Bernard A. Schwetz, D.V.M., Ph.D.
Acting Principal Deputy Commissioner
Food and Drug Administration
5600 Fisher's Lane
Rockville, Maryland 20857

RE: ANTHRAX VACCINE

Dear Commissioner Schwetz:

I am extremely concerned that the Anthrax Vaccine Adsorbed ("AVA"), which has never been proved safe or effective for its current use, continues to be administered to United States and National Guard military personnel. This policy forces able, loyal, highly-trained military personnel to put at risk either their health or their careers. The Commissioner of the Food and Drug Administration ("FDA") has jurisdiction over the anthrax vaccine's distribution and the manufacturing of the drug, including authority over Bioport's site and product license. Bioport is the sole manufacturer, as well as the distributor of the AVA. As the Commissioner of the FDA, you further have the authority to declare the AVA an Investigational New Drug which would have the effect of requiring the Department of Defense to comply with federal law. For the reasons highlighted in this letter, I urge you to do so.

The United States Government so far has refused to recognize or appreciate the danger and the personal dilemma it imposes on military personnel, despite repeated concerns expressed about administering an unlicensed drug never proved safe or effective for humans. In part, my letter is spurred by the experience of current and former Connecticut Air National Guard Pilots, including Major Russell Dingle and Major Thomas Rempfer, who resigned from the Guard in 1999 rather than receive the anthrax vaccination, which they believe poses a serious health risk to them and their fellow members of the military.

Their concerns are justified. The safety and efficacy of the Anthrax Vaccine Adsorbed ("AVA") in current use has, over the past two years, been subject to close scrutiny by the military, medical, and scientific community. Recognizing the seriousness of the issue, the House Subcommittee on Government Reform initiated nine public hearings, eliciting information that both the Food and Drug Administration ("FDA") and the military do not consider the AVA in its current use to be either safe or effective. More specifically, because the AVA is used in a way inconsistent with both its original licensing and for a purpose for which it has never been tested, the vaccine is properly considered as an Investigational New Drug ("IND") under Food and Drug Administration regulations 21 U.S.C. § 321 and may not be used on humans without their specific

and informed consent. Unfortunately, and directly contrary to law, the AVA is being administered to military personnel under threat of imprisonment, loss of pay and discharge. In effect, the military is forcing its personnel to serve as human guinea pigs for an unlicensed drug that has not been proved to be safe or effective.

More than a year ago, I first asked the Department of Defense and other federal agencies to stop this illegal vaccination program for the good of the military personnel who are personally affected and for the benefit of all the citizens of the United States. Unfortunately, replies from the DoD and from the FDA under the prior Administration to my repeated requests were cursory and unresponsive.

On December 27, 1999, I wrote to Secretary of Defense Cohen asking him to suspend the Anthrax Vaccine Immunization Program ("AVIP") (Exhibit A). In response to my request Principal Deputy Assistant Secretary Charles L. Cragin wrote that "the threat of biological warfare using anthrax is real." In reply to my concern that this federal program could subject the states to liability, he stated that "medical care and compensation for injuries or illnesses incurred by members of the National Guard in the line of duty incident to federal requirements are provided for by the Federal government under titles 10 and 37 of the United States Code" (Exhibit B). Assistant Secretary Cragin did not, however, provide any specific provision or make any specific assurance that the federal government would care for and compensate members of the National Guard who suffered adverse effects from the anthrax vaccine.

On February 17, 2000, the Congressional Subcommittee on National Security, Veterans Affairs and International Relations issued a report critical of AVIP. Citing to the Congressional Report, I wrote to Assistant Secretary Cragin on April 5, 2000 expressing my further concerns with the vaccination program (Exhibit C) to which he replied in an undated letter received on May 10, 2000 (Exhibit D). Assistant Secretary Cragin's second letter was more specific, but did not contain any assurances that Connecticut's National Guardsmen would be compensated for injuries they suffered from the AVA.

In my May 4, 2000 letter to Jane E. Henney, M.D., Commissioner of the Food and Drug Administration, I expressed further concerns regarding AVIP (Exhibit E) and received a reply in early June 2000 from Dr. Kathryn Zoon, Director of the Center for Biologics Evaluation and Research (Exhibit F) addressing some of the points in my letter to her. However, Dr. Zoon did not answer all of my questions citing "regulations concerning the confidentiality of information for an unapproved biological process." Her conclusion that "to date, no evidence has been noted by the FDA that AVA is not safe and effective when used in accordance with the prescribed labeling" is not a satisfactory response in view of the lives and careers that are at stake. Withholding relevant information is not helpful to the process of building public confidence.

Despite the federal government's past stonewalling and its apparent efforts to avoid and evade the truth and the law -- prior to the current Administration -- I am sending this letter to you to highlight important information regarding the AVA's questionable safety and efficacy and the lack of legal authority surrounding its use in the AVIP. The plain fact is that the AVA is still an investigational drug and should not be used without appropriate informed consent.

I. BACKGROUND

Anthrax is a bacterial disease caused by Bacillus anthracis. There are three types of anthrax diseases: (a) Cutaneous Anthrax caused by contact with infected animals or contaminated animal products; (b) Gastrointestinal Anthrax caused by ingestion of contaminated meat; (c) Inhalation Anthrax caused by inhalation of anthrax spores. There are two types of AVA available for human use: (a) a live attenuate spore vaccine (used in the Soviet Union); and (b) a protective antigen vaccine, using filtrates of attenuated strains of anthrax bacillus. (Developed in the United States and the United Kingdom).

As early as the 1950's, the first field trial of a human anthrax vaccine known as the Brachman Study was conducted on workers at four goat-hair processing mills. In 1965 a patent was granted to the U.S. Army for an anthrax antigen. An application for a license was submitted to the National Institute of Health ("NIH") in 1967 by the Michigan Department of Public Health ("MDPH") which had at that time set up a facility to manufacture the vaccine. The application was made two years before there was any licensure requirement of proving safety and efficacy. Michigan Biologics Products Institute ("MBPI") obtained the license for the AVA from MDPH and in 1970 obtained approval for the AVA from the National Institute of Health Bureau of Biologics. MBPI was purchased by Bioport Corporation in 1998 and MBPI/Bioport is the sole producer of the anthrax vaccine today. MDPH's 1970 application for a license was approved by the Department of Health, Education and Welfare without proof of efficacy or safety and this is the only valid product license and remains controlling in the present day. However, the original license was obtained only for agricultural and veterinary settings as protection against cutaneous (skin) contact anthrax.

Recent developments in biological warfare have increased the risk a hostile force may disseminate Anthrax as a weapon against military or civilian populations. Fearing the potentially devastating effects of an attack on a unit in the field, the military became interested in providing its personnel protection against Anthrax, but had used the vaccine only sparingly until the Gulf War. "Despite having been licensed for almost 30 years, the vaccine had not been widely used prior to the Gulf War." (The Department of Defense Anthrax Vaccine Immunization Program: Unproven Force Protection. Fourth Report by the Committee on Government Report, 106th Congress, 2nd Session, House Report 106-556, p. 34, "House Report.") On September 20, 1996, after thousands of troops had been inoculated during the Gulf War, Michigan Biologics Products, Inc. ("MBPI") applied to the FDA to approve the old vaccine for a new use; the

prevention of inhalation anthrax. No approval was given. Despite the FDA's failure to approve the vaccine for inhalation anthrax, on December 15, 1997, May 18, 1998, and March 30, 1999, Secretary of Defense Cohen issued directives requiring all U.S. military personnel to be vaccinated with AVA against inhalation anthrax.

Secretary of Defense Cohen's vaccination plan was based on the prior allegedly successful completion of all testing and operational criteria. This testing did not include controlled drug trials on humans. Secretary Cohen's original plan was for the entire force including all new service members to begin receiving the six shot series of the anthrax vaccination in a phased immunization program with full vaccination by 2003.

However, under threat by the FDA of having its site license suspended, Bioport has stopped production of the Anthrax Vaccine. Since the cessation of production, the shortage of newly manufactured vaccine has become severe. To make matters worse and further imperil the safety of military personnel, the FDA has continued to approve for military use certain older batches, or "lots," of the vaccine. Some of these batches or lots are 9 years old whereas the normal life of the vaccine is three years.

II. THERE ARE FOUR REASONS WHY THE CURRENT USE OF THE AVA BY THE DOD IS ILLEGAL.

The current use of AVA is illegal for four reasons: 1) The Anthrax vaccine has not been proved safe and effective for its intended use in that the AVA has never been licensed for protection against inhalation anthrax; 2) The vaccine is not being manufactured in accordance with either its site license or product license; 3) The vaccine is not being administered according to the license; and 4) Since the Anthrax vaccine has not been tested on humans there is no basis for concluding that it is safe and effective.

A. <u>The Anthrax vaccine has not been proved safe and effective for its intended use</u>.

The FDA's underlying prerequisite for the approval of any vaccine or drug is that it be proved safe and effective for its intended use. As described below, the use of the AVA as currently formulated and manufactured has never been proved safe and effective for the purpose of protecting humans against infection following inhalation of anthrax spores. Indeed, it is not licensed for this purpose. In 1972, amendments to the Food Drug and Cosmetic Act ("FDAC") required that drug effectiveness claims be supported by evidence consisting of adequate and well-controlled investigations, including clinical investigations. Before then, proof of safety and effectiveness was not required; therefore, AVA's license by the DBS (Division of Biological Standards) in 1970 was granted under old law and transferred to Bioport without any necessity that it meet current standards of proof of safety and effectiveness. Biologics, such as vaccines, were not subjected to formal efficacy review requirements when the AVA was licensed. In 1972,

authority for the administration of the drug provisions of the FDAC Act for all biological products was transferred to the FDA which in 1973 promulgated regulations implementing effectiveness requirements for all biological products, including vaccines.

As you know, licensing by the FDA is a four step process in which a drug goes through phases of pre-clinical review, testing as an Investigational New Drug ("IND"), a product license application procedure and finally, a post-licensure state. See 21 C.F.R. § 312. An IND is defined as a "new drug or biological drug that is used in a clinical investigation." 21 C.F.R. § 312.3(b). If a pharmaceutical company intends to conduct a clinical trial with an investigational new drug, it must submit an IND application to the FDA. Id.

The clinical investigation of a previously untested drug is usually divided into three phases. Phase 1 studies are the closely monitored introduction of the investigational drug into humans. These studies are designed to determine side effects, metabolism, pharmacological action, and if possible, effectiveness. Phase 2 consists of controlled clinical trials to determine the effectiveness of the drug for the particular indication being studied. During Phase 3 studies the number of subjects is expanded to several hundred or several thousand. These studies are performed to gather additional information about safety and effectiveness, after initial evidence of efficacy is obtained.

A drug that has reached the investigational phase of testing is at that point defined by the FDA as a "new" drug. "New" drugs include previously licensed drugs if the application is for a change in the purpose for which the drug will be used. See U.S. v. Articles of Drug Consisting of the Following: 5906 Boxes, 745 F.2d 105 (1st Cir. 1984). Pursuant to these requirements, on September 21, 1996 MBPI filed an investigational new drug application with the FDA which identified three areas where the current license should be modified, showing a new designation for "inhalation anthrax", changing the "route of administration" and changing the "vaccination schedule." IND Application (September 20, 1996). The significant changes in the proposed designation of the use for AVA and the vaccination schedule, as well as the route of administration, make the AVA currently in use by the military an unapproved "new" drug and an IND because its manufacturer has initiated an application for a new use of an existing drug including a change in formula, dilution or repackaging.

The AVA was licensed in 1972, and its efficacy against cutaneous (through the skin) anthrax was allegedly affirmed in 1985. However, the AVA has never been approved for prevention against inhaled anthrax and its effectiveness in preventing inhalation anthrax has never been assessed. Bioport's 1996 Investigational New Drug request is still pending before the FDA and as of today, your Agency has not approved the AVA for the purpose of preventing inhalation anthrax. The current IND process requires the submission of controlled studies proving that the drug is safe and effective for the proposed new use. No such studies have been conducted on the

AVA. Furthermore, such controlled studies of a new drug pursuant to an IND application cannot be conducted on human subjects without their informed consent.

On March 4, 1997, Stephen C. Joseph, M.D., M.P.H., the Assistant Secretary of Defense for Health Affairs wrote to Michael A. Friedman, M.D., the lead Deputy Commissioner of Food and Drugs at the FDA seeking permission to use the existing licensed AVA "to protect U.S. Forces against the threat of an Iraqi biological warfare attack with Anthrax." Notwithstanding that only eighteen months earlier the Department of the Army had written to MBPI recognizing that the existing license did not indicate the use of the Anthrax vaccine against aerosol exposure, and that further studies were needed to accomplish that goal, Dr. Joseph stated in his letter that "while 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 anthrax. . . Please advise whether the FDA has any objection to our interpretation of the scope of the licensure for anthrax." On March 13, 1997, Michael A. Friedman, M.D., then the lead Deputy Commissioner at the Food and Drug Administration replied to Dr. Joseph, writing that there "is a paucity of data regarding the effectiveness of Anthrax Vaccine for prevention of inhalation anthrax." Dr. Friedman wrote that despite the lack of proof that the vaccine was effective against inhalation anthrax its use for those purposes "is not inconsistent with the current label."

In his very short letter, with a stroke of the pen, Dr. Friedman wiped out ten years of DoD analysis and 25 years of FDA law designed to protect the safety and well being of the citizens of the United States. There was no justification, legal, scientific or otherwise for this action. For example, the Deputy Director for Science and Public Health of the Centers for Disease Control and Prevention stated on December 14, 1999, that: "Although the current anthrax vaccine has been shown to be effective in preventing the cutaneous form of anthrax, CDC is neither aware of definitive data that demonstrates that vaccine's ability to protect against inhalation form of this disease in humans, nor are we aware of any data relative to the efficacy of this vaccine in humans exposed to genetically altered Bacillus anthrax strains."

The current vaccine's safety is in as much question as its efficacy. In a study, conducted in the 1950's in goat hair mills, volunteers receiving AVA were checked at 24 and 48 hours after vaccination. There was no active follow-up for side effects after that time. Based on this study, wholly inadequate by today's standards, the package insert lists a systemic side effect rate of 0.2%. However, two unpublished DoD vaccine studies cited by the Government Accounting Office (of the current vaccine) had systemic side effect rates of 43% and 48%, over 200 times higher than expected, according to the package insert. This alone should have triggered an investigation and vaccine recall according to Dr. Meryl Nass, a physician who has followed the anthrax vaccine closely. Dr. Nass has gone on to state, "There is not a single published study of the efficacy or safety of the current vaccine in humans. There are a number of unpublished studies which give short term systemic reaction rates of 20% to 50%, but no long term rates." (Prepared statement of Dr. Meryl Nass, NSVAIR Anthrax hearing (II) p. 102). See House Report at 38.

The Institute of Medicine's Committee on Health Effects Associated With Exposure During the Gulf War, in response to a DoD request, provided DoD with a letter entitled, "An Assessment of the Safety of the Anthrax Vaccine" on March 30, 2000. The Institute, after examining the literature, was unable to conclude that the vaccine was free from long term health risks. "The Committee concluded that in the peer reviewed literature there is inadequate/insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long term adverse health outcomes." According to the House Report (House Report at p. 41), "Studies have not been performed to evaluate the effects of AVA on carcinogenesis, mutagenesis or impairment of fertility." Because the vaccine is still investigational, the military must seek informed consent from each individual who is to be given the vaccine. However, it is undisputed that service members are not being asked to give their informed consent to the vaccination process. Instead and incredibly, refusal to take the vaccination is treated as insubordination with imprisonment, loss of pay or discharge from the military.

B. <u>The vaccine is not being manufactured in accordance with either its site license or product license</u>.

The method of manufacturing a drug is controlled by both a product license and a site license. The product license sets out the chemical composition of the vaccine. The site license is a second procedure which regulates the actual methods used by the manufacturer to operate its production line. Bioport has repeatedly failed FDA site inspections and in March of 1997 the FDA warned Bioport that its site license would be revoked if Bioport did not correct long-standing and significant deficiencies in the production process. Bioport responded by suspending production. No new AVA has been produced since 1997. Bioport has continued to fail FDA inspections. Although it nominally has a site license, it has yet to show the FDA that it produces AVA within the terms of its site license.

The concepts of site license and product license merge in considering AVA's status as an IND. To the extent that Bioport is not complying with its site license, the vaccine produced at the plant is not the same composition as the product license requires. Where violations of a site license are as extensive as those detailed below, the issue becomes not just compliance with good manufacturing processes but it results in the actual production of a vaccine that is different from the one currently licensed. The FDA has documented numerous violations in the manufacturing of AVA: organization and personnel, buildings, facilities, equipment controls, laboratory controls and records and reports, according to a 1996 report. Some of these same areas were criticized by the FDA in 1997, 1998 and 1999 reports as well. Four fermenters, major pieces of equipment used to formulate the vaccine, were not approved in advance in 1990 by the FDA. The new equipment was made of stainless steel, and was not glass-lined as the originals were. Some lots of the vaccine were not properly labeled, a potential violation of federal law, and one lot's shelf life was extended after it had expired.

According to a 1998 inspection report, "Prior to August 1997, the filters used for harvest on anthrax vaccine were neither validated nor integrity tested. This filter is the sterile filtration step in the anthrax manufacturing process. Filters are used to keep the impurities out of the drug." Responding to complaints about the quality of the vaccine in February 1998, the FDA found that, "the manufacturing process for anthrax vaccine is not validated." "Based on my readings of the 1997 and 1998 inspection reports of MBPI, this is a company that is completely out of control, and they should not be producing medicinal products for human use" said Sammie R. Young, a retired FDA inspector and supervisor for 29 years. Young said he became interested in the FDA inspection of the manufacturers after reading about the dispute over the drug's safety and effectiveness. Young also said, "It appears from the [1996, 1997 and 1998] FDA inspection reports, [MBPI] did not conduct their manufacturing operations in accordance with current good manufacturing practices which guarantee the safety, purity, and potency required under the federal Food, Drug and Cosmetic Act and its related Public Service Act." House Report.

Rather than fix the problem, MBPI sold its AVA license to Bioport in September of 1998 for $25 million. Bioport is the sole manufacturer of the AVA and the DoD is their only customer. The "DoD and the sole vaccine maker are locked in a mutually dependent relationship." (p.2-3 House Report) "The concern I have about the FDA," said U.S. Representative Christopher Shays, "is that they treat Bioport as vigorously as any other vaccine maker, and not show favoritism because the company is the Defense Department's captive customer."

In December 1999 Bioport again failed FDA inspection required to certify its production of AVA. It has yet to receive approval to restart production of the vaccine. All vaccine in current use is from lots manufactured as much as nine years ago.

Bioport also produces AVA under a different procedure and the AVA is apparently chemically different than the original vaccine approved by NIH. However, Bioport has not correctly informed the FDA of changes in the process by which it produces the AVA, nor have they received proper approval for the continuation of their production of the vaccine in light of the changes they have made. They are required by 21 C.F.R. 601.12 to gain prior approval before a product is distributed after a major manufacturing change. A manufacturing change is defined by 21 U.S.C. 356(a) and 21 C.F.R. 601 which classifies major change as that "which has the substantial potential to adversely affect the identity, strength, quality, purity, or potency" of the drug as they may relate to the safety and effectiveness of a drug. Id. Also, 21 U.S.C. 356(a) requires that a drug made with a major manufacturing change not be distributed until the Secretary approves the application.

The original AVA production line consisted of glass-lined fermenters, a glass-lined chill tank, and sintered glass filters. In a June 14, 1990 letter from John R. Mitchell, Chief of the Division of Biologic Products at the Michigan Department of Public Health to the Director for Biologics Evaluation and Research of the FDA, Mitchell states that "on or about August 15,

1990, we will be replacing the existing ____ fermenter and chill tank in the anthrax vaccine facility with a new ____ fermenter and chill tank from ____."[1/] A conversation record of Rebecca Devine of the FDA (Conversation Record, July 9, 1990) confirms that she informed Dr. Robert Myers, Dr. Mitchell's successor, that MDPH's letter of June 14, 1990, announcing use of a new fermenter constituted a "major" change. In a December 6, 1990 letter from Dr. Myers to Dr. Gerald Quinnan of the FDA, Dr. Myers confirmed that the new fermenters had been installed.

The two production lines added in 1990 consist of stainless steel fermenters, stainless steel chill tanks, and low-protein-binding nylon membrane filters. There was an amendment request which did indicate that stainless steel equipment was being used as opposed to the originally licensed glass-lined equipment, but it failed to identify this as a change in equipment type for the additional production lines.

The lack of information left the FDA unaware of the substantial potential of the amendment request to have an adverse effect on the safety and effectiveness of the product. Furthermore, that request was not approved as of 1996, five years after the steel equipment had been implemented. The differences in fermenters, chill tanks and filters is a significant issue due to the fact that since the steel tanks have been used, researchers have found the product produced in the stainless steel containers to be more potent than that in the glass-lined containers. And further, the product that comes from the fermenters is just a preliminary product, it is then stored in lots in bulk. The product from the steel containers is mixed with that of the product from the glass-lined containers when the lots are collected in bulk. Therefore, the more potent product from the new manufacturing process is mixing with the less potent product approved by the NIH making all batches of the product more potent than their license allows them to be.

An on-site review of the BioPort facility released as of February 26, 1996, shows that two fermenters had not been approved yet through the ELA amendment request. These fermenters were the two steel fermenters from 1991. This means that every dose delivered since the 1990 manufacturing change has occurred without an ELA amendment for the change in two fermenters installed in 1991 and without an amendment for the change in filter type. See Report of February 12-16 trip to MDPH, February 26, 1996.

The conductor of the review, James Kenimer commented: "The unreported changes are of particular concern and MDPH should place the highest priority on updating their establishment and product licenses. For example, we are told that the establishment license has not been supplemented to include the two new anthrax fermenters placed in service in 1991, if a subsequent FDA inspection were to uncover significant instances of unreported changes, I think severe consequences would be expected."

1/ This letter was redacted before it was released to the public.

It is clear, therefore, that aside from the fact that the current AVA is an unapproved investigational drug, there are also serious quality control issues with the vaccine that was produced at Bioport's Michigan plant.

C. <u>The vaccine is not being administered according to the license</u>.

Finally, the AVA is not being administered according to the provisions of the existing license because the drug is being injected subcutaneously rather than intermuscularly. This change is significant because 21 C.F.R. § 312 provides that a part of a Product License Application process includes the regime for administering the drugs. By changing this regime, the DoD is engaging in a new use of the AVA.

The new use of the AVA that is not in accordance with its product labeling renders the AVA investigational under FDA regulations and makes the AVA a drug subject to the requirements of 10 U.S.C. § 1107 and subject to the consent of those to whom it is administered.

D. <u>Since the Anthrax vaccine has not been tested on humans there is no basis for concluding that its use is safe and effective for prevention of inhaled anthrax</u>.

As discussed above, the FDA has an established procedure prior to allowing a drug to be labeled "safe and effective." An important component of the procedure for demonstrating that a drug is safe and effective for humans is to conduct human testing. The FDA requires the following steps: (a) Studies are initiated in animals to define a safe and effective dose; (b) Results are submitted to the FDA and acceptance allows for human studies; (c) Human studies are designed to demonstrate safety and efficacy in the investigational product; (d) Two adequate, well controlled studies are necessary to demonstrate the efficacy of the product in humans.

Because exposing humans to a potentially lethal substance would be unethical and immoral, such testing has never been done on the AVA. Thus, the vaccine has never advanced beyond the investigational stage. Absent human testing, there can be no claim by the FDA that the AVA is anything but an Investigational Drug. This fact is recognized by the vaccine's manufacturer, Bioport, in its IND application, which is still currently pending. It is also evidenced 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 for the AVA, federal statutes, and federal case law, all point to the inescapable determination that the AVA is an IND and it is currently and illegally being used on members of the Armed Forces without their consent.

III. THE DEPARTMENT OF DEFENSE IS ADMINISTERING THE AVA EVEN THOUGH IT IS AWARE OF THE VACCINE'S UNTESTED EFFICACY.

The Department of Defense itself has on several occasions recognized the legal limits on the military's ability to use the AVA. On May 16, 1985, the Department of the Army issued a Request for Proposals ("RFP") No. DAMD17-85-R-0078 for the "Production of a live bacillus anthracis spore vaccine for human use." The first narrative paragraph of the RFP shows the army's belief that the vaccine available as of 1985 was not effective against inhalation anthrax. The RFP states "there is no vaccine in current use which will safely and effectively protect military personnel against exposure to this hazardous bacterial agent [Bacillus anthracis]." Document No. DAMD17-85-R-0078 at page four. Ten years later, on October 5, 1995, Anna Johnson-Winegar, Ph.D., Director of the Medical Chemical and Biological Defense Research Program of the Department of the Army wrote to Robert Myers, Ph.D., the Chief of Biologic Products of MBPI, once again recognizing that the anthrax vaccine needed further studies in order to expand the indication for its use to include protection from aerosol exposure.

The issue is not whether the vaccine can be used. The issue is whether it can be administered to military personnel without their informed consent. An IND cannot be used on military personnel without informed consent unless specific legal requirements as outlined in Executive Order 13139 and 10 U.S.C. § 1107 (1999) have been met. The military has sought changes in FDA regulations which would allow for a drug or vaccine intended to protect against biological warfare to be exempt from the requirement of human testing, but these changes have not been approved or implemented.

IV. THE PROBLEMS INHERENT IN TESTING THE ANTHRAX VACCINE ARE NOT UNIQUE, BUT RATHER ARE SHARED BY A NUMBER OF DRUGS OR VACCINES INTENDED TO COMBAT BIOLOGICAL OR CHEMICAL WARFARE.

The FDA is well aware of the problems involved in granting an IND when a drug cannot be tested on humans. On October 5, 1999, the FDA issued a Notice of Proposed Rulemaking ("NPRM") to change the licensing requirements for biowarfare drugs and vaccines. In testimony before Congress on November 9, 1999, William Raub, Ph.D., HHS Deputy Assistant Secretary for Science Policy explained that new regulations were needed in the case of investigational drugs intended to counter the "toxicity of chemical, biological, radiological or nuclear substances which could not be tested ethically on humans." Dr. Raub testified that the rules for human testing should be changed to allow testing on animals alone. 21 C.F.R. §§ 314, 126. This is direct recognition by the FDA that the current procedures do not allow approval of an investigational drug which cannot be tested on humans.

V. CONCLUSION

This letter only highlights the substantial evidence which led the Committee on Government Affairs to recommend suspension of the AVIP Program. Mandatory vaccination of troops with a biologic product not licensed for its current use violates the FDAC Act and 10 U.S.C. § 1107. I call upon the FDA to cease and desist from its illegal conduct, renounce Dr. Friedman's March 13, 1997 letter which illegally cleared the way for the DoD to begin the mass inoculations, declare the Anthrax Vaccine Adsorbed (AVA) an Investigational New Drug (IND) and block its manufacture and sale by Bioport and its illegal use by the Department of Defense.

If you have any questions please feel free to contact me or Assistant Attorneys General Arnold I. Menchel or Jennifer S. Bard at (860)808-5355.

Very truly yours,

RICHARD BLUMENTHAL

RB/JSB/ll
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Attachments

APPENDIX

The Relevant Statutes

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:

(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 to be provided to a member under subsection (a)(1) shall be provided before the **investigational new drug approved 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 unapproved for its applied use.

(2) The reason 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 unknown 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 interest of the member; or

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

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 of 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 C.F.R. 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 supplied).

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 chemical 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 C.F.R. 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 using these procedures:

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:

The drug or device to be used, including the trade and generic name and the manufacturer.

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).

a. 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.
b. Side effects of the proposed drug or device, from most common to rarest.
c. Dosage rate schedule.
d. Modifications in treatment, if side effects occur.
e. Patient selection, including inclusion and exclusion criteria.
f. 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. (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 AV is an IND requiring consent from the service member prior to its application.

(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,

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> ...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 be 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.

It is abundantly clear that failure to get informed consent from Armed Force's members prior to the administration of the AV, 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.