculation status of the entire force, or individual units, it fails to meet the operational standard set by the Secretary as a condition of AVIP implementation.

The data provided to the Subcommittee by DOD also showed most reserve component members receive the first three inoculations on schedule, with compliance deviations occurring with regard to subsequent shots.¹⁸⁶ That may not be entirely inadvertent. DOD documents contain the statement ASoldiers with 3 or more vaccinations are Protected.¹⁸⁷ The DOD position that Afunctional protection¹⁸⁸ is provided after only three of the six required inoculations sets a deployability standard against which reserve component commanders are measured. Once members of a unit have received three shots, there appears to be little incentive to press for further compliance with an increasingly unpopular program.

There is little scientific evidence to support the theory that three shots protect as well as six. DOD expended significant time and resources in 1994 and 1995 on plans and programs to demonstrate the safety and efficacy of a shorter anthrax inoculation regime, and a different route of administration. An Investigational New Drug (IND) application was filed to guide further animal studies and clinical trials in humans. But the effort appears to have all but abandoned when planning for the AVIP began. Support for the FDA application to reduce the shot course seems to have been redirected to vaccine acquisition and AVIP logistics.

In September 1999, the Director of the FDA Center for Biologics Evaluation and Research, Dr. Katherine Zoon, wrote to Dr. Sue Bailey, Assistant Secretary of Defense for Health Affairs

¹⁸³ E-mails from James Dougherty dated September 1, 1999. (in subcommittee files)

¹⁸⁴ Testimony of Charles L. Cragin, Acting Assistant Secretary for Reserve Affairs, NSVAIR Anthrax Hearing (V), p. 104 (in subcommittee files).

¹⁸⁵ See *supra* note 175.

¹⁸⁶ See *supra* note 182.

¹⁸⁷ See *supra* note 134, p. 2, and e-mails from Department of Defense personnel dated February 17 - April 14, 1999 (in subcommittee files); If the manufacturer of a pharmaceutical or biologic product advised patients or physicians that half the FDA approved dosage or administration regimen was as effective against the labeled indication, it would be a serious violation of FDA regulations.

¹⁸⁸ See *supra* note 134, p. 2.

regarding data showing significant deviations from the AVA administration routine:

A... Because we are unaware of any data demonstrating that any deviation from the approval intervals of doses found in the approved labeling will provide protection from anthrax infection, we strongly recommend that the Anthrax Vaccine Immunization Program follow the FDA approved schedule.¹⁸⁹

Prior to the administration of each shot, medical personnel are directed to provide information on the vaccine and the program, and to inform each recipient regarding the health factors that should exclude a person.¹⁹⁰ Exclusionary factors include severe reaction to a previous shot, active infection, pregnancy, current immuno-suppression.¹⁹¹ Service members should also be informed regarding the identification and reporting of adverse health events suffered subsequent to inoculation.¹⁹²

But GAO found medical staff and service members were not well informed about reporting adverse events and found more than forty percent of those sampled had not received information on how to report vaccine related adverse events.¹⁹³ Testimony by service members reflected the GAO findings.

Ms. Randi Martin-Allaire, a civilian employee of the Michigan Air National Guard told the Subcommittee, AI was on antibiotics at the time I received by fourth injection, and was never asked if I was on any type of medication or antibiotics.¹⁹⁴ Her colleagues described similar miscues and confusion over the standards for identifying and treating vaccine adverse reactions.¹⁹⁵

Service members report AVIP information and briefings seem designed to persuade, not educate. The inability of Air Force briefers to answer service members' questions led one commander to suspend the vaccination program until the Air Force Surgeon General personally intervened.¹⁹⁶ Vaccine recipients also report mass inoculations during which no questions

¹⁸⁹ Letter from Dr. Katherine C. Zoon to Dr. Sue Bailey dated September 29, 1999 (in subcommittee files).

¹⁹⁰ See *supra* note 46, p. C-5.

¹⁹¹ See *supra* note 41.

¹⁹² Department of Defense, A Clinical Practice Guidelines for Managing Adverse Events After Anthrax and Other Vaccinations, *en* Nov. 15, 1999 pp. 1-2. (in subcommittee files)..

¹⁹³ See *supra* note 26, pp. 24-26.

¹⁹⁴ Prepared statement of Randi J. Martin-Allaire, NSVAIR Anthrax Hearing (II), p. 170.

¹⁹⁵ Prepared statement of Roberta Groll, NSVAIR Anthrax Hearing (II), p. 176-179; and prepared statement of David Churchill, NSVAIR Anthrax Hearing (II), pp. 183-188.

¹⁹⁶ Debra Funk, A Air Guard Unit Delays Anthrax Inoculations, *en* *Air Force Times*, July 5, 1999, p. 29.

regarding current health status are asked and noVAERS forms made available.¹⁹⁷

¹⁹⁷ E-mails and meeting notes (in subcommittee files).

The AVIP is made more complex by the need to address growing resistance to the vaccine, specifically in reserve component units. The impact of the AVIP on retention in reserve component units could be significant. Informal surveys by service members suggest the Air National Guard may suffer air crew attrition of thirty percent or more.¹⁹⁸ To date, the Defense Department has not acknowledged any unusual pattern of resignations attributable to the AVIP.¹⁹⁹

It is not clear where the Department might look to discern such a pattern. DOD collects no centralized data on refusals or resignations attributable to the vaccine program. Some service members also said unit commanders openly discouraged attribution of resignations or transfers to the AVIP.²⁰⁰ An Air Force Reserve Interim Anthrax Policy forbids the approval of transfer requests made by anyone scheduled or directed to begin the anthrax immunizations.²⁰¹

GAO was critical of this lack of monitoring to determine the effectiveness of the AVIP communications effort.²⁰² Without data on refusals, Ait is difficult to better target educational efforts and address emerging concerns. These problems need to be resolved *if the program is to succeed* in vaccinating the entire force against anthrax.²⁰³ (emphasis added)

DOD developed a detailed program to gain approval for a shortened AVA shot course to address the logistical challenge of the six-shot regime and to reduce problematic levels of systemic (0.7 to 1.3 percent) and significant local reactions (2.4 to 3.9 percent) associated with the prolonged immunization schedule.²⁰⁴ An Investigational New Drug (IND) application was filed on September 20, 1996 at the FDA to study a reduced anthrax vaccine shot course, but

¹⁹⁸ See *supra* note 74.

¹⁹⁹ Testimony of Maj. Gen. Paul Weaver, Director, Air National Guard, DOD, NSVAIR Anthrax Hearing (V), p. 118.

²⁰⁰ E-mails (in subcommittee files).

²⁰¹ Command Anthrax Policy, U.S. Air Force Reserve, June 22, 1999 (in subcommittee files).

²⁰² See *supra* note 26, p. 35.

²⁰³ *Ibid.*

²⁰⁴ See *supra* note 108.

design of a definitive comparison study has not yet been submitted.

4. Safety of the vaccine is not being monitored adequately. The program is predisposed to ignore or understate potential safety problems due to reliance on a passive adverse event surveillance system and DOD institutional resistance to associating health effects with the vaccine.

Based on data gathered during limited occupational use since licensure, the AVA can be considered nominally safe. But the vastly expanded use of the vaccine for a new purpose requires a proactive approach to emerging safety issues. That approach is not now a part of the AVIP.

As with any vaccine, anthrax inoculation can cause adverse health events in some individuals, ranging from soreness or swelling at the injection site (local reactions) to fevers, chills, muscle aches and anaphylaxis²⁰⁵ (systemic reactions). Local reaction may be mild, moderate or severe enough to require medical attention. Systemic reactions are generally considered clinically more significant. Reactions may increase in severity after successive injections.²⁰⁶

More inoculations means more reactions. An immunization program using a vaccine requiring six shots and annual boosters should be prepared to deal with some number and variety of adverse health effects. Despite having been licensed for almost 30 years, the vaccine had not been widely used prior to the Gulf War.²⁰⁷ As noted previously, lack of adequate medical record

²⁰⁵ Hypersensitivity to a drug or antigen. Anaphylactic shock is an often severe, sometimes fatal, physical reaction characterized by respiratory symptoms, fainting, swelling and itching.

²⁰⁶ See *supra* note 41.

²⁰⁷ Prepared statement of Kathryn C. Zoon, Ph.D., NSVAIR Anthrax Hearing (II), pp. 52-

keeping prevents systematic study of that cohort for health effects possibly associated with the anthrax vaccine and other medicines and toxins. The vaccine is being studied as a potential factor in Gulf War veterans' illnesses.²⁰⁸ As GAO noted, "The long term safety of the vaccine has not yet been studied."²⁰⁹

53.

²⁰⁸ See supra note 1.

²⁰⁹ Prepared statement of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Relations Division, GAO, NSVAIR Anthrax Hearing (II), p. 11.

The AVA has been described as a relatively crude, imprecisely characterized vaccine, and estimates of reaction rates vary widely.²¹⁰ According to the FDA-approved AVA product labeling, 30 percent of vaccine recipients can be expected to suffer mild local reactions, 4 percent will incur moderate local reactions and less than .2 percent will experience systemic reactions.²¹¹

In 1994 and '95, DOD considered the need for a new anthrax vaccine based on the reactogenicity of the current vaccine.²¹²

In April 29, 1999 testimony²¹³ before the Subcommittee, the General Accounting Office (GAO) summarized studies of anthrax vaccine reactions, finding rates of systemic reactions ranging from .05 percent to 48 percent. (Table 1, below)

Table I: Reactions to Licensed Anthrax Vaccine Reported in Various Studies

Study	Type of Reporting	Number Vaccinated (or doses)	Local reactions (percent)		Systemic reactions (percent)	
			Mild	Moderate / Severe	Mild	Moderate / Severe
IND	Active / Passive	3,984 ^a	6 B 20 ^b	1 B 10 ^b	None ^b	.05 ^b
Pittman (1997)	Active	508	16	5	29 ^c	14
TAMC (1998)	Active	536	Not Addressed		43 ^d	5
DOD (Current monitoring)	Passive	223,000 ^e	^e	^e	^e	^e

^aThis number represents the number of study participants who received the first dose of the licensed vaccine.

^bThese figures represent the percentage of people who experienced this type of reaction during the study, even if they had previously been inoculated with the Merck vaccine.

^cThis figure also includes persons who had reactions of "unknown" severity.

^dThis figure represents the frequency of the most common side effect, myalgia.

²¹⁰ *Ibid.*, p. 16.

²¹¹ See *supra* note 41.

²¹² A Minutes of FDA Meeting of 5 May 94 Concerning Production and Purification of PA from Delta Sterne, Department of the Army, May 19, 1994, p. 1.

²¹³ Prepared statement of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Relations Division, GAO, NSVAIR Anthrax Hearing (II), p. 16.

^oDOD testified that as of March 16, 1999, more than 223,000 service member have been immunized. There had been 42 reports on adverse effects submitted to the FDA and CDC. Only seven service members required hospitalization or experienced loss of duty for more than 24 hours.

In later testimony, GAO also observed:

In addition to reporting to VAERS, DOD has conducted three efforts to actively collect data on adverse reactions after service members received the anthrax vaccine. Data from these efforts show that women reported twice the rate of adverse reactions than men for both local (e.g. swelling) and systemic (e.g. malaise and chills) reactions. In addition, a higher proportion of women than men reported making an outpatient medical visit after a vaccination, and more than twice the percentage of women reported that they missed one or more duty shifts after their vaccinations than did men.²¹⁴

Captain Michelle L. Piel believes she suffered an adverse reaction to the anthrax vaccine. Fatigue, dizziness, joint pain and severe cold-like symptoms following her first two inoculations resulted in the loss of flight status. When she suggested submitting a report to VAERS, she testified, AMy request met reluctance.²¹⁵ Because her symptoms did not fall within the range of expected vaccine reactions, doctors as Dover Air Force Base did not associate her illness to the AVA. She concluded, AThis is a major reason why adverse events from the anthrax vaccine are underreported.²¹⁶ She added, AIt didn=t make sense to me. I was too sick to fly. I was too sick to get another shot. But my illness wasn=t reportable on a VAERS form?²¹⁷

When others at Dover suspected health effects might be linked to the vaccine, efforts to report a trend Awere met with resistance and discouragement from within Dover=s medical

²¹⁴ Prepared statement of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Relations Division, GAO, NSVAIR Anthrax Hearing (IV), p. 3 (in subcommittee files).

²¹⁵ Prepared statement of Capt. Michelle L. Piel, NSVAIR Anthrax Hearing (IV), p. 3 (in subcommittee files).

²¹⁶ *Ibid.*

²¹⁷ *Ibid.*

community.²¹⁸ According to Capt. Piel, AIIt took 6 months to reach the right, highly specialized doctors to begin to diagnose my immune system problems.²¹⁹

²¹⁸ *Ibid.*

²¹⁹ *Ibid.*, p. 4.

At the reaction rates cited by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID),²²⁰ the anthrax vaccine program, when implemented across the entire 2.4 million member force, could produce 31,200 systemic reactions and up to 93,600 severe local reactions. Recently, the Army Surgeon General conceded that, ASystemic events occur in five to 35 percent of anthrax-vaccine recipients.²²¹ At the range of systemic reactions found by DOD in the Tripler Army Medical Center active surveillance study, the AVIP could generate over one million systemic reactions, many thousands of which will require medical management and treatment.²²²

Given that prospect, it might have been expected by service members that an integral part of the AVIP would be highly sensitive active and passive surveillance systems to Apermit accurate assessments of types and severity of adverse reactions²²³ because Aonly widespread use can provide this assessment.²²⁴ That was one factor which lead DOD to indemnify the vaccine manufacturer against the Aunusually hazardous risks²²⁵ of vaccine production.

To better quantify those risks, and to detect adverse reaction trends early, the program design could have included detailed medical protocols on screening, vaccine administration and adverse events. The AVIP could have assembled and trained a multi-disciplinary network of health professionals to manage the anticipated adverse event caseload. It could have provided each recipient with a simple, one page vaccine information sheet on adverse events and drug inter-actions of the type routinely provided with childhood vaccines. The AVIP could have designed and initiated the controlled, cohort studies only now being discussed to learn more about reaction rate differences by age and gender.²²⁶

The AVIP does not include those safety elements.

Instead, the program now relies primarily on an adverse event surveillance and reporting system known to understate the nature and extent of health effects associated with vaccine administration. Access to immunologists and allergists is limited geographically. Not until one year after the program began did DOD update briefing materials to include information on reporting adverse events and revise program regulations to make reporting requirements more inclusive, clarify patient and provider responsibilities, and explain how to process a Vaccine

²²⁰ See *supra* note 108.

²²¹ Letter from Lt. Gen. Ronald R. Blanck to Mark Zaid dated December 10, 1999, p. 1 (in subcommittee files).

²²² See *supra* chart at note 213.

²²³ See *supra* note 33.

²²⁴ *Ibid.*

²²⁵ *Ibid.*

²²⁶ Deborah Funk, AMilitary Officials Order Study to Determine Vaccine=s Safety, Long-term Side effects,²²⁶ *Army Times*, July 12, 1999, p. 12.

Adverse Event Reporting System (VAERS) form. Only in July 1999 did DOD distribute draft clinical guidelines that outline clinical protocols, pre-treatments, specialty referral processes, contraindications, categorizations of local and systemic reactions and associated treatment algorithms.²²⁷

²²⁷ Prepared statement of Maj. Gen. G. Robert Claypool, Deputy Assistant Secretary for Health Operations Policy, DOD, NSVAIR Anthrax Hearing (IV), p. 12 (in subcommittee files).

According to GAO testimony, studies have shown passive systems sometimes capture only one percent of adverse events temporally or causally related to use of a medical device or vaccine. Reports also vary in quality and utility due to inconsistencies in identifying and interpreting health effects as vaccine related. A passive system is useful as a sentinel to alert clinicians to unexpected events.²²⁸ It does not tell you how often, with what severity, or does not establish causality. The limitations are very well accepted.²²⁹

Because passive systems are voluntary, the data generated are subject to a self-selection bias, in that trends in volunteered data cannot be extrapolated as if representative of an entire cohort or population. As a result, information from a passive reporting system, like VAERS, is not an appropriate source of data for use in generating adverse reaction rates.

Nevertheless, AVIP reports and DOD public statements portray the ratio of VAERS reports to inoculations given as an adverse reaction rate.

In presenting reaction rate data, program and DOD officials have shown reactions reported to VAERS as a percentage of all vaccinations. They did so in several briefings to GAO and congressional staff, in prepared testimony, and on the program's Internet site. However, according to FDA guidance, incidents in the VAERS database reflect a temporal, not necessarily a causal, relationship with vaccination and thus should not be used to calculate the incidence of reactions.²³⁰

GAO found, This is misleading because of potential underreporting of events to VAERS, and the potential for overstating the reaction rate because reports sent to VAERS are not confirmed to be causally linked to the vaccination.²³¹ The potential for overreporting is

²²⁸ Testimony of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Relations Division, GAO, NSVAIR Anthrax Hearing (IV), p. 125 (in subcommittee files).

²²⁹ Testimony of Dr. Shushil K. Sharma, Special Studies and Evaluations Section, National Security and International Relations Division, GAO, NSVAIR Anthrax Hearing (II), p. 25.

²³⁰ See supra note 26, p. 32.

²³¹ *Ibid.*

limited, however, by DOD screening of VAERS reports before inclusion in quarterly AVIP figures. In this regard, GAO concluded, AThus, DOD does not have reliable information on the extent of adverse reactions.²³²

²³² *Ibid.*

Even if useful to gauge short term reactions, passive reporting systems are also unlikely to capture long term or chronic health effects or syndromes, since providers and vaccine recipients do not generally associate an illness with an event far removed in time.²³³ But many service members are concerned over possible long term health effects of the anthrax vaccine, alone or in combination with other treatments and exposures.²³⁴ According to GAO, AA primary reason for dissatisfaction with information about long-term side effects appears to be that research has not been done to address the topic. According to program officials, such studies have recently been discussed but are not yet funded or underway.²³⁵

The AVIP's strict VAERS reporting requirements of hospitalization or more than 24 hours absence from duty limit the scope of any safety surveillance to severe, short term reactions. This overly narrow interpretation of adverse event data could result in DOD missing the types and severity of adverse reactions only widespread use would otherwise reveal. The Astatistical significance of a predicted adverse reaction²³⁶ will only become apparent if the statistics are permitted to capture the full range of available data.

A system already known for underreporting can be made even less reliable in the hands of an institutional culture resistant, even hostile, to reports attributing ill health to the anthrax vaccine. Air Force Lieutenant Richard Rovet, while serving as Health Care Integrator for the Flight Medicine Clinic at Dover AFB, noted a number of individuals reporting potentially vaccine-related symptoms: dizziness, ringing in the ears, joint pain, muscle aches, memory impairment, fatigue, numbness, prolonged fever and chills, localized and persistent rashes.²³⁷ He said there was significant confusion in the field regarding reportable reactions Aespecially in

²³³ Prepared statement of Dr. Meryl Nass, NSVAIR Anthrax Hearing (II), p. 107.

²³⁴ Prepared statement of Capt. Michelle L. Piel, NSVAIR Anthrax Hearing (IV) (in subcommittee files); prepared statement of Capt. Jon Richter, NSVAIR Anthrax Hearing (IV) (in subcommittee files); and e-mails sent to the subcommittee (in subcommittee files).

²³⁵ See *supra* note 26, p. 32.

²³⁶ See *supra* note 30.

²³⁷ Prepared statement of Lt. Richard Rovet, NSVAIR Anthrax Hearing (IV), p. 2 (in subcommittee files).

regard to what constitutes systemic reaction.²³⁸ Lt. Rovet testified medical providers saw the issue of identifying vaccine reactions Apolitically sensitive and like to avoid it.²³⁹

²³⁸ Testimony of Lt. Richard Rovet, NSVIAR Anthrax Hearing (IV), p. 25 (in subcommittee files).

²³⁹ *Ibid.*

That resistance reduces what few incentives already motivate military personnel to report sick. Particularly when complaining of symptoms of unknown origin, a service member risks the label Amalingerer≡ or Adepressed.≡²⁴⁰ If seeking care seems a dead end, Awhy risk your flying status if you are just suffering some of the mild symptoms of joint pain or you feel a little bit tired? Why should you go to the doctor is you feel you can continue to operate an airplane? And that is why people don=t come forward.≡²⁴¹

An Air Force Reservist, Capt. Jon Richter, also suffered chronic symptoms he attributed to the vaccine. While he came forward, he testified there is little incentive for others do so. AI was encountering more of my squadron mates who were vaccinated that said they too had experienced various reactions, including tinnitus, dizziness, muscle and joint pain, and, in one case, gray-outs. However, most were attempting to keep it low profile and did not readily discuss these matters for fear of reprisal.≡²⁴² AWord travels fast. Morale is at an all time low. People are trigger shy about coming forward with their symptoms. There is an air of fear and distrust prevalent throughout.≡²⁴³

A reluctance to acknowledge vaccine related health effects could also block access to the immunologists and allergists experienced in the diagnosis and treatment of adverse reactions. This can be a more acute problem for National Guard and Reserve members whose level of access to military medicine, particularly specialists, for vaccine matters is uncertain. Witnesses at the Subcommittee=s April 29 hearing from the Michigan Air National Guard described a difficult and time consuming process to gain access to medical personnel with relevant expertise.²⁴⁴

According to the Dr. Renata Engler, Chief Immunologist at the Water Reed Army Medical Center, and a consultant to the AVIP, AVaccine administration is serious business and deserves more care and training of those who deliver the service.≡²⁴⁵ One critical issue, she said, Ais that stakeholders who understand the clinical issues have NOT been represented in the organizational policy development.≡²⁴⁶ AThere is a problem that the organization does NOT

²⁴⁰ Prepared statement of Capt. Michelle L. Piel, NSVAIR Anthrax Hearing (IV) p.3 (in subcommittee files).

²⁴¹ Testimony of Capt. Michelle L. Piel, NSVAIR Anthrax Hearing (IV), p. 59 (in subcommittee files).

²⁴² Testimony of Capt. Jon Richter, NSVAIR Anthax Hearing (IV), p. 38 (in subcommittee files).

²⁴³ Ibid, p. 41.

²⁴⁴ Prepared statement of Roberta Groll, NSVAIR Anthrax Hearing (II), pp. 176-179; prepared statement of Randi Martin-Allaire, NSVAIR Anthrax Hearing (II), pp. 167-171; and prepared statement of David Churchill, NSVAIR Anthrax Hearing (II), pp. 183-188.

²⁴⁵ E-mails from Col. Renata Engler dated December 4, 1998 (in subcommittee files).

²⁴⁶ E-mail from Col. Renata Engler dated December 15, 1998 (in subcommittee files).

have a forum for experienced, ongoing clinical input into the many problems that surround immunization delivery and adverse reaction management.²⁴⁷ (emphasis original)

²⁴⁷ *Ibid.*

Those problems include recognition of potentially life-threatening hypersensitive reactions, use of pre-treatments to mitigate vaccine reactions and the criteria to be applied to determine temporary or permanent medical exemption, or waiver, from the AVIP. At the first DOD conference on biological warfare immunizations, held in May 1999, Dr. Engler made a presentation on the clinical challenges posed by the AVIP. She summarized several case studies of those who had suffered adverse reactions to the anthrax vaccine, with data from Walter Reed Army Medical Center, data from Dr. Hoffman=s study in Korea, and patient profiles from Dover AFB.²⁴⁸ In her slide presentation, she noted a Afeared of military medical establishment= and concluded the AVIP message should be, AEvery service member deserves the same quality of care as ANY OTHER PATIENT: investigate problems proactively & objectively, validate suffering, knowledge base and unknowns. Vaccines are drugs & NOT 100% safe.=²⁴⁹

Regarding the availability of medical deferrals and waivers, Dr. Engler asked, AShould medical waivers become a punitive event? ... Do we want rigid administrative guidelines that polarize and antagonize service members with problems? Can we acknowledge risk & include choice of affected AD in final disposition? Does every service member have to be immunized or is there room for a benefit risk ratio discussion?=²⁵⁰

Room for that discussion may be limited. The risk/benefit decision underlying the AVIP can conflict with the clinician=s duty to weigh the risks and benefits to the individual patient. In an e-mail exchange with Col. Fred Gerber, operational head of the AVIP, Dr. Engler posed the following example:

AA rash within 2 hours of the vaccine could represent an increased risk for life threatening anaphylaxis with next dose - if you ignore this and do not handle it appropriately and a subsequent dose results in significant harm, you are outside the standard of care and would NOT be excused by the >active duty= blanket. Our specialty has worked with this type of patient and achieved successful and safe subsequent vaccination but this requires expertise and very carefully prepared informed consent. ETHICALLY, you cannot expose a soldier to a medical treatment if he/she is at increased risk for harm from it and yes we do waiver people for serious vaccine reactions from future reactions and they continue on active duty for the most part. Anthrax brings unique urgency to the scenario and a group discussion on these issues with an ethicist is crucial.=²⁵¹ (emphasis original)

²⁴⁸ See *supra* note 51, pp. 3-7.

²⁴⁹ *Ibid.*, p. 12.

²⁵⁰ *Ibid.*

²⁵¹ See *supra* note 245.

Col. Gerber, while disclaiming any purview over clinical issues, was unwilling to acknowledge that safety considerations might need to overcome the AVIP imperative in some number of cases:

ANot sure I agree with what you've presented Renata. If ... she had a rash within 2 hrs of shot #1 ... [w]hy would that exempt her from getting rest of series and going to Korea? Who should go in her place? Those become the issues. Korea is one of the two AVIP Phase I High Threat Areas ... everyone is at increased risk for exposure to anthrax there. By your algorithm, when we get to Phase II of the AVIP, new soldiers coming into service would be put out of service because of an adverse reaction to anthrax ... what about an adverse to any of the other 17 immunizations? ... Call it like you see it, but I wouldn't quickly exempt soldiers from worldwide assignments who have rashes, pain, swelling, etc. Let's face it, AVA is one of many soldiers have to take. The more exotic vaccines are yet to come. ... Does a rash in 2 hours mean you can't get any more immunizations without additional clinical follow-up/eval? I'm not sure it does.²⁵²

Concerns about the short and long term safety of the anthrax vaccine are legitimate. It is disingenuous for DOD to say 30 years of use has seen no serious short-term or chronic adverse health effects associated with the vaccine. For most of that time, no one was looking.

The short-term adverse reaction rates contained in the FDA-approved labeling were derived from data gathered during testing of an earlier, less reactogenic anthrax vaccine. FDA only establish the Vaccine Adverse Event Reporting System in 1990. That passive surveillance system, while useful to detect sentinel events or clusters for further study, understates the extent of reactions. Limited use of the vaccine since licensure has yielded limited information that suggests higher reaction rates, particularly in women.²⁵³

Since the AVIP began, DOD has undertaken two active follow-up surveys of vaccine recipients, one in Korea and another at Tripler Army Medical Center, Hawaii. The results of both studies indicates both local and systemic reactions at generally higher rates than described in the product labeling. According to GAO, AThe data gathered in Korea also show that after the first two shots, more than twice the proportion of women than men reported systemic reactions of

²⁵² E-mails from Col. Fred Gerber dated November 17, 1998 (in subcommittee files).

²⁵³ AAnthrax Vaccine: Safety and Efficacy Issues, (GAO/NSAID-00-48) U.S. General Accounting Office, October 12, 1999, pp. 1-7.

fever, malaise, or chills than did men.²⁵⁴ The Tripler survey also demonstrates gender differences in reported reactions.²⁵⁵

²⁵⁴ *Ibid.*, p. 3.

²⁵⁵ *Ibid.*, p. 4.

Service members' concerns about the impact of manufacturing process lapses on vaccine quality and safety are well placed. For biological products, the process is the product. A[Q]uality cannot be guaranteed from final tests on random samples but only from a combination of in-process tests, end-product tests, and strict controls of the entire manufacturing process.²⁵⁶ At BioPort, and its predecessor the Michigan Biologics Products Institute, those controls were found to be less than strict.

The long-term safety of the licensed vaccine has not been studied.²⁵⁷ It is of little comfort to service members that no other vaccines have been subject to any post-licensure longitudinal study. Unlike more modern vaccines, the AVA was approved before animal toxicity studies were even required. As a result, studies have not been performed to evaluate the effect of AVA on carcinogenesis, mutagenesis or impairment of fertility. Animal reproduction studies have not been conducted with AVA. Neither is it known whether AVA can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.²⁵⁸

It is unlikely the current anthrax would be approvable under modern regulatory standards for the safety and efficacy of biological products. It seems unlikely BioPort will be able to achieve and sustain modern manufacturing standards for safe vaccines.

²⁵⁶ Prepared statement of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Affairs Division, GAO, NSVAIR Anthrax Hearing (II), p. 13.

²⁵⁷ *Ibid.*, p. 11.

²⁵⁸ See supra note 138, pp. 87-88.

5. Efficacy of the vaccine against biological warfare is uncertain. The vaccine was approved for protection against cutaneous (under the skin) infection in an occupational setting, not for use as mass protection against weaponized, aerosolized anthrax.

Uncertainties about safety might be more readily accepted if there were no questions about the effectiveness of the anthrax vaccine. Safety risks would be tolerable if the benefits were unquestioned. But there are questions. The proposition that the AVA will provide effective protection against the most likely form of weaponized anthrax, aerosolized spores in significant quantities, is unproven.

And, until there is an anthrax attack, the proposition must remain unproven. The industrial settings in which anthrax was a threat have all but disappeared.²⁵⁹ It would be unethical to expose human test subjects to a lethal agent. So, based on proven efficacy against indeterminate levels of cutaneous exposure in a industrial setting, it can only be assumed the vaccine provides equivalent protection against high levels of inhalation exposure.

That assumption is supported by data from tests on vaccinated animals who survive aerosol challenge. But different survival rates between animal species, and between anthrax strains, raise more questions than the vaccine answers about the actual physiological mechanism of protection. Without a way to correlate animal data to human protection (i.e. PA antibody titers), efficacy of the vaccine may never be more than suggested or inferred.

According to GAO:

²⁵⁹ Only research and testing facilities now present an occupational setting posing a danger of anthrax exposure.

AStudies on the efficacy of anthrax vaccine have been limited to a study of the efficacy of the earilier version for humans and studies of the efficacy of the licensed vaccine for animals. The only study of the efficacy of the vaccine for humans was performed by Brachman, using the original vaccine. The Brachman study claimed that the vaccine gave 93 percent (and a lower confidence limit of 65 percent) protection against anthrax penetrating the skin. It found that the number of individuals who contracted anthrax by inhalation was too low to assess the efficacy of the vaccine against this form. There has been no specific study of the efficacy of the licensed vaccine in humans. Rather, its efficacy in humans has been inferred from other data, including a reduction in the incidence of anthrax following immunization of at-risk individuals and from animal experiments.²⁶⁰

All the DOD animal studies support the view that the licensed vaccine can protect some animals against exposure to some strains of anthrax either by inoculation or inhalation. But animal species differ in susceptibility.²⁶¹ In testimony submitted to the Subcommittee, Dr. Meryl Nass summarized the available data from animal studies of anthrax vaccine efficacy. AOne can see varying survival rates from 0 - 100% depending upon the strain of anthrax used and possibly other parameters of the experiment. Survival rates in guinea pigs varied from 23% to 71% when they were exposed to inhaled anthrax.²⁶² Studies in mice showed survival rates between no higher than ten percent.²⁶³

In concluding the current vaccine is effective against aerosol challenge, DOD relies primarily on studies using rhesus monkeys. AThese animal studies showed that the FDA-approved anthrax vaccine provided greater than 95% protection against high-dose aerosol challenge with anthrax in the monkey model. Human antibody response to the FDA-licensed vaccine provides further suggestive evidence that the FDA-licensed anthrax vaccine will protect against inhalation anthrax.²⁶⁴

But, according to GAO, Aseveral studies have shown no direct comparison of immunity in humans to that in monkeys.²⁶⁵ In fact, the one immunized monkey that died in the DOD studies A had a low antibody titer similar to other monkeys that lived following a lethal aerosol

²⁶⁰ Prepared statement of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Affairs Division, GAO, NSVAIR Anthrax Hearing (II), p. 16-17.

²⁶¹ See *supra* note 253, p. 8.

²⁶² Prepared statement of Dr. Meryl Nass, NSVAIR Anthrax Hearing (II), p. 108.

²⁶³ *Ibid.*, p. 110.

²⁶⁴ Prepared statement of Dr. Sue Bailey, Assistant Secretary for Health Affairs, DOD, NSVAIR Anthrax Hearing (I), p. 11.

²⁶⁵ U.S. General Accounting Office, Correspondence to Rep. Steve Buyer from Kwai Cheung-Chan, ASummary of GAO=s Findings on the Safety and Efficacy of the Anthrax Vaccine,²⁶⁵ (GAO-NSIAD-00-54R), November 4, 1999, p. 3.

challenge.²⁶⁶

²⁶⁶ See *supra* note 138, p. 90.

One study comparing the efficacy of a live spore vaccine to a PA-based vaccine, like the AVA, concluded, AImmunization with cell-free preparations which contained components of that anthrax toxin did not provide adequate protective response against some challenge isolates of *B. anthracis*. The fact that the spore vaccine provided protection against all isolates tested suggests that other antigens may play a role in active immunity.²⁶⁷

DOD resists that suggestion because confidence in the efficacy of the current anthrax vaccine in humans, against all known strains, depends heavily on the conclusions 1) that the antibody response to the one antigen, PA,²⁶⁸ protects against the toxic mechanism of all natural anthrax, and 2) that the antibody response in animals correlates to a similar protective response in humans.

The lack of an immunological correlate of protection against anthrax limits the extent of efficacy claims that can be made about the current vaccine, and it poses a profound challenge to the studies needed to approve an improved vaccine or a shorter AVA shot course. In describing the challenges to demonstration of efficacy for proposed changes in the dose and use of the current anthrax vaccine, DOD noted:

APresently there are no precise serological or other immunological correlates of protection to enable conclusions to be drawn from immunization studies in man. The extrapolation from animal studies to humans likewise is seriously complicated by this fact. ...²⁶⁷

AThe demonstration in some animal models that protection with the present vaccine varies across challenge strains further complicates studies and limits the breadth of efficacy claims that can be made.²⁶⁷

ATo date, no animal or other potency test has been demonstrated to be well correlated with protection of humans. ***The potency test required for the present vaccine²⁶⁹ has not been well correlated to efficacy in humans and it is doubtful that it can be.*** (emphasis added)

AIIt has recently been stated that the antigenic components of the licensed vaccine are not well defined and that there is lot to lot variation in the level of protective antigen. Because of these points, efficacy studies will likely have to include

²⁶⁷ Stephen F. Little and Gregory B. Knudson, AComparative Efficacy of Bacillus anthracis Live Spore Vaccine and Protective Antigen Vaccine against Anthrax in the Guinea Pig,²⁶⁷ *Infection and Immunity*, May 1986, Vol. 52, No. 2, p. 511.

²⁶⁸ Protective antigen (PA) is one of three proteins involved in the mechanism of anthrax toxicity.

²⁶⁹ The current potency test uses guinea pigs.

multiple lots to demonstrate consistency of protection.²⁷⁰

²⁷⁰ See *supra* note 138, p. 45 (presentation slide entitled, AChallenges to Demonstration of Efficacy for the Proposed Changes in Dose and Use of Anthrax Vaccine, included in supporting documentation to MBPI IND application) (in subcommittee files).

Regarding efficacy, one author of an anthrax vaccine study wrote, "My concern is not the long-term health effects of this vaccine, but rather that it is not efficacious against all strains of *B. anthracis*. If I were the scientific director of an offensive BW program for a government hostile to the U.S., I would direct my investigators to repeat this experiment, screening a larger number of *B. anthracis* isolates until a strain was isolated that would kill immunized animals, and then use that vaccine resistant strain as the stock for producing spores to be used in filling BW submunitions."²⁷¹

Genetically engineered anthrax strains could also defeat the current vaccine if the resulting organism caused disease in new ways. Reports that Russian scientists successfully inserted genes into a virulent anthrax strain were received by DOD with some skepticism. Col. Gerald Parker, then-commander of USAMRIID, was quoted as saying the claims needed to be evaluated to learn whether the advance is theoretical or practical, and whether it could sidestep the American anthrax vaccine.²⁷² Taking a more skeptical approach to threat assessment than DOD uses with regard to natural anthrax, Col. Parker added, "It's one thing to do this in the lab. But it's a whole different thing to produce it in large quantities to be used as a weapon. That would be very difficult."²⁷³

Concerns about the efficacy, and by implication the necessity, of the vaccine are legitimate given the extent of unproven, unknown, and perhaps unknowable, aspects of the protection afforded. The vaccine almost certainly could be overwhelmed by a high-dose aerosol exposure. Immunized troops near an initial release point could still suffer significant casualties. The vaccine may have diminished effect against highly virulent strains, or combinations of strains. The vaccine may provide no protection against genetically engineered anthrax.

²⁷¹ Memorandum from Gregory B. Knudson to Rep. Christopher Shay dated May 8, 1999. (in subcommittee files)

²⁷² William J. Broad, "Gene-Engineered Anthrax: Is It a Weapon?" *New York Times*, February 14, 1998 (in subcommittee files).

²⁷³ *Ibid.*

1. The force-wide, mandatory AVIP should be suspended until DOD obtains approval for use of an improved vaccine.

Recommendations

The anthrax vaccine program is not sustainable in its present form. Due to the lack of assured production, AVIP Phase II has already been delayed. Confidence in the quality of the vaccine stockpile is low and the capacity to procure sufficient new production remains highly doubtful. The program should be suspended while contingency plans for allocation of available vaccine are formalized and research is conducted to obtain a safer, more effective vaccine.

Signaling an awareness the anthrax immunization effort was on weak conceptual and logistical footing from the start, Secretary Cohen announced four preconditions to the start of the program: supplemental vaccine testing, an adequate tracking system, completed implementation and communication plans and an independent scientific review. Those were appropriate. Had they been more scrupulously addressed, the AVIP might be a very different, much better program.

The military anthrax immunization program should have been conditioned on completion of the same level of research and testing required of other battlefield systems. We would not ask U.S. forces to fight using rifles designed in the 1950's. We should not ask them to rely on 1950's era medical technology, when modern science has the capacity to produce an improved vaccine. Much has changed in the biologics industry since the AVA was first approved in 1970. As evidenced by FDA inspectional findings in 1998 and 1999, not enough has changed at the vaccine production facility to bring it into full compliance with modern manufacturing standards. It is doubtful the AVA would be approved by the FDA today.

As additional assurance the anthrax immunization program is as safe as possible, DOD should test the vaccine for toxicity, mutagenicity, carcinogenicity and reproductive effects in animals. The current AVIP should be suspended while those studies, and other steps recommended by the Subcommittee, are undertaken.

The AVIP should be suspended because it lacks an essential element in a medical program: trust. However well-intentioned, the anthrax vaccine effort is viewed by many with suspicion. It is seen as another chapter in a long, unhappy history of military medical malfeasance in which the healing arts are corrupted to serve a lethal purpose.

The fundamental rationale for the AVIP - that something, even an old, questionably effective vaccine, is better than nothing - gives little comfort to those who daily see their forebears and colleagues grow sicker from radiation testing, Agent Orange and Gulf War illnesses. If the noble experiment fails, if the vaccine ultimately causes more casualties than

weaponized anthrax, many men and women in uniform do not believe their government will acknowledge their sacrifice or treat their wounds.

Trust must be earned. It can be earned only with a degree of candor and openness that has not been the hallmark of the AVIP to date. While claiming a new awareness of the need for effective risk communication, the Pentagon still reverts to absolutist declarations, heavy handed propaganda, and *ad hominem* attacks whenever the risks of the anthrax vaccine are communicated too effectively or persistently. In a culture based on a chain of command and the power to compel, attempts at persuasion and education often devolve into intimidation. Labeling opponents Aparanoics²⁷⁴ and ridiculing the intelligence or courage of those with legitimate questions²⁷⁵ are not the methods of modern risk communication.

Nowhere is DOD=s failure to communicate the relative risks and benefits of the AVIP more obvious than in reserve component units. The bulk of vocal resistance to the AVIP has arisen in the few Reserve and National Guard units included in Phase I. Those service members have more options than active duty personnel. If they conclude the anthrax vaccine poses more risk than benefit to their civilian and military careers, they can resign, or seek a transfer to a non-mobility position. Many have done so.

DOD appears to be in denial on this issue, ignoring clear signs the anthrax program is having, and will certainly have, a substantial impact on retention and morale in reserve component units. At the Subcommittee=s September 29, 1999 hearing on the subject, Maj. Gen. Paul Weaver, Director, Air National Guard, testified there had been Aone known refusal documented.²⁷⁶ Previously, the Subcommittee had received testimony and correspondence from several members of Air Guard units who had refused the vaccine, more than one of whom were in the hearing room when Gen. Weaver made that statement.

²⁷⁴ See *supra* note 79.

²⁷⁵ See *supra* note 80.

²⁷⁶ Testimony of MG Paul Weaver, Director, Air National Guard, NSVAIR Anthrax Hearing (V), p. 119.

Principal Deputy Assistant Secretary of Defense (Reserve Affairs) Charles Cragin testified the impact of the AVIP on retention was negligible²⁷⁷ despite having been given information just days before that more than half the air crew in one unit has submitted resignations attributable directly to the anthrax program.²⁷⁸ At the same hearing, Mr. Cragin conceded the Department's efforts to inform and educate reserve personnel about the anthrax protection program were not initially as robust as they should have been.²⁷⁹

Until much more is known about the true impact of a mandatory vaccine program on retention, readiness and morale in the most voluntary sector of the all-volunteer U.S. armed forces, the AVIP should be suspended.

Rather than risk long term health impairment, some service members would be willing to consider the vaccine-preventable risk of anthrax among the inherent, unavoidable risks of military service. They do not have that option, an opportunity to assume risk made available to essential civilian employees of the Defense Threat Reduction Agency.²⁸⁰

Others view this force protection effort as an untested medical solution to a purely mechanical problem - contamination prevention and avoidance - better solved by physical rather than pharmacological technology. With regard to the anthrax vaccine, DOD appears to accept more unknowns and greater technological risks than would be tolerated in any combat weapon system. As a result, some service members are not convinced this Commander's program is for their long-term protection as much as for battlefield convenience and the preservation of short-term mission capability while under anthrax attack. Suspension of the AVIP would allow DOD to focus more attention and resources on development and deployment of chemical defense doctrine, tactics, detection capability as well as individual and collective protection equipment effective against all threats.

The Subcommittee makes no recommendations regarding the status of those service members who left the armed forces voluntarily, or as the result of disciplinary actions, due to the

²⁷⁷Prepared statement of Charles Cragin, Acting Assistant Secretary for Reserve Affairs, NSVAIR Anthrax Hearing (IV), p. 3.

²⁷⁸Letter (with attachments) from Charles Cragin to Rep. Christopher Shays, attachment p. 1, October 21, 1999. (in subcommittee files)

²⁷⁹Prepared statement of Charles Cragin, Acting Assistant Secretary for Reserve Affairs, NSVAIR Anthrax Hearing (IV), p. 4.

²⁸⁰See *supra* note 134.

anthrax vaccine program. Just as each service branch, operating under the Uniform Code of Military Justice, determined its own approach to vaccine refusals, each should determine through its own processes what appeals, if any, might be available in the event the AVIP is restructured or suspended.

recombinant anthrax vaccine.

Despite the unclear and present danger²⁸¹ posed to U.S. troops by anthrax as a biological weapon, DOD considers development of an improved anthrax vaccine an unfunded requirement.²⁸² Had that requirement been addressed more aggressively after the Persian Gulf War, the eight to ten year development, testing and FDA approval process now posited by DOD as an potential barrier to a new vaccine could have already been breached.

Although an improved vaccine based on recombinant technology may not necessarily have better safety characteristics than the current vaccine,²⁸³ it would address two other problems plaguing the AVIP. Production of a second vaccine, at a second site, would diversify the industrial capacity to support so critical a program, making vaccine supplies more abundant and more secure from attack. And, because recombinant techniques do not require extensive dedicated facilities, capital costs can be allocated across more than one product, increasing the likelihood other manufacturers would compete for DOD contracts.

The second generation vaccine studied by DOD was also more consistently characterized in terms of PA content than the AVA²⁸⁴. Lot-to-lot consistency would address one challenge noted by DOD to demonstrating efficacy of a vaccine that cannot be tested in humans.²⁸⁵ It would also give commanders greater confidence that vaccinated troops, to the greatest extent possible, have achieved a more uniform level of protection.

²⁸¹ See *supra* note 66, p. 1.

²⁸² Testimony of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Affairs Division, GAO, NSVAIR Anthrax Hearing (IV), p. 100.

²⁸³ Testimony of Col. Renata Engler, Chief, Allergy and Immunology Department, Walter Reed Army Medical Center, NSVAIR Anthrax Hearing (IV), p. 155.

²⁸⁴ Prepared statement of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Relations Division, GAO, NSVAIR Anthrax Hearing (IV), p. 13.

²⁸⁵ See *supra* note 108.

David Oliver, Principal Deputy Under secretary of Defense for Acquisition and Technology, said in testimony that DOD would be reviewing procurement options with regard to a second AVA production site versus a new vaccine. He suggested, however, that funds spent on an improved anthrax vaccine would limit funds available to address other bio-threats.²⁸⁶ That trade-off puts anthrax on a par with other biological agents in terms of threat, when in fact DOD considers anthrax the pre-eminent bio-threat. Budgets estimates for the Joint Vaccine Acquisition Program (JVAP) indicate DOD anticipates procurement of limited, deployment-contingent stocks of vaccines against other biological weapons, making anthrax the only agent targeted for universal immunization. Improving the medical prophylaxis against the primary threat should be a DOD funding priority.

DOD concedes, AIn the case of anthrax vaccine, the current FDA-licensed vaccine is not ideal. The vaccine was developed in the 1950's and 1960's by the state-of-the-art procedures at that time, and licensed in 1970. Advances in biotechnology and genetic engineering may enable improvements in the vaccine that allow fewer doses or use of highly purified protective antigen. The DoD scientists are pursuing both of these objectives. A highly-purified recombinant protective antigen vaccine has shown efficacy in animal models.²⁸⁷

But DOD is unwilling to wait for the research, development and FDA approval processes,²⁸⁸ even though DOD believes Awithin a year we will get FDA approval for reduced dose based on the science.²⁸⁹

To address the domestic bioterrorism threat, the Department of Health and Human Services= National Institute of Allergy and Infectious Diseases formed a working group to develop and test a second generation anthrax vaccine, and the Institute has funded some research. DOD should support those efforts.

²⁸⁶ Testimony of The Honorable David R. Oliver, Jr., NSVAIR Anthrax Hearing (III), pp. 68-69.

²⁸⁷ Department of Defense, AInformation About the Anthrax Vaccine and the Anthrax Vaccine Immunization Program,≡ prepared by the AVIP Agency, January 25, 2000, pp. 12-13 (available at: <http://www.anthrax.osd.mil>) (in subcommittee files).

²⁸⁸ *Ibid.*

²⁸⁹ Testimony of Col. Fred Gerber, Director, Health Care Operations, Office of the Army Surgeon General, NSVAIR Anthrax Hearing (V), p. 153.

With regard to an improved anthrax vaccine, the American Public Health Association adopted a policy statement in November 1999 urging DOD to delay any further immunization against anthrax using the current vaccine or at least to make immunization voluntary²⁹⁰ and to convene a commission of military and non-military public health experts to review safety and efficacy evidence for the current vaccine, attempt to determine when an improved vaccine might be available, and make recommendations about continuation of the current program.²⁹¹ Their recommendations were based on the concern that mandatory immunization with a vaccine of unproved efficacy when an improved vaccine may soon be available, is contrary to public health principles and may adversely effect the acceptance of voluntary or mandatory immunization programs in which there is good evidence of efficacy and safety....²⁹²

²⁹⁰ Anthrax Immunization, American Public Health Association, Policy Statement No. 9930, Nov. 10, 1999.

²⁹¹ *Ibid.*

²⁹² *Ibid.*

3. DOD should pursue testing of the safety and efficacy of a shorter anthrax inoculation regimen.

A shorter shot course could reduce the cost of the immunization program, simplify delivery logistics, and lower the incidence of adverse reactions.

According to GAO testimony, No studies have been done to determine the optimum number of doses of the anthrax vaccine.²⁹³ The original inoculation schedule of three doses was based on a regimen developed using animals in the early 1950s. However, three people who received three doses of a weaker formulation of the vaccine became infected after exposure to anthrax. The number of doses was then arbitrarily increased to six, the number used in the only human efficacy study published in 1962, and thus the number approved by FDA.²⁹⁴

Even if a prolonged, multi-shot regimen is necessary to generate an initial immune response, the annual booster may be unnecessary. GAO noted:

In November 1971, the Division of Biologics Standards, NIH, noted an apparent increase in reports of adverse reactions after individuals received booster shots. The Division considered it advisable to reevaluate the need for annual boosters and possibly the amount of the booster dose. Although the record is unclear as to whether or not NIH requested a reevaluation, to date, no such reevaluation has been done.²⁹⁵

The 1993 DOD Directive on biological warfare defense mandates immunization against validated biological warfare threat agents, for which *suitable* vaccines are available, in sufficient

²⁹³Testimony of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Affairs Division, GAO, NSVAIR Anthrax Hearing (IV), p. 97.

²⁹⁴Prepared statement of Kwai-Cheung Chan, Director, Special Studies and Evaluation Section, National Security and International Affairs Division, GAO, NSVAIR Anthrax Hearing (IV), p. 5.

²⁹⁵*Ibid.*, p. 6.

time to develop immunity before deployment to high threat areas....²⁹⁶ (emphasis added) For this purpose, Asuitable[≡] should not just mean FDA approved, but demonstrably as safe and effective as possible for the intended military use. A vaccine that takes 18 months, and annual boosters, to confer immunity should not be considered suitable under the policy.

²⁹⁶ See *supra* note 7.

In 1995, the Joint Program Manager for Biological Defense reported, AThe immunization schedule of 6 shots over 18 months has stopped the approval process for an annual immunization program against this high threat biological warfare agent. Moreover, it has been used by critics to question the relevance of the biological defense (BD) vaccine program to the DOD.²⁹⁷

If the time to develop immunity could be reduced substantially, use of the anthrax vaccine would be safer and could be targeted far more effectively to forces deploying to high threat areas.

Based on animal studies and research into the immunological response to the vaccine in humans, DOD concludes most persons acquire the bulk of whatever protection is achieved after two or three shots.²⁹⁸ DOD documents assert that three inoculations provide functional protection, and the services= AVIP implementation plans set as A desirable \cong the goal that A all personnel assigned to high threat areas receive their first three shots prior to deployment.²⁹⁹ In the interest of reducing adverse reactions, particularly in persons whose immune systems have already mounted a complete response to the vaccine, DOD should put its belief in the efficacy of a reduced shot course to the test of rigorous scientific trials.

To the extent those efficacy studies were put aside due to the lack of a correlates of human immunity, that challenge will have to be overcome in any event as DOD attempts to develop and deploy other vaccines against other bio-threats. That work might as well be done in support of a safer vaccine against the primary biological warfare threat, anthrax.

In terms of increased safety, there is also some evidence an intravenous injection would

²⁹⁷ Col. John C. Doesburg, Joint Program Manager for Biological Defense, Memorandum on A Urgent Requirement for Integrated Command Support to Revise the Immunization Schedule for Anthrax Vaccine \cong (JPO 0045) from the Department of the Army, November 17, 1995 (in subcommittee files).

²⁹⁸ Testimony of Maj. Gen. Robert Claypool, Deputy Assistant Secretary for Health Operations Policy, NSVAIR Anthrax Hearing (IV), p. 179; Arthur M. Friedlander, Philip R. Pittman, and Gerald W. Parker, A Anthrax Vaccine: Evidence for Safety and Efficacy Against Inhalational Anthrax, \cong The Journal of the American Medical Association, December 8, 1999, Vol. 282, No. 22, pp. 2104-2106.

²⁹⁹ See *supra* note 46, p. 1, sec. 1(a)(8).

produce fewer side effects and adverse reactions than subcutaneous administration. DOD expended significant time and resources in 1994 and 1995 on plans and programs to demonstrate the safety and efficacy of a shorter anthrax inoculation regime, and a different route of administration, but appears to have all but abandoned those efforts when planning for the AVIP began. Support for the FDA application to reduce the shot course seems to have been redirected to vaccine acquisition and AVIP logistics.

4. DOD should enroll all anthrax vaccine recipients in a comprehensive clinical evaluation and treatment program for long term study.

DOD only recently began to design a set of studies to better evaluate the long term safety of the anthrax vaccine ... to conform with present-day, post-marketing practices.³⁰⁰ While employing active surveillance techniques, these will be cohort studies because A[i]t would be labor-intensive, cost-prohibitive, and would not conform to civilian expectations for us to use this in all 2.4 million service personnel whom we will administer the vaccine to.³⁰¹ According to Gen. Claypool, DOD will also use linked databases to conduct active surveillance of vaccine recipients, using DEERS and the large medical database residing at a tri-service defense medical surveillance system here in the National Capital region of the Walter Reed installation.³⁰²

But these steps, coming more than one year after AVIP implementation, are not enough to monitor the impact of the vaccine program on military health. Having missed the opportunity to study the large cohort of service members who received the AVA during Operations Desert Shield and Desert Storm, DOD has an obligation to reach beyond civilian expectations to evaluate the safety of this vaccine.

Particularly for members of reserve component units, access to primary care and specialists at military facilities can be limited. According to DOD, adverse events after the anthrax vaccine are a line of duty illnesses.³⁰³ Therefore,

A member of the Reserve Component may present themselves for initial treatment and evaluation at any military treatment facility, after vaccination during a period of duty. The member will be examined and provided necessary medical care. Once treatment is rendered or the individual's emergent condition is stabilized, a Line of Duty and/or Notice of Eligibility status will be determined by the member's unit, as required. No treatment beyond that justified to stabilize the condition or emergency is authorized until Service connection is validated.

³⁰⁰ Testimony of Maj. Gen. Robert Claypool, Deputy Assistant Secretary for Health Operations Policy, NSVAIR Anthrax Hearing (IV), p. 108.

³⁰¹ *Ibid.*

³⁰² *Ibid.*, p. 109.

³⁰³ Dr. Sue Bailey, *What Everyone Needs to Know about the Anthrax Vaccine*, quarterfold brochure, Department of Defense, November 1, 1999, p. 3 (in subcommittee files).

But requiring an immediate determination of service-connection for vaccine related health effects means many short term, and most long term, adverse reactions will not be monitored by DOD physicians. The causal attribution of health effects to inoculations is difficult, becomes more difficult over time, and remains unlikely in a military program institutionally resistant to any suggestion the vaccine is not safe. Service members should not bear the burden of proof the vaccine caused their ill-health subsequent to inoculation. The process of proving service-connection has frustrated Gulf War veterans' efforts to obtain accurate diagnoses, effective treatments and fair compensation for their unexplained illnesses. It should not be repeated in the AVIP.

Enrollment of every vaccine recipient in a clinical evaluation and treatment protocol would allow DOD to capture a unique and valuable data set for use in their longitudinal studies, avoiding disputes over cohort selection bias and other methodological issues. The evaluation and treatment program could also be the vehicle for assembly of the multidisciplinary teams envisioned by Dr. Engler³⁰⁴ to develop and implement clinical protocols and maintain a consistent standard of care in the AVIP. It would also help assure service members the vaccine program, as a medical force protection effort, has as its primary purpose the protection of the health of the force.

³⁰⁴ E-mails from Col. Renata Engler dated December 4-8, 1998 (in subcommittee files).

5. While an improved vaccine is being developed, use of the current anthrax vaccine for force protection against biological warfare should be considered experimental and undertaken only pursuant to FDA regulations governing investigational testing for a new indication.

Under FDA regulations, use of an FDA-approved product in an unapproved way, or for an unapproved purpose, can only be undertaken pursuant to clinical trial protocols contained in Investigational New Drug (IND) applications.³⁰⁵ IND protocols must be approved by an Institutional Review Board charged to monitor the scientific credibility and ethical soundness (i.e. patient protections) of the trial. FDA must agree the trial proves the product is safe and effective for the proposed use. Informed consent must be obtained from persons enrolled in IND drug or vaccine trials.

If DOD proposed to use the anthrax vaccine against a disease or indication not currently described in the FDA-approved product labeling (i.e. high blood pressure), an IND application would be required. If DOD proposed to alter the FDA-approved AVA inoculation regimen (i.e. by eliminating one or more of the six shots), an IND would be required.

Despite the fact the vaccine was approved as safe and subsequently deemed effective only against cutaneous anthrax infection, DOD asserts use of the FDA-approved AVA as prophylaxis against weaponized, inhalation anthrax does not constitute an off-label use against a new indication because A[w]hile the package insert for this vaccine is nonspecific as to the route of exposure, DOD has long interpreted the scope of the license to include inhalation exposure, including that which would occur in a biological warfare context.³⁰⁶

While some in DOD may have interpreted the scope of MBPI's FDA license to include inhalation anthrax by implication, others proceeded as if explicit labeling for the indication would be necessary. Throughout development of the anthrax policy that eventually became the AVIP, some in DOD interpreted FDA regulations as requiring approval of both a reduced number of inoculations and the new indication. A 1995 memo states:

³⁰⁵ 21 CFR Part 312.

³⁰⁶ Letter from Dr. Stephen C. Joseph to Dr. Michael A. Friedman dated March 4, 1997 (in subcommittee files).

The use of a reduced schedule to protect service members from aerosol exposure to anthrax can only legally be done if the FDA licenses the vaccine for that specific schedule and indication. ... Obtaining FDA license approval for a specific immunization schedule change and for a labeled indication change (aerosol challenge) must provide data that establish safety of two doses of the vaccine given at 0 to 4 weeks since this schedule does not mimic the current schedule of 0, 2 and 4 weeks. More extensive problems exist in demonstrating vaccine efficacy against an aerosol challenge.³⁰⁷

In September 1996, the vaccine manufacturer, MBPI, submitted an IND application which said, The ultimate purpose of this IND is to obtain a *specific indication for inhalation anthrax* and a reduced vaccination schedule.³⁰⁸ (emphasis added) Briefing slides produced by USAMRIID in October 1997 reference two separate objectives to be met in a supplement to the AVA license:

- X Supplement to AVA license to reduce the number of immunizations and change the route of immunization.
- X Supplement AVA license to explicitly include inhalational anthrax as an indication.³⁰⁹

Since 1997, the *Department of Defense Nuclear/Biological/Chemical (NBC) Defense - Annual Report to Congress* has referred to medical CBW countermeasures proven safe because they have been widely used to treat other medical conditions.³¹⁰ The report cites pyridostigmine

³⁰⁷ Micheal J. Gilbreath, Ph.D., *Is the current Anthrax vaccination regimen necessary?* Department of Defense Information Paper (JPO 0044), November 10, 1995, p. 1-2.

³⁰⁸ See *supra* note 138, p. 1.

³⁰⁹ Department of Defense, *Supplemental to AVA License* USAMRIID presentation slides, October 28, 1997 (in subcommittee files).

³¹⁰ *Department of Defense Nuclear/Biological/Chemical (NBC) Defense - Annual Report to Congress*, March 1999, pp. 3-3 to 3-4; *Department of Defense Nuclear/Biological/Chemical (NBC) Defense - Annual Report to Congress*, February 1998, pp. 3-4 to 3-5; *Department of*

bromide, the botulinum toxoid vaccine, both used for CB prophylaxis only pursuant to INDs, and the anthrax vaccine. But DOD's interpretation of the current AVA labeling rests on the conclusion there is but one indication - anthrax infection acquired by any means. Against what other medical condition was the anthrax vaccine used to prove its safety?

When DOD asked the FDA to concur with the implicit inclusion of inhalation anthrax in the current product labeling, the response was affirmative but tepid. FDA Lead Deputy Commissioner Michael Friedman wrote: A While there is a paucity of data regarding the effectiveness of Anthrax Vaccine for prevention of inhalation anthrax, the current package insert does not preclude this use. The original efficacy trial clearly showed that the vaccine conferred a high level of protection against cutaneous exposure. None of the 5 inhalation cases in this trial occurred in Anthrax Vaccine recipients, but these data alone are insufficient to allow definitive statistical conclusions. Results from animal challenge studies have also indicated that pre-exposure administration of Anthrax Vaccine protects against inhalation anthrax.

Defense Nuclear/Biological/Chemical (NBC) Defense - Annual Report to Congress, March 1997, pp. 3-4 to 3-5.

Therefore, I believe your interpretation is not inconsistent with the current label.³¹¹

It was on this basis DOD proceeded to design the AVIP without informed consent procedures, or an informed consent waiver, and without other elements of a clinical trial such as consistent data gathering and detailed health outcome monitoring.

DOD was aware of the extensive problems confronting the effort to prove vaccine efficacy for the new indication, most notably that A...no animal or other potency tests has [sic] been demonstrated to be well correlated with protection of humans.³¹² DOD conducted, and plans to continue, studies attempting to validate an animal model so findings can be extrapolated to humans.

In launching the AVIP, DOD did not confront those problems but sidestepped them by concluding use of the vaccine to prevent anthrax infection, however acquired, would not require an IND as long as the approved inoculation schedule was followed. So the AVIP=s cumbersome logistics, additional costs, and increased risk of adverse reactions all flow directly from an unwillingness to do the research and testing to develop a better vaccine or improve the safety and efficacy of the current AVA.

That research and testing will have to be done in any event. In 1997 DOD told Congress:

³¹¹ Letter from Dr. Michael A. Friedman to Dr. Stephen C. Joseph dated March 13, 1997 (in subcommittee files).

³¹² See *supra* note 307, p. 2. The memo continues, AThe potency test required for the present vaccine has not been well correlated to efficacy in humans.≡ The current potency test uses guinea pigs. Tests challenging different animal species with a range of anthrax strains showed the vaccine provides varied levels of protection. Against some strains, vaccinated guinea pigs and mice suffered 100 mortality. In DOD studies using nonhuman primates (rhesus monkeys) between 88 and 100 percent of the vaccinated animals survived.

ADOD complies with all Food, Drug and Cosmetic Act requirements. The Food and Drug Administration (FDA) requires large-scale field trials in human subjects to demonstrate efficacy of drug and biologicals prior to licensure. There are, however, legal and ethical constraints that preclude such efficacy studies for NBC countermeasures. Field studies of efficacy cannot be performed, since exposure to most NBC agents does not usually occur naturally. Moreover, the high lethality and/or toxicity of NBC agents also makes it unethical to expose human subjects in controlled efficacy studies usually required by the FDA for product licensure (*e.g.*, test of effectiveness of the product against the threat in humans). For these reasons, ***many NBC countermeasures are likely to remain in an Investigational New Drug (IND) status, requiring their administration under provisions of an approved protocol and with written informed consent*** from their service members. In contingency situations, DOD may request a waiver of informed consent from the FDA. DOD continues to work with the FDA to seek alternative methods for demonstrating safety and efficacy of NBC medical countermeasures and to obtain their licensure.³¹³ (emphasis added)

Given the predicted likelihood NBC vaccines will be available only in IND status for some years to come, DOD will need to develop the capacity to conduct broad-based clinical trials and effectively communicate risk/benefit assessments through informed consent processes. In the interests of deploying a safer, presumably more effective vaccine against the pre-eminent biological warfare threat, DOD should be willing to develop that capacity now. Instead, DOD has chosen to address the primary threat with a dated, secondary countermeasure with substantial unknowns regarding quality, safety and efficacy.

In prescribing the vaccine, DOD is engaging in the practice of medicine. It is true doctors can use drugs off label. It is never true they can do so without informed consent of the patient... You are not immunized from getting informed consent.³¹⁴ If DOD were to concede administration of AVA against inhalational battlefield exposure is an off label use, informed consent would be required. The AVIP could be transformed, for most, into a voluntary program, with limited mandatory usage of the vaccine possible only pursuant to a carefully monitored informed consent waiver.

³¹³ See *supra*, note 310, 1998 Report, p. 3-4.

³¹⁴ Testimony of Arthur Caplan, Ph.D., *Force Protection: Improving Safeguards for Administration of Investigational New Drugs to Members of the Armed Forces*, 106th Cong. 1st sess. (1999), unofficial transcript, p. 77 (subcommittee on National Security, Veterans Affairs and International Relations hearing of November 9, 1999) (in subcommittee files).

In a statement submitted to the Subcommittee, the Association of American Physicians and Surgeons asserted:

AA distinction must be made between treatment and experimentation. It may be asserted that anthrax vaccine (unlike pyridostigmine bromide as used in the Gulf War or anti-botulinum vaccine) constitutes >reatment,= or that it is not experimental because of being declared safe and effective by FDA. ... In fact, the anthrax vaccine was licensed by the FDA before efficacy studies were required. Its efficacy against inhalational anthrax has been questioned.... British epidemiologist suggested that troops be publicly randomized to receive active vaccine or placebo, clearly implying that many consider the vaccine to be experimental.≡³¹⁵

The AAPS recommended a careful examination of the medical ethics involved in military, and civilian, vaccination efforts, noting the entire point of informed consent in combat is >not to prevent soldiers from obtaining whatever protection may be afforded them by an investigational agent that has not been adequately tested, but rather, it is to give them the choice of whether they think the >protection= is worth the risks of adverse effects=≡³¹⁶

Although DOD=s track record administering INDs or informed consent waivers is not exemplary,³¹⁷ current procedural safeguards, adopted since the Gulf War, provide far more

³¹⁵ Submitted statement of Dr. Jane M Orient, Executive Director, Association of American Physicians and Surgeons, NSVAIR Anthrax Hearing (I), p. 119, citing the *European Journal of Epidemiology* 4:12-19, 1998 and Ness AR, Harvey I, Gunnell D, Smigh GD: AAll troops sent to Gulf should be randomized to receive anthrax vaccination or placebo.≡ *British Medical Journal* 316:1322, 1998.

³¹⁶ *Ibid.* (quoting Grodin MA, Annas GJ: *Journal of the American Medical Association* 277:712-713, 1997).

³¹⁷ In 1990, DOD requested authority to administer IND products, pyridostigmine bromide and botulinum toxoid vaccine, to certain military personnel. DOD also requested a waiver of informed consent requirements in connection with the use of those products by the armed forces. The FDA granted the DOD requests under the terms of an interim rule establishing the procedures and conditions under which informed consent waivers could be obtained by DOD. But DOD did not meet the conditions FDA placed on the waivers, failing to provide information to individual service members about the IND products and failing to keep the medical records necessary to fulfill the protocols and capture data about the safety of the drugs. Despite some improvements in medical record keeping, DOD=s next use of an IND vaccine showed similar problems. In 1997, the General Accounting Office observed A nearly one fourth of the soldiers who received an investigational tick-borne encephalitis vaccine before deploying to Bosnia did not have this information noted in their files.≡ (A Defense Health Care: Medical Surveillance Improved Since Gulf War, but Mixed Results in Bosnia,≡ [GAO/NSIAD-97-136] U.S. General

protection to service members receiving investigational products than the AVIP now provides.

Accounting Office, May 13, 1997, p. 33.)

In November, 1997 the Subcommittee proposed, and the full Government Reform and Oversight Committee approved, an oversight report on Gulf War veterans= illnesses containing 18 findings and 18 recommendations.³¹⁸ Among them was the finding that A[t]he FDA was passive in granting and failing to enforce the conditions of a waiver to permit use of PB by DOD≡ and the recommendation that AFDA should grant a waiver of informed consent requirements for the use of experimental or investigational drugs by DOD only upon receipt of a Presidential finding of efficacy and need.≡³¹⁹

Legislation reflecting that recommendation was introduced in both chambers of Congress.³²⁰ The 1999 Defense Authorization Act contained provisions, codified at 10 USC 1107(f), implementing the recommendation by strengthening notice requirements and by requiring a presidential authorization for any waiver of informed consent.

In view of the new statutory provision, FDA on October 5, 1999 revoked the 1990 interim final rule and issued a new regulation to govern DOD compliance with IND conditions and informed consent waivers.³²¹

On September 30, 1999 the White House issued Executive Order 13139 establishing the procedures by which the president would comply with the new law.³²² The EO says A[w]aivers of informed consent will be granted only when absolutely necessary≡ and only upon a written determination by the president that obtaining consent is not feasible, is contrary to the best

³¹⁸ *Gulf War Veterans= Illnesses: VA, DOD Continue to Resist Strong Evidence Linking Toxic Causes to Chronic Health Effects*, 2d Report by the Committee on Government Reform and Oversight, House Rpt. 105-388, November 7, 1997, pp. 3-6.

³¹⁹ *Ibid.*

³²⁰ H.R.4035, 105th Congress, 2d Session; S.2057, 105th Congress, 2d Session

³²¹ Federal Register, 21 CFR Parts 50 and 312, October 5, 1999, p. 54180.

³²² Executive Order of September 30, 1999, AImproving Health Protection of Military Personnel Participating in Particular Military Operations≡ No. 13139, The White House, Washington, D.C.

interest of the service member or is not in the interest of national security. In the event a waiver is granted, the DOD Secretary must notify Congress and publish a notice in the Federal Register. No waiver may last more than one year. Waivers may be renewed based on a new, fully documented request.³²³

The statute establishes clear U.S. policy that waiver of informed consent in military operations is deemed appropriate and necessary under certain circumstances. The statute, the FDA interim rule and EO 13139 describe, and limit, those circumstances and attempt to ensure any decision to use IND drugs or vaccines without informed consent is as open as possible, supported by sufficient information and authorized at the highest level.

The new regime for waiving informed consent requirements appears far more rigorous and transparent than the system employed under the original interim rule. The statute is very explicit in describing the information that must be provided to each individual service member being given an IND drug or vaccine. The written information must include a clear statement the substance is investigational, the reason the drug or vaccine is considered necessary, information regarding possible side effects and drug interactions, and any other information FDA may require as part of the IND protocol.

That is more clinically useful information than the AVIP now routinely conveys. Consistently providing balanced risk/benefit assessments in an IND setting would also move DOD closer to its stated goal of more effective risk communication. According to an article linked to the DOD AVIP web site:

³²³ *Ibid.*

People are different. One size does not fit all when it comes to explaining risk. Some prefer short, simple messages about a vaccine's benefits and risks.^{8,12,68} These people, presumably a majority of the population, will be satisfied with the summary information comprising the Vaccine Information Sheets (VISs) published by the Centers for Disease Control and Prevention. Others want more detailed information. Some will scour the literature to explore every fact they can find. The goal of risk communication involving vaccines should be informed consent.⁶⁸ True consent to vaccination is only possible if the individual has received all the information he or she wants and understands that information. Then an informed vaccine decision can be made. Providing this information demonstrates respect for the individual. From the clinician's perspective, the consent process can be part of the efforts to identify contraindications to vaccination (e.g., severe hypersensitivity, immunodeficiency).³²⁴

The FDA believes that exceptions from the informed consent requirement should apply rarely and only when sufficient additional protections are provided to the military personnel affected.³²⁵ The agency also expresses the view that DOD should pursue drug development through normal regulatory procedures, despite the obvious difficulty of acquiring efficacy data regarding chemical and biological warfare exposures. In the future, requests for informed consent waivers must be accompanied by a history and projected time line for full scale development of the drug or vaccine in question.³²⁶ No more waiting until the eve of war to shortcut a process that could have been underway for months or years.

Under the new law, only the president may waive prior consent requirements, and only after certifying in writing that obtaining consent is not feasible, is contrary to the best interest of the service member, or is not in the interest of national security. With regard to the first two

³²⁴ Department of Defense, Anthrax Vaccine Immunization Program at Internet page <http://www.anthrax.osd.mil/> citing John D. Grabenstein and James P. Wilson, Are Vaccines Safe? Risk Communication Applied to Vaccination, *Hospital Pharmacy*, Vol. 34, No. 6, pp 713-729 (available at <http://www.anthrax.osd.mil/SCANNED/ARTICLES/grabedocs/vaccines.htm>).

³²⁵ See *supra* note 321 p. 51484.

³²⁶ *Ibid.*

justifications, the president must apply the standards and criteria used by the FDA for waivers. Those standards and criteria are detailed in the new FDA interim rule. To meet them, the Secretary of Defense must document for the president all the scientific data, threat assessment, lack of alternatives, and conditions under which the IND product will be used.

The FDA regulation strengthens the role of the Institutional Review Board (IRB) in approving and monitoring the IND protocols for which waivers are granted. IRBs are panels charged with assuring that clinical trials have legitimate scientific goals and that protocols protect human subjects. Under the regulation, an IRB must review all aspects of the proposed IND and waiver. Significantly, the IRB must include at least three members who are not employees of the federal government. This should add some element of independent review to DOD waiver requests. The rule also requires detailed certifications from DOD regarding record keeping systems, medical staff training, and communication of benefits and risks.

The Executive Order of September 30, 1999 mirrors the FDA regulation in many respects, requiring the DOD Secretary to support a waiver request with written justification, rationale, and proof of IRB review. The Assistant to the President for National Security Affairs and the Assistant to the President for Science and Technology must also review the request. After approval of a waiver, the EO requires monitoring and periodic reports on compliance with IND protocols and waiver conditions.

These more explicit and elaborate procedures address many of the problems noted in the execution of the Gulf War waivers. If applied rigorously, those safeguards could also form the basis for a mandatory anthrax vaccine program for certain deployed forces, Special Forces, or other elements determined by the president to warrant vaccination in the interests of national security. The remainder of the force could choose to enroll in an IND protocol³²⁷ or assume the risks of biological warfare not addressed by individual and collective protection, detection, battle tactics and deterrence.

In July 1999, the *Air Force Times* editorialized it was time to AStop Mandatory Anthrax Inoculations≡ because the manufacturer appeared unreliable, and because:

³²⁷ Open protocols could be established for the on-going trial of a reduced vaccine regimen or a trial of a purer vaccine.

More research is needed to understand the long-term risk of using the anthrax vaccine. And now, long after initiating the vaccination program, the Pentagon is finally planning such a long-term study of the vaccine's health effects. That's good, but until those risks are understood, the Pentagon should proceed with caution -- not reckless abandon.³²⁸

The editorial concluded the risks of the vaccine are outweighed by the risk of contracting anthrax³²⁹ and advised service members to take the shots. But in the absence of empirical evidence proving the vaccine's long-term safety, the troops should be given the chance to decline. Give them the information they need make wise, informed decisions for themselves. Let those who decline live with what they consider a reasonable risk.³³⁰

³²⁸"Stop Mandatory Anthrax Inoculations," *Air Force Times*, Army Times Publishing Co., Jul. 12, 1999, p. 44.

³²⁹*Ibid.*

³³⁰*Ibid.*