DEPARTMENT OF THE NAVY
BOARD FOR CORRECTION OF NAVAL RECORDS
2 NAVY ANNEX
WASHINGTON DC 20370-5100

ELP
Docket No. 7985-00
5 April 2002

[redacted]

[redacted]

This is in reference to your application for correction of your naval record pursuant to the provisions of Title 10, United States Code, Section 1552.

A three-member panel of the Board for Correction of Navy Records, sitting in executive session, considered your application on 3 April 2002. Your allegations of error and injustice were reviewed in accordance with administrative regulations and procedures applicable to the proceedings of this Board. Documentary material considered by the Board consisted of your application, together with all material submitted in support thereof, your naval record and applicable statutes, regulations and policies. In addition, the Board considered the advisory opinions furnished by the Occupational Medical Specialty Leader for the Navy Surgeon General, dated 1 August 2001, and the Deputy Director of the Criminal Law Division in the Office of the Judge Advocate General, dated 29 November 2001, copies of which are attached.

After careful and conscientious consideration of the entire record, the Board found that the evidence submitted was insufficient to establish the existence of probable material error or injustice. In this connection the Board substantially concurred with the comments contained in the advisory opinions.

The Board found that you served continuously on active duty after your graduation from the U.S. Naval Academy in May of 1997. While assigned to USS LAKE ERIE (CG 70), you submitted two requests for waivers from the Department of Defense (DOD) Anthrax Vaccination Immunization Program (AVIP). Both requests were denied.

On 24 August 1999, you officially refused to submit to the AVIP by signing an administrative remarks (page 13) entry to that effect. As a result, on 12 September 1999, you received nonjudicial punishment (NJP) for violation of Article 92 of the

Uniform Code of Military Justice (UCMJ) for failure to obey a lawful order to take the anthrax vaccination. You were awarded a punitive letter of reprimand. Your appeal of that NJP was denied.

You also were awarded NJP on 24 October 1999 for disrespect to your commanding officer by sending an inappropriate e-mail, conduct unbecoming an officer, and failure to obey a lawful order. On appeal, this NJP and the 30 days of restriction for disrespect toward the commanding officer were upheld. The two other charges and an oral reprimand were set aside.

On 10 December 1999, you submitted an unqualified resignation and requested an honorable discharge. This request was denied, and on 24 April 2000 the Chief of Naval Personnel (CNP) advised the Secretary of the Navy you were recommended for separation as a probationary officer with a general discharge. CNP also recommended recoupment of $38,812 in advanced educational funds received at the U. S. Naval Academy. The Assistant Secretary of the Navy (Manpower and Reserve Affairs) approved the general discharge and directed recoupment. On 26 May 2000 you were separated with a general discharge due to misconduct.

The Board first considered your contentions that the order to submit to the AVIP was unlawful since it was inconsistent with existing Federal laws and regulations; the AVIP is not sanctioned by law, but only by military order; and administration of the anthrax vaccine was prejudicial to your health. The Board also considered your contentions that 10 U.S.C.§ 2005 does not authorize recoupment of educational expenses if a policy decision prevents an individual from completing his military obligation; refusal to submit to the AVIP does not meet the definition of misconduct as defined in U.S. V Gears, 835 F. Supp.1093 (N.D. Ind. 1993); recoupment may only be sought if the failure to fulfill a service obligation was voluntary or was due to misconduct; and such action is unfair in your case since the midshipmen involved in cheating and sex scandals in 1993 and 1995 were not subjected to recoupment.

The Board took particular notice of the arguments in the legal memorandum prepared by two Air Force Reserve judge advocates who contend that orders requiring service members to submit to anthrax vaccinations are illegal because they contradict the terms expressed in Presidential Executive Order 13139 and 10 U.S.C. § 1107 as well as the letter to the Secretary of Defense, signed by 36 members of Congress, requesting immediate suspension of the AVIP; the Committee on Government Reform Report titled, "The Department of Defense Anthrax Vaccine Immunization Program: Unproven Force Protection"; and the bills that were introduced in

Congress to suspend the AVIP to provide for additional study, and to make the program voluntary for all service members.

The Board noted that despite all of the material you cite, the AVIP was not and has not been suspended, and no evidence has been submitted to show that Congress enacted any legislation supporting your position. Additionally, federal case law clearly shows that orders to submit to an anthrax vaccination are lawful. Ponder v. Stone, 54 M.J. 613, 616-17 (N.M.Ct.Crim.App. 2000); United States v. Washington, 54 M.J. 935, 940 (A.F.Ct.Crim App. 2001); O'Neil v Secretary of the Navy, 76 F. Supp.2d 641, 645 (W.D. Pa. 1999). Furthermore, Secretary of Navy Instruction 6230.4 of 24 April 1998, which implemented the Navy's AVIP, states that the anthrax vaccine is a FDA-licensed product and not an "Investigative New Drug", requiring informed consent for its administration. Accordingly under the provisions of this directive, mandatory anthrax immunization is proper and those who refuse the vaccine are subject to disciplinary action. Clearly, the AVIP is intended to be a force-wide protective measure against a biological anthrax agent, which is the primary biological weapons threat against U.S. Naval forces.

The Board then considered the documentation detailing your request for a medical waiver of the anthrax vaccine, the two nonjudicial punishments and appeals, your request for redress of injuries, and other documentation detailing the circumstances which led to your discharge. There appears to be no merit to your assertion that taking the anthrax vaccination was prejudicial to your health based on a chronic bronchial condition. The Bureau of Medicine and Surgery (BUMED) thoroughly and thoughtfully reviewed the arguments in your waiver request and found no justification for approving a medical wavier.

Since you were discharged by reason of misconduct, specifically, the two NJPs, proportional recoupment was proper and appropriate in accordance with 10 U.S.C.§ 2005. The Board was well aware that certain midshipman involved in various scandals in 1993 and 1995 have had their academy debts forgiven. However, their cases are not similar to yours. The Board believed your misconduct as a commissioned officer was especially serious in view of its potential adverse impact on good order and discipline of the command. The Board concluded that given the two NJPs, discharge by reason of misconduct was proper and appropriate. The Board further concluded that you were fortunate to receive a general discharge, since your record of misconduct could have resulted in processing for separation under other than honorable conditions.

Accordingly, your application has been denied. The names and votes of the members of the panel will be furnished upon request.

It is regretted that the circumstances of your case are such that favorable action cannot be taken. You are entitled to have the Board reconsider its decision upon submission of new and material evidence or other matter not previously considered by the Board. In this regard, it is important to keep in mind that a presumption of regularity attaches to all official records. Consequently, when applying for a correction of an official naval record, the burden is on the applicant to demonstrate the existence of probable material error or injustice.

Sincerely,

W. DEAN PFEIFFER
Executive Director

Enclosures

1 Aug 01

From: Occupational Medicine Specialty Leader
To: Chairman, Board for Correction of Naval Records

Subj: REQUEST FOR COMMENTS AND RECOMMENDATION IN THE CASE OF [redacted]

Ref: (a) Your ltr ELP Docket No. 7985-00 of 3 Jul 01 (w/encl)
(b) BUMED ltr 6230 Ser 24B/1999U114000346 of 12 Aug 99

1. As requested in reference (a), I have reviewed the documentation forwarded in this case. The following responses to your questions are provided.

a. *Are there any medical conditions which preclude administering of the anthrax vaccination because it would have long-term or permanent adverse affects on an individuals health?*

The only medical contraindication to receipt of anthrax vaccine is a history of a severe reaction to a previous dose of anthrax vaccine. Indications for temporary deferral of vaccination include active infection or acute respiratory disease; immune suppression; or pregnancy. There are no chronic medical conditions that would preclude administration of anthrax vaccine. Specifically, anthrax vaccine can be safely administered to individuals with asthma or chronic bronchitis (or chronic bronchial illness). Based on my review of the record, this member did not have a medical condition that would preclude administration of anthrax vaccine.

b. *Have there been any medical developments since Petitioner's waiver request was denied that would warrant granting the relief he seeks?*

No.

c. *Any other comments you believe may be pertinent to this case and Petitioner's medical contentions are also solicited.*

There have been additional studies of anthrax vaccine safety since the time that Petitioner's waiver request was denied by reference (b). While research is continuing in this area, studies

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done to date show that the rate of adverse effects after receipt of anthrax vaccine are similar to the adverse effects after many other commonly administered vaccinations. In addition, there are no known long term health effects from anthrax vaccine.

2. If there are additional questions, please contact me at [redacted] 762-3496.

[redacted]

CAPT, MC, USN

DEPARTMENT OF THE NAVY
OFFICE OF THE JUDGE ADVOCATE GENERAL
WASHINGTON NAVY YARD
1322 PATTERSON AVENUE SE SUITE 3000
WASHINGTON DC 20374-5066

IN REPLY REFER TO

5800
Ser/0020
29 Nov 2001

From: Deputy Director, Criminal Law Division
To Chairman, Board for Correction of Naval Records

Subj: REQUEST FOR COMMENT AND RECOMMENDATIONS ICO [redacted]

Ref: (a) BCNR ltr Docket No. 7985-00 (w/encl)
(b) 21 U.S.C. § 355 (2001)
(c) SECNAVINST 6230.4 of 29 April 1998
(d) DoD Information About the Anthrax Vaccine and the Anthrax Vaccine Immunization Program (AVIP) of 15 Aug 2001

Encl: (1) Lt.Col. [redacted], USAFR and Maj. Smith, USAFR legal memorandum
(2) Executive Order 13139 of 30 Sep 99
(3) Dep't of Health and Human Services, Food and Drug Administration ltr of 26 Nov 99

1. Reference (a) requests comments and recommendation on the petition of ex-Ensign [redacted] USN, 615-10-8596 (Petitioner) to correct his naval record. Petitioner requests an upgrade of his discharge and waiver of the action to recoup his "academy debt" for failure to fulfill his service obligation due to misconduct.

2. BACKGROUND: Petitioner was on continuous active duty from his graduation from the U.S. Naval Academy in May of 1997 until his separation with a General discharge on 26 May 2000. While assigned to USS LAKE ERIE (CG 70), Petitioner submitted two requests for waivers from the Department of Defense Anthrax Vaccination Immunization Program (AVIP). Both requests were denied. On 24 August 1999, Petitioner officially refused to submit to the AVIP by signing a page 13 to that effect. As a result, on 12 September 1999, Petitioner received non-judicial punishment (NJP) for violation of Article 92 of the Uniform Code of Military Justice (UCMJ) for failure to obey a lawful order to take the anthrax vaccination. He was awarded a punitive letter of reprimand. Petitioner's appeal of that NJP was denied. Petitioner also was awarded NJP on 24 October for separate offenses. On appeal, the second NJP and the 30 days restriction awarded for Violation of UCMJ Article 89, disrespect toward his Commanding Officer, were upheld. Two other charges and an oral reprimand were set aside.

On 10 December 1999, Petitioner submitted an unqualified resignation and requested an honorable discharge. His request was denied, and on 24 April 2000, the Chief of Naval Personnel advised the Secretary of the Navy that the Petitioner was recommended for separation from the Naval service as a probationary officer with a General (under honorable conditions)

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discharge, and that $38,812 in advanced educational funds received at the U.S. Naval Academy be recouped. The Assistant Secretary of the Navy (Manpower and Reserve Affairs) approved the General discharge. On 26 May 2000, Petitioner was separated with a General discharge due to misconduct.

3. DISCUSSION: The sole question in the subject request is whether the Petitioner's Commanding Officer issued a lawful order for Petitioner to submit to the AVIP; specifically whether the order was consistent with existing federal laws and regulations. The Petitioner cites enclosure (1) as justification why the order was not lawful. The authors of the memorandum conclude that orders to submit to the AVIP are unlawful because:

> they contradict the express terms of Presidential Executive Order 13139 and 10 U.S.C Sec. 1107 (1999). Because the anthrax vaccine is being used in a manner inconsistent with both its original licensing and for a purpose for which it has never been tested, the vaccine is properly considered an Investigational New Drug under Food and Drug Administration (FDA) regulations and court decisions. Both the executive Order and the statute mandate that informed consent is a prerequisite to all vaccinations with an Investigational New Drug. It is undisputed that service members are not giving their informed consent to the vaccination process.

Enclosure (1).

The basic premise of the memorandum in Enclosure (1) is incorrect. Although Executive Order 13139, Enclosure (2), does require informed consent[1] for administration of "Investigative New Drugs" (IND), the anthrax vaccine as utilized by DOD is not experimental, and not an IND. The definition of IND, *i.e.*, "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs," can be found in subsection (i) of Reference (b). In addition, the Navy's implementing instruction in reference (c) states that the anthrax vaccine is a FDA-licensed product and not an IND requiring informed consent for its administration.

An FDA approved drug in use for years may in essence become new again and require IND testing if it is to be put to an unapproved use, that is a use not listed on the label as its approved intended purpose. As outlined in Enclosure (3), the question of whether DOD's use of the anthrax vaccine as prophylaxis against inhalation anthrax constituted an unapproved application was raised with the FDA, the agency solely responsible for making such a determination. On November 3, 1999, Congressional Representatives wrote the FDA proposing the vaccine be considered experimental and that IND testing be carried out. In Enclosure (3), the FDA found no basis for the challenge and refuted the misconception that the vaccine's license only covers use "by a limited population of individuals at risk for cutaneous exposure to anthrax." The FDA also expressly concluded that "use of the vaccine for protection against both

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[1] There are certain circumstances under 10 U.S.C. 1107(f) where the President may waive the informed consent requirement for the administration of an investigational drug to a member of the Armed Forces in connection with the member's participation in a particular military operation.

cutaneous and inhalation anthrax exposure is not inconsistent with the labeling." (Enclosure (3)) Accordingly, the anthrax vaccine is not considered an IND, and informed consent is not required of service members before requiring them to submit to vaccination. The Navy-Marine Corps Court of Criminal Appeals (NMCCA) considered and rejected a similar argument in *Ponder v. Stone*, 54 M.J. 613 (N.M.Ct.Crim.App. 2000).

Orders issued to service members to submit to these vaccinations are lawful orders. The following DoD guidance is set forth in a section entitled "Mandatory Anthrax Immunization" in reference (d):[2]

> Service members who disobey a lawful order to take anthrax vaccination are subject to administrative or disciplinary actions. There is no DoDwide policy directing a specific disposition when a Service Member refuses a lawful military order. Rather, local military commanders apply the principles in the Uniform Code of Military Justice (UCMJ) and the guidance in the Manual for Courts Martial and Service regulations that apply to all cases involving refusal to obey a lawful order.

According to Reference (c), anthrax immunization is mandatory within the Department of the Navy and those refusing the vaccine are subject to disciplinary action. The Navy Marine Corps Court of Criminal Appeals has affirmed the lawfulness of an order to submit to anthrax vaccination in *Ponder v. Stone*, 54 M.J. 613 (N.M.Ct.Crim.App. 2000) and *United States v. Bolton*, No. 200001021 (N.M.Ct.Crim.App.)(unpublished 16 Nov 2001).

4. RECOMMENDATION: While the effectiveness and propriety of the AVIP may be subject to continued public debate, the validity of a military commander's order designed to "promote or safeguard the morale, discipline and usefulness of members of a command and (that is) directly connected with the maintenance of good order in the service" does not rest on public consensus or a service member's consent (see UCMJ Article 90 and MCM 2000, para. 14.c.(2)(a)(iii)). The order given to the Petitioner to submit to anthrax vaccinations was consistent with Federal law and pertinent implementing regulations, properly related to a valid military purpose, and accordingly, was lawful. A subordinate who disobeys such an order does so at his own peril. Based on the foregoing analysis, I respectfully recommend that Petitioner's requests be denied.

R. L. Gilchrist
LCDR, JAG Corps, U.S. Navy

[2] This paper, as well as other information on the AVIP program are available on the official DoD website at http://www.anthrax.osd.mil.

LEGAL MEMORANDUM

RE: Legality of Orders to Submit to Anthrax Vaccination

FROM: [redacted]

> "I think medicine is based on trust. If for whatever reason, in any individual's mind he loses trust in his medicine, in his doctor, or he loses trust in his government, then those sorts of feelings will fall on more fertile ground... Our job is to regain that trust and make sure that our message is clear, that we are protecting our people, that we are doing everything we possibly can to make sure we are not harming them with the thing we give them to protect them."
>
> -- Unidentified Defense Department Spokesman at Department of Defense ("DoD") Background Briefing on the Anthrax Vaccine, August 5, 1999.

I. ISSUE PRESENTED:

Are orders currently being given to members of the U.S. Armed Forces to submit to anthrax vaccinations consistent with federal law?

II. SHORT ANSWER:

Orders currently being given to members of the United States Armed Forces to submit to anthrax vaccinations are illegal because they contradict the express terms of Presidential Executive Order 13139 and 10 U.S.C. § 1107 (1999). Because the anthrax vaccine is being used in a manner inconsistent with both its original licensing and for a purpose for which it has never been tested, the vaccine is properly considered an Investigational New Drug under Food and Drug Administration ("FDA") regulations and federal court decisions. Both the Executive Order and the statute mandate that informed consent is a prerequisite to all vaccinations with an Investigational New Drug. It is undisputed that service members are not giving their informed consent to the vaccination process.

III. ANALYSIS:

A. Introduction

Members of the Armed Forces of the United States are currently being vaccinated against anthrax (Bacillus anthracis), a relatively common, spore-forming soil bacterium that can cause death within 1-6 days of exposure to a lethal dose. Anthrax is postulated as a likely biological warfare (BW) agent because it is relatively easy to synthesize, exists naturally as spores that are readily dispersed in the atmosphere and because a variety of second and third world nations are known to have at least attempted to create BW versions of the disease. See Atch. 1, Excerpt of Dept. of Defense Background Briefing p. 13 (August 5, 1999).

There are essentially two ways to medically counter anthrax BW – antibiotics and vaccines. Antibiotics must be administered shortly before or after anthrax exposure to be effective.

Antibiotics cannot prevent a lethal infection once the anthrax spore has produced signs of illness. Vaccines, on the other hand, can be administered years before exposure, are theoretically effective as long as the victim has enough immunity to neutralize the bacillus, and generally do not provide the kind of logistics problems associated with long-term, forward storage of antibiotics.

In December 1997, Secretary of Defense William Cohen announced [illegible] of Reserve and National Guard service members. Cohen's directive, requiring that all active and Reserve component members receive anthrax vaccinations was ostensibly based on a threat to U.S. Forces from second and third world nations who sought ready access to a weapon of mass destruction ("WMD").

The sole production facility for anthrax vaccine was originally owned by the Michigan Department of Public Health ("MDPH"). In the mid 1990s the facility was sold to a corporation known as Michigan Biologic Products, Inc. ("MBPI"). In September 1998, MBPI was sold to a group of investors heading up a company called Bioport, Inc.

MDPH obtained approval for the anthrax vaccine in 1970 from the National Institute of Health ("NIH") Bureau of Biologics. This was some two years before efficacy and safety data were required by the FDA for drug approval and licensing. Long-term safety data for the vaccine was not supplied with the original license application and none has ever been supplied to the FDA. In addition, the vaccine now being produced by MBPI's successor, Bioport, is produced under a different procedure and is apparently chemically different from the original vaccine approved by the NIH.

The license to produce anthrax vaccine was originally the property of MDPH and later, MBPI and Bioport. The original license for the anthrax vaccine reflects its use in agricultural and veterinary settings as a protection against cutaneous (skin) contact anthrax. See Atch. 2, Anthrax Vaccine Adsorbed, various package inserts, Michigan Dept. of Pub. Health, 1978. The vaccine has never been licensed as a prophylaxis against airborne anthrax, the most likely BW variant.

B. The Anthrax Vaccine Used By DoD Is An Investigational New Drug

The key to understanding why current Defense Department policy is illegal is the recognition that the anthrax vaccine as currently used by DoD is properly characterized under FDA regulations as an "Investigational New Drug" ("IND"). The vaccine (hereafter referred to as "AVA" for "anthrax vaccine adsorbed") was originally approved only for protection against cutaneous anthrax. However, it is undisputed that the DoD vaccination program is aimed at protecting vaccine recipients from pulmonary, or airborne, anthrax. In addition, the DoD vaccination regimen differs from the regimen originally approved by the NIH.

These substantive changes in the way the vaccine is used and the purpose for which it is used render the vaccine an IND under current federal law. As an IND, the vaccine may not be administered to service members without their informed consent, as directed by President Clinton's Executive Order 13139 and 10 U.S.C. § 1107. Accordingly, orders to military personnel to submit to the vaccine without their consent are per se violative of a direct order from the President in his role as Commander-in-Chief.

1. Investigational New Drug Status.

Vaccines, like other medical drugs, are closely monitored by the FDA and are licensed for production and marketing. The Center for Biologics Evaluation and Research ("CBER") is the FDA agency charged with oversight of the four-stage licensing process. See Bascom & Sutton, New Generation Vaccines, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration (1997), at Atch. 3. The process consists of a pre-clinical stage, followed by an IND stage, followed by a Product License Application process, and finally, a post-licensure stage. See generally 21 C.F.R. § 312. The FDA and CBER govern a vaccine license applicant in both its manufacturing and marketing procedures. The FDA does not govern the behavior of the end user, in this case, the Department of Defense.[1]

It is clear that the term "investigational" drugs also embraces so-called "new" drugs as defined by the FDA itself. See 21 C.F.R. § 312.3(b) (cited in EO 13139). The determination of what is a "new" drug for purposes of FDA regulatory coverage (and coverage under EO 13139) hinges on a variety of factors. A drug is "new", even if it has been in use for years, if there is a proposed change in the target use of the product, a change in the formula, dilution of the drug, a change in its route of administration, or even repackaging of the drug product. See generally What Is A "New Drug" Within the Meaning of § 201(p) of the Federal Drug and Cosmetic Act, 133 ALR Fed 229 (1999), and cases cited therein.

Court decisions reinforce FDA's interpretation. For example, in Hoffman v. Sterling Drug, Inc., 485 F.2d 132 (3d Cir. 1973) the court held that marketing a drug that had been approved by the FDA for the treatment of malaria as suitable for use in treating lupus caused the already approved drug to be considered a "new" drug, at least as far as the lupus treatment was concerned. Similarly, in U.S. v. Articles of Drug, etc., 442 F. Supp. 1236 (S.D.N.Y. 1978) the court found that a drug may be considered "new" if there is a change in the dosage, or method or duration of administration or application, or other condition of use prescribed, recommended or suggested in the labeling of such drug, despite the fact that the drug had previously had been approved, albeit with a different dosage and for a different purpose.

In addition, drugs that are not adequately tested are also considered "new" and investigational, regardless of usage. In U.S. v. Articles of Drug Consisting of the Following: 5906 Boxes, 745 F.2d 105 (1st Cir. 1984) the court found that a nausea-suppressing drug was a "new" drug in the absence of substantial evidence that it was recognized by experts as safe and effective. The court defined "substantial evidence" to mean consisting of adequate and well-controlled investigations, including clinical investigations conducted by experts. The court noted that substantial evidence that a drug is generally recognized by experts as safe and effective means adequate and well-controlled investigations including clinical investigations conducted by experts.

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[1] It is important to note that the FDA approval is not a prerequisite for use by a medical practitioner or the DoD. The FDA regulates the manufacturer in the marketing of drugs, vaccines and devices, not the use of the products. In fact, the FDA does not have jurisdiction to regulate the administration of the AVA. It is commonplace in the practice of medicine for physicians to make use of drugs and devices that do not bear FDA approval. See e.g. FTC v. Simeon Mgmt. Corp., 391 F. Supp. 697 aff'd. 532 F.2d 708 (9th Cir. 1978); Talley v. Danek Medical Inc., 179 F.3d 154 (4th Cir. 1999); In re: Orthopedic Bone Screw Products Liability Litigation, 159 F.3d 817 (3d Cir. 1998).

Finally, in U.S. v. Rutherford, 442 U.S. 544 (1979) the Supreme Court held that under 21 U.S.C. § 321(p)(1) the term "new drug" described a drug not generally recognized as being safe and effective for use under the conditions prescribed, recommended or suggested in the labeling. Rutherford, 442 U.S. at 552-3.

Clearly then, federal statutes, regulations and case law show indisputably that even an established and licensed drug that is modified with regard to its dosage regimen or the purpose

EO 13139 and 10 U.S.C. § 1107.

2. **The Current Use of AVA for Pulmonary Anthrax and the Altered Vaccine Schedule for U.S. Soldiers Makes the AVA an Investigational Drug under FDA Regulations.**

The 1970 NIH-approved license for AVA indicates that it was approved as a prophylaxis only against cutaneous exposure to anthrax for a specific methodology of administration, and a specific vaccination schedule. See Atch. 2.

Recognizing the need for certification for pulmonary infections, in 1995 MDPH and the Army discussed establishing a plan for Investigational New Drug approval by the FDA. See Atch. 4, Anthrax Vaccine License Amendment Project Plan briefing slides (October 20, 1995). The briefing slides clearly show that the Army was well-aware that the AVA, in order to meet the above-described legal requirements for licensure, had to pass through the IND application process in order to become fully licensed as a prophylaxis for pulmonary anthrax. The focus of the proposed plan was to get approval from the FDA for a change to the immunization schedule (in this case to a series of three doses of vaccine versus the prescribed six) and to change the labeling to reflect that the vaccine was properly administered as protection against pulmonary or airborne anthrax. Id.

In fact, less than one year from the date of the briefing, on September 20, 1996, MBPI filed an Investigational New Drug application with the FDA. The application identified the three areas where the current license would be modified – showing a new designation for "inhalation anthrax", changing the "route of administration", and changing the "vaccination schedule". The application indicates that it is an "initial" investigational new drug application. See Atch. 5, IND Application (September 20, 1996).

Thus, as the DoD was preparing to kick-off its anthrax vaccination program, the sole producer of anthrax vaccine recognized that its product, as labeled, was not legally viable and undertook the appropriate steps to change product use labeling, method of administration, and vaccination schedule. These substantial changes in how this drug was to be used rendered it an IND. This is explicitly acknowledged by the September 20, 1996 application by MBPI. That application has never been withdrawn by MBPI or Bioport, nor has it ever been modified or acted on in any way.

The formal record of the anthrax program is littered with references to the vaccine's IND status. For example, as the Army began to move forward to try and license the vaccine as a prophylaxis against inhaled or pulmonary anthrax, it followed up its October 1995 meeting with a series of meetings designed to request that MBPI file an IND application for the vaccine. On November

13, 1995 the Joint Program Manager for Biological Defense, Army Brigadier General Walter L. Busbee, instructed the Joint Program Office for Biological Defense that the DoD needed to "...develop a ... package for initiating and completing an amendment to MDPH anthrax license for: (1) reduced immunization schedule, (2) immunization by the intramuscular route, and (3) indication for protection against an aerosol challenge". Minutes of the Meeting on Changing the Food and Drug Administration License for the Michigan Department of Public Health (MDPH) Anthrax Vaccine to Meet Military Requirements (November 13, 1995), Atch. 6. As late as June 30, 1999, in testimony before the House Subcommittee on National Security, Veterans Affairs and International Relations, Atch. 7, at 12, Mr. Fuad El-Hibiri, President and CEO of Bioport, stated

> [w]e continue to hold an Investigational New Drug application - IND 6847 - to improve administration of the anthrax vaccine.

The use of the AVA as currently contemplated by DoD is a clear change in how the drug was to be originally used and for which it was licensed, rendering the AVA an IND. There can be no doubt that "administration of the anthrax vaccine for mass prophylaxis in Biological Warfare should be considered an off-label use of the product to treat an indication for which it is not explicitly licensed... both the new indication and the new schedule should be undertaken only pursuant to FDA regulations governing clinical trials on investigational new drugs". The Department of Defense Anthrax Vaccination Immunization Program: Unproven Force Protection, p.3, House of Representatives Government Oversight Committee (March 9, 2000) Atch. 8.

This current vaccine is obviously a "new" drug under any FDA standard. Moreover, the Anthrax Vaccine is apparently is not even the same substance originally tested and approved by NIH. This bizarre conclusion is borne out in a GAO report dated April 29, 1999, entitled Medical Readiness: Safety and Efficacy of the Anthrax Vaccine, Atch. 9 where, at p. 3, it was revealed that the AVIP vaccine being administered to DoD members is not the same vaccine as originally tested prior to 1970. The import of this fact cannot be emphasized enough; the vaccine in current DoD inventories is NOT the same chemical compound as the original compound tested in advance of the 1970 NIH approval.

Finally, the AVA's IND status is further bolstered by the fact that there is no reputable study or clinical evidence supporting the AVA's use as safe and effective protection against pulmonary anthrax. In 5906 Boxes, the court held that a drug was a "new drug" in the absence of substantial evidence that it was generally recognized by experts as safe and effective. 5906 Boxes, 745 F.2d at 108. The manufacturer conceded that no investigations of any kind had ever been conducted to test the particular product's efficacy; at trial it attempted to introduce three studies that had been conducted using a drug that was similar to the product in question containing the same amounts of active ingredients. Even though an expert testified that his theoretical opinion was that tests of a similar drug would lead to results identical to the drug in question, the court rejected the evidence and found that the material was a "new drug". 5906 Boxes, 745 F.2d at 118.

In United States v. Sene X Eleemosynary Corp., 479 F. Supp. 970 (S.D. Fla. 1979) the court found an orally administered solution of buffered novocaine originally used as a cardiovascular

medicine was a "new drug" under 21 U.S.C. § 321(p) when marketed for the treatment of arthritis and other geriatric diseases. The court noted that its conclusion was based in part in a letter written by the defendant stating that the defendant and others were currently conducting clinical trials of the drug to determine its effectiveness. The court specifically pointed out that anecdotal evidence by numerous individual patients or doctors concerning the efficacy of the medicine could not be used to establish general recognition of safety and efficacy. Sene X, 479 F. Supp. at 977, citing Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 629 (1973).

There is no question that the claims of efficacy of the vaccine against pulmonary anthrax are unproven. In its March 9, 2000 report, the House Government Oversight Committee specifically noted that "no adequate and well-controlled investigations, including clinical investigations conducted by experts, have been performed regarding either the safety or the efficacy of the vaccine in humans". Unproven Force Protection, Atch. 8, supra.[2]

In what is generally regarded as the seminal test of the efficacy of the AVA as a prophylaxis against cutaneous or skin contract anthrax, there were no indications that the AVA provided significant protection against aerosolized anthrax. Brachman, Gold, et al., Field Evaluation of a Human Anthrax Vaccine, American Journal of Public Health, Vol. 52, No. 4, at 632 (April, 1962). Nothing has changed this early assessment of the AVA's role, at least regarding human beings. The AVA is still considered untested as a mechanism for protecting human beings from aerosol anthrax exposure. See Col. Stanley L. Weinner, Strategies for the Prevention of a Successful Biological Warfare Aerosol Attack, Military Medicine, Vol. 161, No. 5 at 251-254 (May, 1996); Letter of Dr. Claire V. Broome, M.D., Deputy Director for Science and Public Health, Center for Disease Control, U.S. Department of Heath and Human Services, December 14, 1998, Atch. 11.[3]

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[2] Indeed, it is unlikely that any BW vaccine could pass muster under the current FDA testing regimen. In a particularly frank article in Military Medicine, Vol. 157, (August 1992), attached as Atch. 10, Army physicians Col. Garland E. McCarty and Lt. Col. Gregory P. Berezuk said :

> the studies of new drug or vaccine products are initiated in the appropriate animal species in order to define a safe and effective dose. The results of those studies are then submitted to the [FDA] as part of an Investigational New Drug (IND) application, and acceptance of the IND by the FDA allows for the initiation of studies in humans. Human studies are designed to demonstrate safety and efficacy of the investigational product. Once sufficient human data are collected, the sponsor of the IND may file a New Drug Application (NDA) for the product, and this can lead to approval or licensure for marketing. Approval of the NDA by the FDA is dependent upon the results of at least two adequate and well-controlled studies that demonstrate the efficacy of the product in humans. For products designed to protect against chemical and biological agents, a clear demonstration of efficacy would require exposure to humans to these lethal agents. ***Since this practice would be unethical and immoral, these products never advanced beyond the investigational stage***.

[3] In fact, there have been only a few relevant animal studies regarding the efficacy of the AVA. These are widely touted by DoD officials as proving the efficacy of the vaccine. However, the Senate Committee on Veterans' Affairs in a 1994 report evaluating an anthrax program study stated

Accordingly, there can be absolutely no claim by DoD that the AVA is anything but an IND. This fact is recognized by the AVA's manufacturer, Bioport, in its IND application, which is still current and pending, and by the complete failure of Bioport, DoD or any other entity to provide verifiable clinical testing showing that the AVA is either safe or effective, in humans, as a prophylaxis to pulmonary anthrax. The FDA testing regimen, which has not been waived or excepted for the AVA, federal statutes, and federal case law, all point to the inescapable determination that the AVA is an IND as it is currently being used on members of the Armed Forces without their informed consent.[4]

C. Federal Statutes, A Presidential Order, And Air Force Regulations Require Informed Consent From Service Members Prior To The Administration Of The Anthrax Vaccine

A determination that the AVA is an IND renders inescapable the conclusion that service members as a consequence of federal law and service regulations must give their informed consent prior to submitting to vaccinations.

1. The Federal Statute.

10 U.S.C. § 1107 (1999) entitled "Notice of Use of an Investigational New Drug or a Drug Unapproved for its Applied Use" specifically provides:

> although the results of this study suggest the vaccine might protect against anthrax that has been sprayed, it is not sufficient to prove that anthrax vaccine is safe and effective as used in the Persian Gulf. The vaccine should therefore be considered investigational when used as a protection against biological warfare. (emphasis added).

U.S. Senate Committee on Veterans' Affairs Report at 14 (December 8, 1994) (citations omitted).

[4] DoD has produced two letters that it relies on in an effort to show that the AVA is not an IND when used for inhalation anthrax. The first is a letter from Dr. Michael Friedman to former DoD ASD/HA Dr. Joseph, dated March 13, 1997. The second letter was written to Representative Dan Burton by FDA Associate Commissioner Melinda Plaisier on November 26, 1999. Both letters are circumspect in their assessment of the status of the AVA as an IND, but indicate that the AVA is not investigational. However, such letters have absolutely no effect on the legal status of the AVA. FDA regulations specifically note that

> a statement made or advice provided by an FDA employee constitutes an advisory opinion only if it is issued in writing under this Section. A statement or advice given by an FDA employee orally, or given in writing but not under this Section or § 10.90 is an informal communication that represents the best judgment of that employee at that time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

21 CFR § 10.85(k).

Neither of the letters referenced by DoD were issued pursuant to the above Section. They do not bind the agency, they do not carry the weight of law and they cannot constitute a change in the legal status of the AVA from an IND to something else.

(a) Notice Required. - (1) Whenever the Secretary of Defense requests or requires a member of the armed forces to receive an *investigational new drug* or *a drug unapproved for its applied use*, the Secretary shall provide the member with notice containing the information specified in subsection (d).

(b) Time of Notice. - The notice required under subsection (a)(1) shall be provided before the *investigational new drug* or *drug unapproved for its applied use* is first administered to the member.

(c) Form of Notice. - The notice required under subsection (a)(1) shall be provided in writing.

(d) Content of Notice. - The notice required under subsection (a)(1) shall include the following:

(1) Clear notice that the drug being administered is an investigational new drug or a drug unapproved for its applied use.

(2) The reasons why the investigational new drug or drug unapproved for its applied use is being administered.

(3) Information regarding the possible side effects of the investigational new drug or drug unapproved for its applied use, including any known side effects possible as a result of the interaction of such drug with other drugs or treatments being administered to the members receiving such drug.

* * *

(e) ***Limitation and Waiver. - (1) In the case of the administration of an investigational new drug or a drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation, the requirement that the member provide prior consent to receive the drug in accordance with the prior consent requirement imposed under section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)) may be waived only by the President.*** The President may grant such a waiver only if the President –
determines, in writing, that obtaining consent –

(1) is not feasible;

(2) is contrary to the best interests of the member; or

(3) is not in the interests of national security.

(emphasis added).

2. **The Order of the President.**

An Executive Order is a lawful order of the Commander-in-Chief of the United States Armed Forces. On September 30, 1999, the President issued Executive Order 13139, entitled "Improving Health Protection of Military Personnel Participating in Particular Military Operations." EO 13139 provides in pertinent part:

> Sec. 2. Administration of Investigational New Drugs to Members of the Armed Forces. (a) The Secretary of Defense (Secretary) shall collect intelligence on potential health threats that might be encountered in an area of operations. The Secretary shall work together with the Secretary of Health and Human Services to ensure appropriate countermeasures are developed. ***When the Secretary considers an investigational new drug or a drug unapproved for its intended use (investigational drug) to represent the most appropriate countermeasure, it shall be studied through scientifically based research and development protocols to determine whether it is safe and effective for its intended use.*** (b) It is the expectation that the United States Government will administer products approved for their intended use by the Food and Drug Administration (FDA). However, in the event that the Secretary considers a product to represent the most appropriate countermeasure for diseases endemic to the area of operations or to protect against possible chemical, biological, or radiological weapons, but the product has not yet been approved by the FDA for its intended use, the product may, under certain circumstances and strict controls, be administered to provide potential protection for the health and well-being of deployed military personnel in order to ensure the success of the military operation. The provisions of 21 CFR Part 312 contain the FDA requirements for investigational new drugs.
>
> Sec. 3. Informed Consent Requirements and Waiver Provisions.
>
> (a) ***Before administering an investigational drug to members of the Armed Forces, the Department of Defense (DoD) must obtain informed consent from each individual unless the Secretary can justify to the President a need for a waiver of informed consent in accordance with 10 U.S.C. 1107(f). Waivers of informed consent will be granted only when absolutely necessary.***

(emphasis added).

In addition, the provisions of 21 C.F.R. §§ 50, 312 (October 5, 1999) support both the federal statute and the Executive Order by specifically noting situations where the informed consent requirements may be waived. Echoing 10 U.S.C. § 1107, the Regulations note that only the

President of the United States may waive the informed consent requirements mandated by his Executive Order and federal law. Waiver is allowed only if one of three preconditions is met if obtaining informed consent is not feasible; if obtaining informed consent is contrary to the best interests of the recipient; or if informed consent is contrary to national security interests. The President has yet to issue any such waivers, or even initiate action to do so regarding the AVA

3. Air Force Instruction 40-403

Air Force Instruction ("AFI") 40-403, "Clinical Investigations in Medical Research Guidance and Procedures" (May 19, 1994) deals directly with Air Force mandated policies on use of INDs on Air Force personnel. AFI 40-403 dictates that Air Force members must provide "informed consent" before any clinical use of an IND. Pertinent portions of that AFI follow:

> CLINICAL INVESTIGATIONS IN MEDICAL RESEARCH GUIDANCE AND PROCEDURES
>
> THE SCOPE OF THIS INSTRUCTION
> 2.1. Investigations Covered by This Instruction:
> 2.1.1. Clinical investigations...
> 2.1.1.1. Examples of clinical investigations are:
> *Field trials of vaccines and prophylactic drugs.*
>
> 2.1.2. Use of drugs...that are not approved by the FDA, or use of FDA approved drugs...in a manner not provided for in the FDA approved indications. Using FDA approved drugs, devices or radiopharmaceuticals for therapeutic effects that are widely reported and are generally accepted within the scope of normal medical practice, does not constitute clinical investigation or research in the sense of this instruction.
>
> ***All medications or devices will be used within the FDA approved indications for the drug ...***
>
> 3.1.3. The investigator must avoid all unnecessary physical or mental discomfort to human subjects, by planning for adequate facilities and making proper research preparations. Studies are not permitted if there is significant possibility that the subject could suffer disease, injury, or death. The investigator must: Conduct an evaluation of the subject before the study begins and record the results.
>
> 3.1.6. Before a subject is permitted to give consent, the investigator or associate investigator must accurately explain the investigation in language the subject can understand. ***This explanation must be made a part of the informed consent document.***
>
> 3.1.6.1. The informed consent document should contain, in addition to the components identified in 32 CFR 219, the following statements:
> **Any medical misadventure or unanticipated medical event will be brought immediately to the attention of the subject, or the subject's guardian or next of kin, if the subject is not**

competent at the time to understand the nature of the misadventure or unanticipated medical event.
Records of the study may be inspected by the FDA or sponsoring institution, if appropriate.

3.1.7 Informed Consent. *The subject must give consent in writing.* The investigator must attach a copy of the voluntary consent form to the protocol [illegible]

3.1.7.1. The subject must sign the consent form in the presence of at least one witness, who attests to the subject's signature by signing in the place provided. If the subject is military (whether active duty or retired), enter the social security number (SSN) of the subject on the form under the subject's signature...

3.1.7.2. The investigator or associate investigator gives the advice that forms the basis for the informed consent. This individual must sign the consent form in the presence of the same witness.

3.1.7.3. Sign or reproduce the consent document in at least four copies.

3.4. Active Duty Personnel as Human Subjects. The investigator, in consultation with the subject, should determine whether participation in a study would affect the ability of the subject to mobilize for readiness, to perform duties, or to be available for duty. Normally, if their participation could affect their performance, they should not be considered for the clinical investigation.

Terms

Informed Consent:
Informed Consent Process. The informed consent process is intended to give a subject all the information that he or she reasonably would want about a study; to ensure that the subject understands this information; ***and to give the subject an opportunity to agree or decline to participate*** in the study. The process provides for interaction between the investigator and the subject.

Investigational Drugs or Devices--Drugs or devices that are not FDA approved for marketing. These include drugs or devices for which the FDA has provided either a notice of exemption as an Investigational New Drug (IND), or an Investigational Device Exemption (IDE), as appropriate...

2. Additional Information. If you will be using investigational drugs or devices, the following additional information is required:
a. The drug or device to be used, including the trade and generic name and the manufacturer.
b. If the drug or device is FDA approved, but it will be used outside of its approved labeling, indicate that this is an "investigational use" and give rationale (for example,

route of administration, higher dose level, or treatment of another condition not approved by FDA).

c. FDA compliance. If an investigational new drug (IND) number or an investigational device exemption (IDE) number has been assigned, indicate the number and identify the holder, that is, Principal/or Associate Investigator, Medical Center, or manufacturer.

d. Side effects of the proposed drug or device from previous experience.

e. Dosage rate schedule.

f. Modifications in treatment, if side effects occur.

g. Patient selection, including inclusion and exclusion criteria.

h. Schedule of patient evaluation studies to be performed before, during, and after completing the study.

5. Use of Investigational Drugs. If the investigation concerns human studies of treatment or diagnostic procedures involving the use of medications or radiopharmaceuticals not approved by the FDA, include the approved IND number and the following information about the investigational drug. [5]

(emphasis added).

The overwhelming authority cited above is concisely summarized in a February 18, 1997 memorandum written by Dr. Karen L. Goldenthal of the FDA CBER Office of Biologics, Atch. 12:

> ...if the military is interested in using a vaccine time schedule different from the currently licensed schedule for a mass vaccination effort, then informed consent would appropriate...

The same holds true, presumably, for the military's use of a vaccine for a purpose different from the original licensing, as well as using a different route to administer the vaccine....a fact most recently recognized by the Army in a November 1997 briefing. Atch. 13.

It is abundantly clear that failure to get informed consent from Armed Forces' members prior to the administration of the AVA, an IND, violates federal law and supporting regulations, Presidential Order, and, in the case of the Air Force, service regulations. *An order to submit to the DoD anthrax vaccination program, as it is currently constructed, is therefore illegal.*

D. The DoD Vaccination Program May Violate International Law

1. The AVA program is experimental under FDA regulations.

In Atch. 8, Unproven Force Protection, at 72, Congress said plainly:

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[5] **Note that the AFI is completely consistent with FDA definitions as to what compromises an IND. Of particular note is the text identifying an "investigational use" – use outside of approved labeling, route of administration, higher dose level, or treatment of another condition not approved by the FDA. Obviously, even under Air Force regulations, the AVA is an IND requiring consent from the service member prior to its application.**

> Use of the 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. (emphasis added).

The findings and recommendations of the Congressional report were underscored in a GAO report dated April 29, 1999, entitled *Medical Readiness: Safety and Efficacy of the Anthrax Vaccine*, supra, at Atch. 9. Therein, at 3, the report specifically reveals that *The long-term **safety of the vaccine has not yet been studied.***

The same conclusion was reached in an October 1999 GAO report entitled, *Medical Readiness: **DoD Faces Challenges in Implementing Its Anthrax Vaccine Immunization Program***, p. 8, Atch. 14. The GAO reiterated that the effectiveness of the AVA against inhalational anthrax in humans has not been proven ***as it would be unethical to conduct such studies on humans***. The report continued, noting that while some studies had proven that the vaccine was effective in animals no valid scientific evidence exists to link the results of animal studies to proof of efficacy in humans.

The most significant indictment of DoD's repeated assurances that the AVA is effective against weaponized anthrax is contained in a March 13, 1997 letter from Michael A. Friedman, M.D., Lead Deputy Commissioner, Food and Drug Administration, Department of Health and Human Services (Atch. 15) which plainly said:

> *...there is a paucity of data regarding the effectiveness of the Anthrax Vaccine for prevention of inhalation anthrax.*

Even more troubling to the AVA program is the statement in 21 C.F.R. Part 312.3(b) that an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. Clearly, as evidenced by the 1996 investigational new drug application and the failure to show its effectiveness, the AVA is investigational only and has never been licensed for marketing by the FDA. The AVA is, therefore, experimental and its use falls within the ambit of both the Nuremberg Code, Atch. 16 and 50 U.S.C. §1520a. and 50 U.S.C. §1520a, Atch. 17. Both proscribe, inter alia, the inoculation of military members with the AVA without their prior expressed and informed consent.

1. Nuremberg Code

The Nuremberg Code provides assurance that human beings will not be used as unwilling subjects of chemical or biological experimentation without their specific and informed consent. The Code arose as part of the trials Karl Brandt and others at Nuremberg for crimes against humanity committed in their roles as the Nazi high command.

It is indisputable that such international law is an integral part of United States domestic law, via treaties, executive agreements and customary international law. Paquete Habana, 175 U.S. 677 (1900). And, it is equally well grounded that the Nuremberg Code is a part of our domestic law. See dissent, Gibbons, Circuit Judge, Jaffee v. United States, 663 F. 2d 1226 (3rd. Cir., 1981) (Per the Nuremberg Code, "The international consensus against involuntary human experimentation

is clear;" See also, Annas, GJ., ***Protecting Soldiers from Friendly Fire: The Consent Requirement for Using Investigational Drugs and Vaccines in Combat***, 24 Am. J. Law & Med. 245-260 (1998), Atch. 18.

The Code has ten requirements, but the essence of the Code prohibits medical experimentation on human subjects without their expressed informed consent.

[illegible] declared that the AVA program is nothing more than an experiment. As such, it must meet the requirements of the Nuremberg Code which requires, absent the fully informed consent of military members. See Annas, CG, ***Changing The Consent Rules for 'Desert Storm***, Am. J. Law & Med., Vol. 326, No. 11 at 770 (March 12, 1992).

2. 50 U.S.C. §1520a.

The principles of the Nuremberg Code are codified in 50 U.S.C. §1520a (which also prohibits the Department of Defense from conducting a grand-scale experiment of the AVA drug on its members).

50 U.S.C. §1520a provides in pertinent part:

Sec. 1520a. Restrictions on use of human subjects for testing of chemical or biological agents

(a) Prohibited activities
The Secretary of Defense may not conduct (directly or by contract)
(1) any test or experiment involving the use of a chemical agent or biological agent on a civilian population; or
(2) any other testing of a chemical agent or biological agent on human subjects.

(b) Exceptions
Subject to subsections (c), (d), and (e) of this section, the prohibition in subsection (a) of this section does not apply to a test or experiment carried out for any of the following purposes:
(1) Any peaceful purpose that is related to a medical, therapeutic, pharmaceutical, agricultural, industrial, or research activity.
(2) Any purpose that is directly related to protection against toxic chemicals or biological weapons and agents.
(3) Any law enforcement purpose, including any purpose related to riot control.

(c) ***Informed consent required***
The Secretary of Defense may conduct a test or experiment described in subsection (b) of this section only if informed consent to the testing was obtained from each human subject in advance of the testing on that subject. (emphasis added).

The government's use of a drug that has never been proven effective against preliminary BW anthrax is properly construed as a large-scale test. The fact that the government is attempting to field the drug on a wide scale does not, a fortiori, determine that the vaccinations are routine medical treatment. Indeed, even the anecdotal evidence regarding the questionable safety of the drug dictates otherwise. The informed consent provisions of 50 U.S.C. §1520a, therefore, mandate that the government administer the anthrax drug to military members only after receiving their informed and voluntary consent.

IV. CONCLUSION:

The purpose of this Memorandum has been to clearly delineate the legal requirements surrounding the use of an unproven and unapproved vaccine on members of the Armed Forces. Whatever the original intent of the DoD anthrax vaccination program, its originators and proponents have not followed the law in carrying out the Secretary of Defense's instructions. The legal requirements described in this Memorandum may seem onerous to a military commander worried about the safety of her troops, however, the law provides adequate mechanisms to bypass the regulatory requirements established by the FDA for the protection of American forces in the event a real threat exists.

Simply put, federal law requires certain steps to be taken before the AVA legally can be administered without getting informed consent from service members. DoD has not taken those steps, nor has DoD or any other entity gone to the trouble of getting applicable waivers for the informed consent requirement.

Before Congress takes this matter completely out of the services' hands, a prudent course of action for DoD would be to immediately suspend the AVA program until:

1. Bioport or other suitable contractor secures a full FDA license and approval for marketing of AVA as a prophylaxis against pulmonary anthrax (Note: the DoD is presently seeking a change to those FDA regulations to allow animal surrogate testing, vice the present requirement for two studies, in humans, to prove safety and efficacy. Atch. 19);

2. The Surgeon General designs and implements a scientifically and medically valid and appropriate adverse reaction reporting system for service members presently suffering reactions to the AVA; and

3. The DoD Inspector General, together with the Veterans Administration, openly investigates and reports on all adverse reactions involving Air Force members past and present, to date.

Such a response would cure the current aura of illegality that surrounds the anthrax program orders as well as provide a mechanism for accounting for the variety of reactions that may or may not be related to the vaccine. It is undeniable that certain units have been hit hard by what appear to be adverse vaccine reactions. The situation needs to be fully investigated by competent authorities in an environment free from political pressure to approve the program. The proposed steps will result in a better and efficacious vaccine, and will allow the Air Force to properly deal

with whatever lasting damage has been done to its personnel and its morale as a result of this ill-considered program.

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64 FR 54175, *

FEDERAL REGISTER

Vol. 64, No. 192

Presidential Documents

PRESIDENT OF THE UNITED STATES

Executive Order 13139 of September 30, 1999

Title 3 -

The President

Improving Health Protection of Military Personnel Participating in Particular Military Operations

Part IV

64 FR 54175

DATE: Tuesday, October 5, 1999

To view the next page, type .np* TRANSMIT.
To view a specific page, transmit p* and the page number, e.g. p*1

[*54175]

By the authority vested in me as President by the Constitution and the laws of the United States of America, including section 1107 of title 10, United States Code, and in order to provide the best health protection to military personnel participating in particular military operations, it is hereby ordered as follows:

Section 1. Policy. Military personnel deployed in particular military operations could potentially be exposed to a range of chemical, biological, and radiological weapons as well as diseases endemic to an area of operations. It is the policy of the United States Government to provide our military personnel with safe and effective vaccines, antidotes, and treatments that will negate or minimize the effects of these health threats.

Sec. 2. Administration of Investigational New Drugs to Members of the Armed Forces.

(a) The Secretary of Defense (Secretary) shall collect intelligence on potential health threats that might be encountered in an area of operations. The Secretary shall work together with the Secretary of Health and Human Services to ensure appropriate countermeasures are developed. When the Secretary considers an investigational new drug or a drug unapproved

for its intended use (investigational drug) to represent the most appropriate countermeasure, it shall be studied through scientifically based research and development protocols to determine whether it is safe and effective for its intended use.

(b) It is the expectation that the United States Government will administer products approved for their intended use by the Food and Drug Administration (FDA). However, in the event that the Secretary considers a product to represent the most appropriate countermeasure for diseases endemic to the area of operations or to protect against possible chemical, biological, or radiological weapons, but the product has not yet been approved by the FDA for its intended use, the product may, under certain circumstances and strict controls, be administered to provide potential protection for the health and well-being of deployed military personnel in order to ensure the success of the military operation. The provisions of 21 CFR Part 312 contain the FDA requirements for investigational new drugs.

Sec. 3. Informed Consent Requirements and Waiver Provisions.

(a) Before administering an investigational drug to members of the Armed Forces, the Department of Defense (DoD) must obtain informed consent from each individual unless the Secretary can justify to the President a need for a waiver of informed consent in accordance with 10 U.S.C. 1107(f). Waivers of informed consent will be granted only when absolutely necessary.

(b) In accordance with 10 U.S.C. 1107(f), the President may waive the informed consent requirement for the administration of an investigational drug to a member of the Armed Forces in connection with the member's participation in a particular military operation, upon written determination by the President that obtaining consent:

(1) is not feasible;

(2) is contrary to the best interests of the member; or

(3) is not in the interests of national security. **[*54176]**

(c) In making a determination to waive the informed consent requirement on a ground described in subsection (b)(1) or (b)(2) of this section, the President is required by law to apply the standards and criteria set forth in the relevant FDA regulations, 21 CFR 50.23(d). In determining a waiver based on subsection (b)(3) of this section, the President will also consider the standards and criteria of the relevant FDA regulations.

(d) The Secretary may request that the President waive the informed consent requirement with respect to the administration of an investigational drug. The Secretary may not delegate the authority to make this waiver request. At a minimum, the waiver request shall contain:

(1) A full description of the threat, including the potential for exposure. If the threat is a chemical, biological, or radiological weapon, the waiver request shall contain an analysis of the probability the weapon will be used, the method or methods of delivery, and the likely magnitude of its affect on an exposed individual.

(2) Documentation that the Secretary has complied with 21 CFR 50.23(d). This documentation shall include:

(A) A statement that certifies and a written justification that documents that each of the criteria and standards set forth in 21 CFR 50.23(d) has been met; or

(B) If the Secretary finds it highly impracticable to certify that the criteria and standards set forth in 21 CFR 50.23(d) have been fully met because doing so would significantly impair the

Secretary's ability to carry out the particular military mission, a written justification that documents which criteria and standards have or have not been met, explains the reasons for failing to meet any of the criteria and standards, and provides additional justification why a waiver should be granted solely in the interests of national security.

(3) Any additional information pertinent to the Secretary's determination, including the minutes of the Institutional Review Board's (IRB) deliberations and the IRB members' voting record.

(e) The Secretary shall develop the waiver request in consultation with the FDA.

(f) The Secretary shall submit the waiver request to the President and provide a copy to the Commissioner of the FDA (Commissioner).

(g) The Commissioner shall expeditiously review the waiver request and certify to the Assistant to the President for National Security Affairs (APNSA) and the Assistant to the President for Science and Technology (APST) whether the standards and criteria of the relevant FDA regulations have been adequately addressed and whether the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request. FDA shall base its decision on, and the certification shall include an analysis describing, the extent and strength of the evidence on the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation.

(h) The APNSA and APST will prepare a joint advisory opinion as to whether the waiver of informed consent should be granted and will forward it, along with the waiver request and the FDA certification to the President.

(i) The President will approve or deny the waiver request and will provide written notification of the decision to the Secretary and the Commissioner. **[*54177]**

Sec. 4. Required Action After Waiver is Issued. (a) Following a Presidential waiver under 10 U.S.C. 1107(f), the DoD offices responsible for implementing the waiver, DoD's Office of the Inspector General, and the FDA, consistent with its regulatory role, will conduct an ongoing review and monitoring to assess adherence to the standards and criteria under 21 CFR 50.23 (d) and this order. The responsible DoD offices shall also adhere to any periodic reporting requirements specified by the President at the time of the waiver approval. The Secretary shall submit the findings to the President and provide a copy to the Commissioner.

(b) The Secretary shall, as soon as practicable, make the congressional notifications required by 10 U.S.C. 1107(f)(2)(B).

(c) The Secretary shall, as soon as practicable and consistent with classification requirements, issue a public notice in the Federal Register describing each waiver of informed consent determination and a summary of the most updated scientific information on the products used, as well as other information the President determines is appropriate.

(d) The waiver will expire at the end of 1 year (or an alternative time period not to exceed 1 year, specified by the President at the time of approval), or when the Secretary informs the President that the particular military operation creating the need for the use of the investigational drug has ended, whichever is earlier. The President may revoke the waiver based on changed circumstances or for any other reason. If the Secretary seeks to renew a waiver prior to its expiration, the Secretary must submit to the President an updated request, specifically identifying any new information available relevant to the standards and criteria under 21 CFR 50.23(d). To request to renew a waiver, the Secretary must satisfy the criteria for a waiver as described in section 3 of this order.

(e) The Secretary shall notify the President and the Commissioner if the threat countered by the investigational drug changes significantly or if significant new information on the investigational drug is received.

Sec. 5. Training for Military Personnel. (a) The DoD shall provide ongoing training and health risk communication on the requirements of using an investigational drug in support of a military operation to all military personnel, including those in leadership positions, during chemical and biological warfare defense training and other training, as appropriate. This ongoing training and health risk communication shall include general information about 10 U.S.C. 1107 and 21 CFR 50.23(d).

(b) If the President grants a waiver under 10 U.S.C. 1107(f), the DoD shall provide training to all military personnel conducting the waiver protocol and health risk communication to all military personnel receiving the specific investigational drug to be administered prior to its use.

(c) The Secretary shall submit the training and health risk communication plans as part of the investigational new drug protocol submission to the FDA and the reviewing IRB. Training and health risk communication shall include at a minimum:

(1) The basis for any determination by the President that informed consent is not or may not be feasible;

(2) The means for tracking use and adverse effects of the investigational drug;

(3) The benefits and risks of using the investigational drug; and

(4) A statement that the investigational drug is not approved (or not approved for the intended use).

(d) The DoD shall keep operational commanders informed of the overall requirements of successful protocol execution and their role, with the support of medical personnel, in ensuring successful execution of the protocol.

Sec. 6. Scope. (a) This order applies to the consideration and Presidential approval of a waiver of informed consent under 10 U.S.C. 1107 and does not apply to other FDA regulations. **[*54178]**

(b) This order is intended only to improve the internal management of the Federal Government. Nothing contained in this order shall create any right or benefit, substantive or procedural, enforceable by any party against the United States, its agencies or instrumentalities, its officers or employees, or any other person.

S WILLIAM J. CLINTON

THE WHITE HOUSE,

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 26 1999

The Honorable Dan Burton
House of Representatives
Washington, D.C. 20015

Dear Mr. [redacted]

Thank you for your interest in the anthrax vaccine. This is in response to your letter dated November 3, 1999, co-signed by three of your colleagues, to Dr. [redacted] Commissioner of the Food and Drug Administration (FDA or the Agency). You raised a number of issues related to the pending license supplement application of BioPort Corporation to produce the anthrax vaccine. Ms. [redacted] Dupont of my staff has had several conversations with Mr. [redacted] of your staff, on November 12 and November 17, 1999, concerning the status of this response. As was explained to Mr. [redacted], the response provided below is based on information available under the Freedom of Information Act (FOIA) and FDA implementing regulations.

Inspections

As you know, BioPort Corporation, (previously known as Michigan Department of Public Health or Michigan Biologics Products Institute), holds a license to manufacture Anthrax Vaccine Adsorbed. FDA has inspected this facility on many occasions during the past decade, identifying a number of deficiencies requiring correction. Your statement that the anthrax vaccine-specific portion of the manufacturing facility was not physically inspected in 23 years is not accurate. A review of inspection reports from 1972 to 1998 shows that Anthrax Vaccine Adsorbed was covered as part of the inspection on 12 separate occasions either by record review, observation of manufacturing areas or interviews with engineering and manufacturing staff. This information was contained in the written testimony of Dr. [redacted] Director, Center for Biologics Evaluation and Research (CBER), before the Committee on Government Reform, Subcommittee on National Security, Veterans Affairs and International Relations, on April 29, 1999. In response to Members' questions, Dr. [redacted] also stated that FDA did conduct inspections for the anthrax vaccine prior to 1996.

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Product Testing and Specifications

FDA agrees that products must be consistently manufactured to meet specifications prior to product approval. FDA review does include product characterization. Because of the complex manufacturing process for most biological products, each lot of the product undergoes thorough testing for purity, potency, and sterility. Manufacturers may release lots of product only after testing is documented. FDA may require lot samples and protocols showing results of applicable tests to be submitted for review and possible testing by the Agency. The anthrax vaccine manufactured by BioPort is subject to lot release, under which a manufacturer may not distribute a lot of product until CBER releases it. The lot release program is part of FDA's multi-part strategy that helps assure biological product safety by providing a quality control check on product specifications.

Anthrax Vaccine Adsorbed Indications

Dr. Zoon's testimony before the Committee on Government Reform on October 12, 1999, stated that the indication is based on risk. She did not state that the anthrax vaccine is indicated only for individuals at risk for cutaneous exposure to anthrax, nor that the use is for a "limited" population. The labeling for the anthrax vaccine product is enclosed. The labeling for Anthrax Vaccine Adsorbed does not mention route of exposure (e.g., cutaneous), per se. Use of the vaccine for protection against both cutaneous and inhalation anthrax exposure is not inconsistent with the labeling for Anthrax Vaccine Absorbed.

The term "paucity of data," used in the 1997, letter to Dr. Stephen Joseph, then Assistant Secretary of Defense for Health Affairs, from Dr. Michael A. Friedman, then FDA Lead Deputy Commissioner, is used to describe the relatively few reported cases of inhalation anthrax in the efficacy trial. Requiring the anthrax vaccine to be returned to an investigational new drug (IND) status will not generate more human efficacy data, as inhalation anthrax in humans is not amenable to study, due to the low incidence and sporadic occurrence of disease in natural settings. It should be noted that in the United States, in this century, only 18 human cases of inhalation anthrax have been reported (Brachman, P.S. Inhalation anthrax. *Ann N Y Acad Sci* 353:83-93, 1980). This low incidence of naturally occurring inhalation anthrax since introduction of the vaccine makes it impossible to duplicate the findings in the Brachman and the Centers for Disease Control and Prevention (CDC) surveillance data of the 1950's to early 1970's. In the past several years, the Department of Defense (DOD)

In the past several years, the Department of Defense (DOD) has concluded that the threat of biological attack is great enough that troops should be considered part of the high-risk population for which this vaccine is an appropriate prophylactic measure. (This information was provided to Chairman Dan Burton, in a response to an August 11, 1999, letter seeking information on vaccines.) You may wish to contact DOD to discuss its risk assessment.

There is presently no basis for concluding that the anthrax vaccine, a licensed product, when used in accordance with current labeling, should be used pursuant to an IND application or, as requested in your letter, that FDA "place the anthrax vaccine back under IND status."

Data to Support Indications and Administration Schedule

There is a misperception that no clinical or scientific studies have been conducted to support the current Anthrax Vaccine Adsorbed-dosing schedule. The currently licensed anthrax vaccine administration schedule was used in the Brachman efficacy trial and CDC IND.

The Brachman et al. trial was used to support the licensure of the anthrax vaccine. This trial was a single-blinded, well-controlled trial conducted in four United States textile mills processing imported goat hair with an "exposed, susceptible, supervised population." The average incidence of anthrax prior to the study was 1.2 cases per 100 employees per year. The dose administration schedule was the same as the currently licensed vaccine dose administration schedule: 0, 2 and 4 weeks; 6, 12, and 18 months, followed thereafter by annual boosters. Of the 1,249 mill workers, 909 individuals participated in the controlled part of the study. Individuals who received neither vaccine nor placebo served as an unvaccinated observational control. A total of 26 anthrax cases occurred during the trial: 21 cutaneous cases and five inhalation cases (four fatal). Of these 26 cases, three (all cutaneous) occurred in anthrax vaccine recipients. One case occurred after two doses, one case occurred 13 months after the third dose (fourth dose not given), and one case occurred five months after the third dose. Five cases of inhalation anthrax occurred at one site (the Manchester, New Hampshire goat hair processing plant) during the trial. Two of the inhalation cases were in the placebo group and three inhalation cases were in the unvaccinated group. No cases of inhalation anthrax occurred in anthrax vaccine recipients.

The efficacy level of 92.5 percent, as presented in the major publication of the efficacy trial (Brachman, et. al., 1962 Field evaluation of a human anthrax vaccine. Am J Public Health. 52:632-645) includes anthrax cases in the vaccine and placebo groups and is not limited to cutaneous anthrax cases. The efficacy of the anthrax vaccine in this study was calculated to be 92.5 percent. This calculation (92.5 percent) is sometimes erroneously presented as the vaccine efficacy against cutaneous anthrax.

Following the 1957 trial and the five cases of inhalation anthrax in placebo and unvaccinated individuals, the Manchester, New Hampshire goat hair processing plant vaccinated all employees against anthrax (starting in December 1957). The case rate in this plant fell from 8.2 cases per year prior to 1957 to 0.4 cases per year from December 1957 to June 1966, the latter consisting of four cutaneous cases. In July 1966, an employee (unvaccinated) of an adjacent facility (metal fabricator shop) died from inhalation anthrax. The source of the agent was thought to be the adjacent goat hair processing plant. In a follow-up investigation by CDC (January 30 - February 6, 1967), environmental sampling of both facilities identified *B. anthracis* inhalation anthrax (LaForce FM et al.: Epidemiologic study of a fatal case of inhalation anthrax. Arch Environ Health 18:798-805, 1969).

Under CDC IND, approximately 16,000 doses of the vaccine were administered to approximately 7,000 study participants who were at risk for anthrax. These doses were administered according to the same six-dose schedule that is the approved dosing schedule today.

Furthermore, in CDC surveillance data (1962-1974), 27 cases of anthrax occurred in "at-risk" industrial settings: 24 cases in unvaccinated individuals, one case after one dose of vaccine and two cases after two doses of vaccine. No cases of anthrax were reported in individuals who received all six doses of anthrax vaccine.

It is interesting to note that CDC publication, *Biosafety in Microbiological and Biomedical Laboratories 4th Edition* (1999), states that laboratory associated cases of anthrax have not been reported in the United States since the late 1950s when the human anthrax vaccine was introduced. Before that date, numerous cases of laboratory associated anthrax, occurring primarily at facilities conducting anthrax research, were reported.

Additional Findings Supporting Anthrax Vaccine Adsorbed

The Public Health Service Act, under which biologicals such as vaccines were licensed in 1970, requires evidence of safety, purity and potency. After the Division of Biologic Standards was transferred from the National Institutes of Health to FDA, expert panels were assigned to review information on biological products, including vaccines that had been licensed prior to the transfer. The review was initiated in order to assess the safety, effectiveness and labeling of products licensed prior to July 1, 1972. Based upon their review of available data, the Advisory Review Panel recommended that marketing of Anthrax Vaccine Adsorbed manufactured by Michigan Department of Public Health be allowed to continue based upon substantial evidence of safety and effectiveness of the product. The safety data from CDC IND, as well as the efficacy data from the Brachman et al. trial, and CDC surveillance data (1962-1974) from "at-risk" industrial settings were the basis for these findings. These findings were published in the Federal Register of December 13, 1985.

Furthermore, data from a well-controlled monkey study has become available since the time of the 1985 Panel report. The efficacy of the Anthrax Vaccine Adsorbed licensed for use in humans also was tested in rhesus monkeys challenged by an aerosol of virulent Bacillus *anthracis* spores. The data from this study suggests vaccine efficacy against inhalation anthrax. It should be noted that monkeys are quite similar to humans with regard to the clinical course and pathological findings following inhalation anthrax.

While these studies cannot prove that the vaccine would be 100 percent effective in a terrorist or wartime situation, they are the only known data on pre-exposure protection currently available against inhalation anthrax.

DOD Vaccine Administration Schedule

In the September 29, 1999, letter to Dr. [redacted] Assistant Secretary of Defense Health Affairs, Dr. [redacted], Director, CBER, stated in the final paragraph, "We reiterate our previous statement made to DOD on December 16, 1997, that FDA approval of the anthrax vaccine is based on the six-dose regime found in the approved labeling. Because we are unaware of any data demonstrating that any deviation from the approved intervals of doses found in the approved labeling will provide protection from anthrax infection, we strongly recommend that the Anthrax Vaccine Immunization Program follow FDA-approved schedule." Similar information was included in a letter dated

September 28, 1999, to Dr. [redacted] from Dr. [redacted]
Copies of both of these letters are enclosed.

DOD has conducted a pilot study, under a BioPort IND, to evaluate several dosing schedules and routes of administration for the anthrax vaccine. This pilot study used full informed consent. The pilot study evaluated anti-protective antigen antibody levels in vaccines. One purpose of the pilot study was to evaluate the feasibility of eliminating the week two dose as well as to evaluate differences between the subcutaneous and intramuscular routes of administration. This pilot study was intended to select a dosing schedule(s) for further evaluation in a larger, comparative, statistically definitive study to potentially support a change in the label. In December 1998, DOD met with FDA representatives to discuss such a study. To date, DOD has not yet submitted a definitive study protocol to evaluate and potentially support a change in the dosing schedule for the anthrax vaccine.

Product Expiration Dating

The expiration date of a biological product may be changed pursuant to Title 21, Code of Federal Regulations (CFR) 5610.50, Date of Manufacture, which states in part that the date of manufacture shall be the date of initiation by the manufacturer of the last valid potency test. As stated in 21 CFR §610.53 (b), the dating period for a product shall begin on the date of manufacture, as prescribed in section 610.50. A valid potency assay is required prior to an extension of dating. The expiration date is based on the last valid potency assay.

BioPort's License Application

The content of license applications under FDA review, including the number and characterization of lots, are not releasable under FOIA. Please be assured, however, that FDA will not approve an application until a manufacturer demonstrates that a product can be consistently manufactured under current good manufacturing practices (cGMPs) to meet product specifications. Lots manufactured to support a license application or supplement cannot be sold without approval of the application or supplement and remain subject to FDA lot release requirements as described above.

Proposed rule

In response to your comments on the proposed rule for animal studies, FDA agrees that there needs to be a scientifically verifiable extrapolation from animal data. FDA's Proposed Rule, "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted," was published in the October 5, 1999, Federal Register. The docket is open for comment until December 20, 1999. Your letter will be forwarded to the docket so that your comments regarding the proposed rule can be entered into the docket for consideration. After the comment period has closed, FDA will review the comments and determine the appropriate next step in the process. At this time, there is no date for publication of a final rule.

We trust this information responds to your concerns. If you have further questions, please let us know. A similar response has been provided to your co-signers.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

3 Enclosures
"Package Labeling for Anthrax Vaccine Adsorbed"
"September 28, 1999 letter to Dr. [redacted] Assistant Secretary of Defense Health Affairs, from Dr. [redacted] Commissioner, FDA"
"September 29, 1999, letter to Dr. [redacted] Assistant Secretary of Defense Health Affairs, Dr. [redacted] Director, CBER"

cc: Dockets Management Branch