Time Line: Development and use of the Anthrax Vaccine and the Anthrax Vaccine Immunization Program

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1. **January 1955**. An anthrax vaccine supplied by the U.S. Army Chemical Corps was used in the first human field trial. During this clinical trial five workers contracted inhalation anthrax and four died in the first anthrax epidemic of the 20th Century.[1]
2. **September 1965**. A human anthrax vaccine patent was awarded to Milton Puziss and George Wright, representing the U.S. Army.[2] (The vaccine described in this patent was materially different from the vaccine used in the 1955 to 1959 New Hampshire field trial.)
3. **July 1967**. An application is made with the Health Education and Welfare's Division of Biologic Standards to license an anthrax vaccine based on the patented vaccine production method.[3]
4. **July 1967**. First required annual progress report submitted to the Division of Biologic Standards.[4]
5. **February 1969**. The Division of Biologic Standards recommended license approval, but noted that clinical data establishing efficacy had not been submitted and requested data be gathered to establish efficacy.[5]
6. **November 1970**. The Division of Biologic Standards approved the anthrax vaccine.[6]
7. **February 1972**. Final Progress Report on the anthrax vaccine was submitted to the Division of Biologic Standards.[7] (Data establishing efficacy of this vaccine as requested in February 1969 had yet to be generated, collected, submitted or reviewed by the Division of Biologic Standards.)
8. **June 1972**. The responsibility of regulating biologic products, including vaccines, is transferred from the Division of Biologic Standards to the Food and Drug Administration.[8]
9. **August 1972**. The Food and Drug Administration announced a review of all products transferred from the Division of Biologic Standards for safety, effectiveness and labeling.[9] AVA was one such product.
10. **May 1985**. The DoD (through the Department of the Army) issued a Request for Proposals (DAMD17-85-R-0078) to the pharmaceutical industry soliciting the development of a new anthrax vaccine. The reasons stated in the Request for Proposals was that there was no vaccine in current use that safely and effectively protects military personnel against exposure to anthrax and that the current anthrax vaccine was highly reactogenic, required multiple boosters to maintain immunity, and may not protect against all strains of anthrax.[10]
11. **December 1985**. The review required by the Food and Drug Administration in 1972 was published in the Federal Register as a Proposed Rule. The review panel recommended that AVA be placed in Category I as safe, effective and not mislabeled. The review panel did note the lack of efficacy data: "*the vaccine…has not been employed in a controlled field trial.*" The panel also noted the inability to determine the vaccine's use in preventing inhalation anthrax: "*efficacy against inhalation anthrax is not well documented . . . no meaningful assessment of its value against inhalation anthrax is possible due to its low incidence.*" Finally, based on the extremely limited use of the vaccine the panel felt the possible benefit outweighed the risk: "*In general, safety of this product is not a concern especially considering its very limited distribution and the benefit-to-risk aspects of occupational exposure in those individuals for whom it is indicated.*"[11] This panel also found the dosage of the anthrax vaccine to be incorrect, and recommended a correction to the labeling to only 3 shots. The FDA has not finalized the anthrax vaccine license proposed rule.

12. **March 1988**. USAMRIID researcher Bruce Ivins wrote in the European Journal of Epidemiology of the inability of the anthrax vaccine to adequately protect against certain strains of anthrax.[12]

13. **May 1989**. When asked by the U.S. Senate Committee on Governmental Affairs to explain the DoD's assessment that the U.S. cannot adequately defend its service personnel against anthrax, Assistant Secretary of Defense Robert B. Barker answered,

> "*The assessment in the 1986 report is accurate. Current vaccines, particularly the anthrax vaccine, do not readily lend themselves to use in mass troop immunization for a variety of reasons: ...a higher than desirable rate of reactogenicity, and, in some cases, lack of strong enough efficacy against the aerosol route of exposure.*"[13]

14. **March 1990**. Army Colonels E.T. Takafuji and P. K. Russell published an article describing the human anthrax vaccine as a "*limited use vaccine*" and an "*unlicensed experimental vaccine*". [14]

15. **September 1990**. The anthrax vaccine producer, then the Michigan Department of Public Health (MDPH), increased its production capacity and modified its production process to accommodate DoD needs. These production changes included changing the filtration system, using different fermentation equipment, different sterilization procedures, chill tanks, etc. FDA was eventually notified of some of these changes after the fact. FDA was unaware of others until Congressional and GAO inquires were made in 2000. DoD involvement to some unknown degree is apparent from a review of declassified documents.[15]

16. **October 1990**. US Army medical research personnel from Fort Detrick, Maryland determined that the changes in the anthrax vaccine manufacturing process produced a 100-fold increase in protective antigen levels of the vaccine.[16]

17. **May 1993**. First in a series of FDA inspections of the anthrax vaccine manufacturing facilities began noting serious deviations from regulations and that the vaccine manufacturer was in violation of current Good Manufacturing Practices (cGMP).[17]

18. **1994**. U.S. Army officer and researcher Col. Arthur M. Friedlander co-authored a chapter on the anthrax vaccine for the medical reference textbook "Vaccines". Friedlander wrote that:

> "*No assessment of the effectiveness of the vaccine against inhalation anthrax could be made because there were too few cases. ... There have been no controlled clinical trials in humans of the efficacy of the currently licensed U.S. vaccine. ... The current vaccine against anthrax is unsatisfactory for several reasons. The vaccine is composed of an undefined crude culture supernatant absorbed to aluminum hydroxide. There has been no quantification of the protective antigen content of the vaccine or of any of the other constituents, so the degree of purity is unknown. ... The vaccine is also less than optimal in that six doses are required over 18 months, followed by annual boosters. There is also evidence in experimental animals that the vaccine may be less effective against some strains of anthrax.*"[18]

19. **June 1994**. FDA inspection of manufacturer noted non-compliance with regulations and cGMPs.[19]

20. **December 1994**. Senate Veterans Affairs Committee determined that the use of the anthrax vaccine during the Gulf War was investigational. Future Army Surgeon General Ronald Blanck testified that the anthrax vaccine should be considered a possible cause of Gulf War Illness.[20]

21. **April 1995**. FDA inspection of manufacturer noted continued non-compliance with regulations and cGMPs.[21]

22. **August 1995**. FDA issued a warning letter to the anthrax vaccine manufacturer for their continuing failure to comply with the regulations and remedy the deficiencies noted in the various

inspections. The manufacturer was warned that failure to promptly correct those deviations could result in regulatory action to include seizure, injunction, and license suspension.[22]

23. **October 1995**. The U.S. Army contracts with Science Applications International Corporation (SAIC) to develop a plan to obtain FDA approval for a license amendment for the anthrax vaccine. The license amendment would enable the manufacturer of the vaccine to indicate that the anthrax vaccine was effective against "*inhalation anthrax*." The SAIC license amendment plan stated that the anthrax vaccine was not licensed as protection for aerosol anthrax exposure (inhalation anthrax) as expected in a biological warfare environment.[23]

24. **October 1995**. The Army's newly formed Joint Program Office for Biological Defense (JPOBD) met to discuss the proposed anthrax vaccine license amendment. The participants noted that studies showed the vaccine to be effective for tannery workers, but that there was insufficient data to demonstrate protection against inhalation anthrax.[24]

25. **February 1996**. A U.S Army representative was presented with a report on the anthrax vaccine manufacturer, which indicated equipment in use had not been approved by FDA and could result in severe consequences if FDA found out.[25]

26. **September 1996**. The anthrax vaccine manufacturer submitted an investigational new drug application for the anthrax vaccine to the FDA (IND #6847). At this point the anthrax vaccine was now considered an investigational new drug when used for the purpose described in the application, i.e. "*inhalation anthrax*".[26]

27. **November 1996**. FDA inspected the anthrax vaccine manufacturer and noted continued non-compliance with regulations and cGMPs.[27]

28. **March 1997**. FDA issued a Notice of Intent to Revoke letter to vaccine manufacturer for failure to remedy regulatory deficiencies and non-compliance.[28]

29. **March 1997**. DoD Joint Program Manager for Biological Defense briefed the Deputy Secretary of Defense concerning the anthrax vaccine production problems. A worst-case scenario was laid out, which threatened the as yet to be announced anthrax vaccination program. The AVIP was revealed as the launch program for a larger initiative called the Joint Vaccine Acquisition Program (JVAP), which would field up to 18 more biowarfare vaccines[29]

30. **March 1997**. Acting FDA Commissioner Dr. Friedman wrote a personal memo to DoD Assistant Secretary of Defense (ASD) for Health Affairs, Dr. Joseph, which accepted DoD's new position that the anthrax vaccine could be used for inhalation anthrax. The IND application, which requested that the new use be added to the product label, was not addressed. Friedman's memo or opinion had no legal authority. The Code of Federal Regulations at 21 C.F.R. § 10.85 -- Advisory Opinions – explained why the March 1997 letter by FDA Lead Deputy Commissioner was legally irrelevant – yet the DoD used this memo to justify product approval for an experimental use.[30] In his memo to the DoD, Dr. Friedman wrote that, "*Results from animal challenge studies have also indicated that pre-exposure administration of anthrax vaccine protects against inhalation anthrax*."[31]

31. **December 1997**. A Joint Program Office for Biological Defense report continued to note that "*Anthrax and Smallpox are the only licensed vaccines that are useful for the biological defense program, but they are not licensed for a biological defense indication*."[32]

32. **December 1997**. FDA interoffice memorandum indicated that the vaccine manufacturer routinely redated vaccine without proper authority or approval.[33]

33. **December 1997**. DoD announced a multi-service vaccination program for all active duty, Reserve and National Guard service members using the anthrax vaccine as a preventative measure for inhalation anthrax.[34]

34. **February 1998**. FDA inspected the anthrax vaccine manufacturer, found multiple deviations from cGMPs and determined that the manufacturing process was no longer validated.[35] Manufacturer "voluntarily" quarantined 11 of 19 Lots of the anthrax vaccine.

35. **February 1998**. Within one day of the FDA inspection, which revoked the validation of the anthrax vaccine manufacturing process, an independent expert completed a four-point review of the AVIP, mandated by Defense Secretary Cohen.[36] Later this expert admitted in a letter to Congressional investigators he had no expertise in anthrax. One aspect of the four-point review included supplemental testing of the vaccine, which DoD officials later admitted to Congressional investigators was suspended due to "*inconsistencies*."[37] Internal documents later revealed that testing results where "*all over the board*," and were terminated to preclude having to report the problems to FDA.

36. **September 1998**. Army Secretary Louis Caldera authorized indemnification of the manufacturer stating:

> "*the obligation assumed by MBPI under this contract involves* ***unusually hazardous risks*** *associated with the potential for adverse reactions in some recipients and the possibility that the desired immunological effect will not be obtained by all recipients. ...[T]he size of the proposed vaccination program may reveal unforewarned idiosyncratic adverse reactions. Moreover, there is no way to be certain that the pathogen used in tests measuring vaccine efficacy will be sufficiently similar to the pathogen that US forces might encounter to confer immunity*."[38]

37. **1999**. New Edition of the civilian medical textbook "Vaccines" printed with minor changes to the anthrax vaccine chapter.[39] 1994 chronology, verbiage and assessments of the unsatisfactory nature of the vaccine by Friedlander and Brachman remain unchanged.

38. **1999**. 10 U.S.C. § 1107 became law. 10 U.S.C. § 1107 provided that investigational new drugs or drugs unapproved for their intended uses may not be given to members of the Armed Forces without their prior consent except in the case of a waiver by the President of the United States. 10 U.S.C. § 1107 reiterated and codified language already established in federal and military regulations.[40]

39. **January 1999**. A British journal, The Lancet, published a study establishing a link between Gulf War vaccinations and Gulf War Illness.[41]

40. **January 1999**. Investigational New Drug application #6847 is updated with the FDA's Center for Biologics Evaluation and Research. The primary reason, and the only one listed on the application update, was for a clinical indication for "*inhalation anthrax*" on the anthrax vaccine product label.[42]

41. **March 1999**. Hearings on AVIP began in House Government Reform Committee, the Government Reform Committee Subcommittee on National Security, International Relations and Veterans Affairs, the House Armed Services Committee and the Senate Armed Services Committee. Nine hearings were conducted in 1999.[43]

42. **March 1999**. The General Accounting Office (GAO) testified and issued the first of many critical reports on the anthrax vaccine and the AVIP.[44]

43. **March 1999**. Dr. Meryl Nass reviewed the anthrax vaccine in a biologic warfare context in Infectious Disease Clinics of North America concluding that when the DoD controls all steps in the vaccine development and production process, along with being the employer of both physicians and the servicemember recipients, there will be problems, including ethical conflicts, insufficient testing of products, inadequate quality control, inadequate record keeping, and lack of proper surveillance for side effects.[45]

44. **April 1999**. DoD admitted the use of the anthrax vaccine was only routine in military research laboratories and that they did not intend to mislead or confuse the public with their previous pronouncements of routine civilian veterinarian use. DoD modified tri-fold brochure replacing "*civilian*" with "*at risk*".[46]

45. **May 1999**. Internal DoD correspondence by Brigadier General Cain, following Congressional testimony, revealed:

> "*… two key areas we came up flat were the GAO's assertion that #1, the anthrax vaccine licensed was NOT the one tested and #2, how can DoD say that reported desert storm illnesses were not cause (sic) by the anthrax vaccine when we have no record of who received the shots. If we cannot answer these questions we (DoD & the Administration) are in big time trouble*."[47]

46. **September 1999**. President Clinton issued Executive Order (EO) 13139. EO 13139 stated that before administering an investigational drug, or a drug unapproved for its intended use, to members of the Armed Forces, the DoD must obtain informed consent from each individual unless the President of the United States signs a waiver of this requirement. This EO reiterated the requirements already codified in US law.[48]

47. **October 1999**. The FDA and the DoD proposed to amend the law in a 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 Human Ethically Cannot be Conducted*". [49] This amendment would allow evidence of effectiveness derived from appropriate studies in animals, without adequate and well-controlled efficacy studies in humans, to be used to earn full approval for vaccines or drugs for soldiers.[50]

48. **2000**. The House Government Reform Committee, the Government Reform Committee Subcommittee on National Security, International Relations and Veterans Affairs, the House Armed Services Committee and the Senate Armed Services Committee held a total of ten hearings.[51]

49. **2000**. GAO testified and issued seven more critical reports on the AVIP and the threat of weaponized anthrax.[52]

50. **February 2000**. After eight hearings the Committee on Government Reform issued its findings in a report – Unproven Force Protection. They found the use of the anthrax vaccine by the military was experimental, that the AVIP lacked a consistent standard of care, and was designed to reach far beyond those at risk.[53] The DoD refused to modify the AVIP in order to comply with FDA regulations and US law as recommended by the Government Reform Committee.

51. **March 2000**. The Institute of Medicine issued a Letter Report assessing the safety of the anthrax vaccine and concluded there was a paucity of data on both the safety and efficacy of the anthrax vaccine.[54]

52. **March 2000**. FDA admitted to Representative Metcalf of WA in a written response that trace amounts of an unapproved adjuvant, squalene, was found in all anthrax vaccine Lots tested. Previously, DoD had categorically denied that the anthrax vaccine has ever contained squalene.[55]

53. **April 2000**. An article reviewing the anthrax vaccine in the journal "Infectious Diseases" acknowledged that "*The pre-clinical, clinical, pharmacological and safety data that would be required for a new product to be licensed today [was] never generated*."[56]

54. **May 2000**. A Canadian Judge, Col. Guy Brais, dismissed a case against a Canadian soldier, Michael Kipling, who refused the anthrax vaccine. The Judge deemed the anthrax vaccine was "*unsafe*."[57]

55. **July 2000**. DoD slowed AVIP due to a lack of vaccine supply.[58]

56. **October 2000**. GAO issued a report titled: Preliminary Survey of Guard and Reserve Pilots and Aircrew, 01-92T. The report's abstract states:

> *"Many questions have been raised about the program since DoD began vaccinating its 2.4 million active duty and reserve members in 1998. A major concern has been the program's effect on the National Guard and Air Force Reserve's retention of trained and experienced personnel. A questionnaire sent to 1,253 randomly selected Guard and Reserve pilots and others revealed that the anthrax immunization was a key reason these individuals left or otherwise changed their military status. Since September 1998, an estimated 25 percent of the pilots and aircrew members of the Guard and Reserve in this population transferred to another unit, left the military, or moved to inactive status."*

57. **November 2000**. The American Journal of Epidemiology published a study of Kansas's veterans, which described the Gulf War Illness symptoms of servicemembers who didn't deploy to South West Asia but received the anthrax vaccine.[59]

58. **December 2000**. The Center for Disease Control's Advisory Committee on Immunization Practices issued a report on the use of the anthrax vaccine. They did not recommend the vaccine for emergency first responders, federal responders, medical practitioners or private citizens. Further, the Committee determined that the target population could not be predetermined and that the risk of exposure to anthrax could not be calculated.[60]

59. **2001**. GAO testified and issued six critical reports on the AVIP and the threat of weaponized anthrax.[61]

60. **June 2001**. Senator Daschle, the Senate Majority Leader, and Representative Gephardt, the House Minority Leader, wrote a joint letter to Secretary of Defense Rumsfeld questioning the anthrax vaccine program and the punishments of soldiers.[62]

61. **June 2001**. DoD suspended the AVIP due to a lack of vaccine.[63]

62. **August 2001**. DoD Undersecretaries submitted recommendations to Secretary of Defense Rumsfeld to minimize use of the current anthrax vaccine, develop a new vaccine, procure biodetection systems, and institute a coherent process for dealing with biological warfare threats in the future.[64]

63. **September 2001**. Gen. Shelton, Chairman of the Joint Chiefs of Staff, responded to the Undersecretaries' recommendations, adamantly insisted that the AVIP was supported by his subordinate commanders and was the "*centerpiece*" for biological defense.[65]

64. **October 2001**. Anthrax, delivered through the US postal service, arrived in Senator Daschle's office on the 15th of October. One business day earlier BioPort applied for an expedited approval of its anthrax manufacturing line. Senator Daschle ultimately recommended his staff take the anthrax vaccine. It is unknown if Senator Daschle ever followed up on the anthrax vaccine questions presented to the DoD several months earlier.

65. **October 2001**. A Citizen Petition was filed with the FDA requesting they declare the anthrax vaccine adulterated based on the unapproved and illegal manufacturing alterations, and revoke the anthrax vaccine manufacturer's license based on meeting the threshold of license revocation on both the scientific and regulatory grounds. [66] The petition also covered the fact that the DoD's contracts for the anthrax vaccine were in conflict with FDA policy guidance, since the manufacturer had received warning letters and other adverse regulatory actions, and the fact that the FDA proposed rule noted that the vaccine regimen was intended to be only 3 shots, not 6.[67]

66. **October 2001**. DoD reported to Congress on their co-sponsorship of the proposed rule to change the law to allow licensure of biological warfare defensive protection measures based on animal data. The proposed rule was attached to the 2001 Bioterrorism bill that passed without dissent.[68]

67. **November 2001**. An article in The Lancet reviewed how early and aggressive post exposure treatment with antibiotics saved the lives of several anthrax letter victims.[69]

68. **November 2001**. A trade journal article, Nursing Times, published an article expressing reservations on recommending the vaccine to their members based on published reports of adverse reactions.[70]

69. **December 2001**. An article published by members of the US Army expressed the belief that the vaccine was effective, in contrast to previous DoD admissions that the vaccine was not effective against all known strains. The article purported to review the adverse reaction data, and minimized the deleterious effects of the vaccine on the military population. These findings were refuted several months later by a civilian review of the same data.[71]

70. **January 2002**. The anthrax vaccine manufacturer's license to manufacture and distribute vaccine (under a new trademark, BioThrax) was approved after the FDA accepted the expedited application. A review of FDA's newly approved anthrax vaccine product label revealed systemic adverse reaction rates now published at 5 to 35% based on post-surveillance studies, which was up to 175 times or 17,500% higher than the original 0.2% on the old product label when the AVIP was announced in 1997. The new anthrax vaccine product label also listed six reported deaths including cardiac arrest, myocardial infarction, aplastic anemia, central nervous system (CNS) lymphoma. Birth defects were also listed based on a US Navy retrospective study. The FDA revised the product labeling, confirming positive risk of birth defects based on human data, and downgraded the vaccine to Category D. Approximately 40 serious adverse events were now on the product label including: cysts, sepsis, angioedema, asthma, aplastic anemia, lymphoma, leukemia, vascular disease, systemic lupus, multiple sclerosis, arthritis, Guillain-Barré syndrome, immune deficiency, seizures, tremors, facial palsy, hearing and visual disorders, meningitis, encephalitis, atrial fibrillation, spontaneous abortion, liver abscess, fatigue, mood-cognition, musculoskeletal disorder.[72]

71. **January 2002**. A paper establishing the existence of squalene in the anthrax vaccine was published. Squalene was a substance known to be present in virtually every person with Gulf War Illness.[73]

72. **January 2002.** 24 January 2002 Congressional testimonial exchange with GAO investigators revealed that the DVA had data linking anthrax vaccine to GWI, but data was not released to the public:

> Mr. Shays. "*OK. In your testimony, you said according to studies in both the U.K. and the U.S. veterans of the Gulf war who reported receiving biological warfare inoculations for anthrax or other threats were more likely to report a number of symptoms than non-Gulf war veterans who did not report receiving such inoculations. This pattern was observed in data collected in the United Kingdom in an unpublished data collected by the U.S. Department of Veterans Affairs. Why do you think the VA has not published its finding regarding the link between advance symptoms and the anthrax vaccination?*"
>
> Ms. Kingsbury. "*I don't know why they didn't publish it. We are aware of it. We have asked them. They said to us what they said to you this morning, things about the analysis not being completed and that sort of thing. I'm not in a position to second-guess it. We consider it to be valid, useful information that ought to be in the public domain.*"[74]

73. **March 2002**. The Institute of Medicine issued a Congressionally mandated, DoD funded, report on the anthrax vaccine. The report recommended the vaccine for soldiers, and was authored by the same experts that had been involved with the DoD's anthrax vaccine program and other experts that were involved with the DoD's original anthrax vaccine trial in 1957[75] The report was used to justify the subsequent relaunch of the AVIP, but held no regulatory relevance.

74. **March 2002**. A civilian review of adverse reactions was published showing a significant increase in joint symptoms following vaccination with AVA when compared to joint symptoms following vaccination with hepatitis A and Td.[76]

75. **April 2002**. A study of over 900 Reserve members showed that Gulf War veterans were more likely to report poor health than non-Gulf War veterans, including veterans who received the anthrax vaccine who reported more reactions to vaccines than those who did not receive the anthrax vaccine.[77]

76. **April 2002**. A published article demonstrated that the anthrax vaccine caused statistically significant adverse reactions ranging from arthralgia, to vasculitis, to joint disease, to gastrointestinal disease and weight loss.[78]

77. **June 2002**. DoD formally restarted the AVIP.[79]

78. **July 2002**. DoD Inspector General (IG) referred an amended complaint (#84142) to the Defense Criminal Investigative Service (DCIS) concerning the anthrax vaccine program. MG Randall West, the Office of the Secretary of Defense officer responsible for the AVIP, was tasked with investigating a previous, similar complaint. Following his investigation, he dismissed the complaint. The original complaint included concerns about questionable testimony to the US Senate, and a Canadian Judge concerning the IND application by military officers. The amended complaint added additional questionable testimony to the House of Representatives, and broader concerns about the adulteration of the vaccine, the failure to properly study the vaccine as a possible cause of Gulf War Illness (GWI), and concerns about the willfully blind nature of the DoD's conduct despite soldiers documenting the risks of the vaccine.[80] The new complaint's investigation is pending.

79. **July 2002**. Article by Kansas State University scientists critiqued the National Academies of Sciences Institute of Medicine Report, which found the anthrax vaccine safe and effective, based on its "*omissions and limitations*." The critique explained that the report "*ignored evidence of several recent research studies from three different nations that have implicated vaccines, often including anthrax vaccine, in the epidemiology of Gulf War illnesses*."[81]

80. **August 2002**. FDA responded to a Citizen Petition filed under Title 21 of the US Code. The response confirmed the fact that FDA never finalized the anthrax vaccine license as required by law, and that none of the old anthrax vaccine would be released.[82]

81. **October 2002**. Air Force Chief of Staff General Jumper promulgated AVIP policy and guidance for all active duty and reserve units. The policy stated that, "*The vaccine must be given in accordance with the ... dosing schedule, as approved by the Food and Drug Administration*." Notwithstanding the CSAF's guidance to follow the licensed vaccination schedule, Paragraph 4c of Annex B of the plan stated: "*Personnel whose vaccination series was interrupted during the previous AVIP slowdown will not need to repeat any doses already received in the vaccine series or receive extra doses. Once these individuals are identified as requiring the vaccine, they will just continue with the next dose in the series*."[83]

82. **October 2002**. GAO's final report[84], Survey of Guard and Reserve Pilots and Aircrew, report #02-445, revealed on page 5 that:

> *"The systemic reaction rate reported through the survey represents a level more than a hundred times higher than the 0.2 percent published in the product insert. We were unable to determine why the AVIP reaction rates so exceeded the product insert rates for the vaccine as approved in 1970. However, we found two studies conducted by DoD that looked at the short-term safety of the vaccine -- one in Korea and one in Hawaii. Both reported reaction rates similar to those reported in our survey and disclosed a markedly higher rate of reaction for female shot recipients. Since we first reported these results from our survey in September 2000, the manufacturer's*

product insert has been revised to include the adverse reaction rates reported in post licensure survey studies."

83. **October 2002 Continued**. GAO report #02-445 also revealed on pg. 23 that:

> *"In addition, although DoD has maintained from AVIP's outset that the anthrax vaccine is very safe and causes minimally adverse effects, our survey disclosed that a significantly large number of vaccine recipients reported experiencing adverse events. Further, the results of two DoD studies on anthrax vaccine reactions, both of which used active monitoring systems, as opposed to a passive system such as VAERS, for gathering information on adverse events, are consistent with and support the results of our survey. The rates disclosed in the survey and the DoD studies are each significantly higher than those stated in the vaccine product insert until recently. Such marked variances from the product insert data suggest the possibility of change in the composition of the vaccine from the vaccine originally approved in 1970."*

84. **October 2002 Continued**. The GAO report #02-445 abstract summarized the readiness implications of the AVIP:

> "*GAO reviewed the views of pilots and aircrew members of the Air National Guard and Air Force Reserve regarding the Anthrax Vaccine Immunization Program (AVIP) of the Department of Defense (DoD). ...Between September 1998 and September 2000, 16 percent of the pilots and aircrew members of the guard and reserve had (1) transferred to another unit (primarily to nonflying positions to avoid or delay receiving the anthrax shots), (2) moved to inactive status, or (3) left the military. Additionally, one in five of those still participating in or assigned to a unit in 2000 indicated their intention to leave in the near future. At the time of the survey, two-thirds of the guard and reserve pilots and aircrew members did not support DoD's mandatory AVIP or any future immunization programs planned for other BW agents. However, these negative views did not appear to indicate a general anti-vaccine bias. On the basis of the survey, GAO estimated that 37 percent of the guard and reserve pilots and aircrew members had received one or more anthrax shots as of September 2000. Of these recipients, 85 percent reported experiencing some type of reaction. ...*"

85. **February 2003**. FDA approved pyridostigmine bromide (PB) for use to protect soldiers from chemical weapons. The approval marked the first application of the "animal efficacy rule" proposed by the DoD in October 1999, reported to Congress in October 2001 and passed in to law in the summer of 2002 following passage of the Bioterrorism bill. Opponents of the use of PB referenced a 1999 study by the RAND Corporation and a 2000 report by the Institute of Medicine that concluded PB could not be ruled out as cause of Gulf War Illness. Evidence of efficacy inferred from animal data and the unresolved issues pertaining to Gulf War Illness were identical to that of the anthrax vaccine.

86. **February 2003**. United States District Court ruling, for a US Army soldier's discharge upgrade case, cautioned that:

> *" ... It is important for the parties and the public to understand exactly what the Court is ruling. The Court is not passing on the merits of the anthrax program. The plaintiff has raised significant questions about that program. If the Court were reviewing the program, the Court would be very concerned about the question that the plaintiff has raised. Title 10 United States Code Section 1107 provides that whenever the Secretary of Defense requests a member of the armed forces to receive an investigational new drug, the Secretary must provide a member with notice about the investigational nature of the drug and require the member's consent prior to administration ... There have been no tests showing that the vaccine is effective at protecting human beings from exposure to inhalation anthrax, although animal studies by the Army exist. The Court will not substitute its opinion for that of the*

Army, but it will not review the matter. And its ruling today should not be understood as an approval of what the military is doing in this case. The military will be held accountable to the public if it is using its own soldiers as guinea pigs to determine whether the anthrax vaccine has long-term health consequences and whether it protects against airborne anthrax. Those decisions, are, as I said, decisions that are committed to the Executive Branch of the Government. The Court neither approves nor disapproves of those decisions, because it is not the function of the Court to do that. Those decisions will be debated, and ultimately the Executive Branch will be held accountable to the public for those decisions. And that is the way the system of government works. ..." [85]

87. **March 2003**. Case 1:03-cv-00707-EGS JOHN DOE et al v. RUMSFELD et al filed in the United States District Court for the District of Columbia requesting that a federal judge declare that the anthrax vaccine an experimental drug and illegal. A separate motion was also filed seeking a Temporary Restraining Order or Preliminary Injunction against the defendants to prevent further anthrax inoculations without informed consent or a presidential waiver according to law and Executive Order. Specific aspects of the suit include:

a. FDA Failure to properly finalize the anthrax vaccine license;

b. Anthrax vaccine experimental use for inhalation anthrax;

c. And DoD deviation from anthrax vaccine license requirements.

88. **March 2003.** Additional multiple Federal lawsuits were filed against the manufacturer for wrongful injury, with specific counts including:

Negligence

Breach of Warranties

Breach of the right to be treated with essential human dignity

Strict products liability

Fraud

Deprivation of civil rights and

Spouse's loss of assistance, companionship and consortium.

[1] See supra note 23.

[2] U.S. Patent No. 3,208,909; 28 September 1965.

[3] Michigan Department of Public Health application to the Public Health Service Division of Biologic Standards, 11 July 1967.

[4] Ibid.

[5] Pittman M, Division of Biologic Standards Memorandum dated 10 February 1969.

[6] Health, Education and Welfare letter to Michigan Department of Public Health, dated 10 November 1970.

[7] Michigan Department of Pubic Health Final Report, dated 3 February 1972.

[8] Federal Register at 37 FR 12865, 29 June 1972.

[9] Federal Register at 37 FR 16679, 18 August 1972.

[10] DoD Request for Proposals (RFP) -- DAMD17-85-R-0078. 16 May 1985.

[11] Federal Register at 50 FR 51058, 13 December 1985

[12] Ivins BE, Welkos SL. Recent Advances in the Development of an Improved Human Anthrax Vaccine. European Journal of Epidemiology. Vol. 4 pp 12-19.

[13] Global Spread of Chemical and Biological Weapons. Hearings before the Committee on Governmental Affairs and its Permanent Subcommittee on Investigations. Senate Hearing 101-744.

[14] Takafuji ET, Russell PK, Military Immunizations: Past, Present, and Future Prospects. Infectious Disease Clinics of North America. Vol. 4, No. 1 pp 143-58 1990

[15] Excerpts from DoD declassified chronology: "14 SEP 90 -- ... task from DJS to form a special group to develop proposed PA guidance for the BW Vaccination Program ... under the auspices of J-5 (Deputy Director for Political Military Affairs -- BG Jumper)...

21 SEP 90 – 'Special Topic' briefed in the TANK to the Operations Deputies by J-4 (RADM Smyth) and J-5 (BG Jumper) ... Bottomline: decision necessary were no longer "medical" in origin; rather were political, social, and military / operational. Also, no matter what decision made, insufficient vaccines (both AX and BT) to cover all US forces at risk existed.

25 Sep 90 -- AX Production Charts provided DJS with explanation regarding commencement of production ... 25 Oct 90 -- Memo from DDMR (ADM Smyth) on status of AX production ... 2 Nov 90 -- Third TANK informational briefing held with OPSDEPS and Joint Chiefs ... No change in threat; AX vaccine production has been maximized ...

9 Nov 90 -- Trip to Michigan Department of Public Health Lab (Lansing, MI) by J5 (BG Jumper, COL Fleming) and J4 (ADM Smyth, COL Fry). Purpose: Determine problems and prospects affecting production of BW vaccines. Visited Director of the Lab (Dr. George Anderson) and the Chief of Biologic Products Division (Dr. Robert Myers). -- Increases in AX vaccine production favorable. ... here is need for an additional fermentor however. -- MDPH has suspended production of BT vaccine in favor of AX vaccine.

9 Nov 90 -- J5 / DDPMA (BG Jumper) formed a working group consisting of DIA, J3, J4, J5 to assure accurate tracking of vaccine production. 16 Nov 90 -- BG Jumper provided summary of BW threat and general overview of US defensive capabilities (to include vaccines). Briefing showed existing inventories fell short of requirements in the near term.

16 Nov 90 -- COL Lewis furnished latest information on MDPH fermentor. New fermentor installed and pre-production testing is beginning. Provided to BG Jumper and DJS by DDMR. 19 Nov 90 -- ASD (HA) memorandum to SECARMY, "Expansion of Industrial Base for Biological Vaccine Production." ... on short term production of AX and BT. -- Requested steps be taken on a priority basis to monitor ongoing efforts at MDPH (increased production by 20 Feb 91)...

19 Nov 90 -- Initial information on quantities of antibiotics (doxycycline, ciprofloxacin) ... furnished by COL Lewis to DDMR and BG Jumper.

21 Nov 90 -- DA OTSG sent tasking from SECARMY to form Task Force to evaluate ways to increase production of AX and BT vaccines. Implementation Working Group, chaired by BG Blanck, would provide weekly production reports to DASD (MR).

3 Dec 90 -- J5/BG Jumper outlined course of action needed prior to next TANK session. Need to push toward total integration of all planning efforts associated with BW defensive measures. ... VCSA has tasked Surgeon General to get plan together (public affairs, psyops, POLMIL, medical, doctrine).

Draft memorandum to SECDEF prepared by J5 / COL Fleming requesting SECDEF direct accelerated procurement actions to improve the US biological defensive posture. Memorandum was not finalized.

10 Dec 90 -- Paper submitted to ADM Smyth and BG Jumper on "Rationale for Antibiotics in Prophylaxis Against Inhalation Anthrax" (Rhesus Monkey Paper). Research effort has been used in considering the use of antibiotics following exposure to AX and before initiation of symptoms. Only one monkey died following treatment with 30 days of Ciprofloxacin antibiotic.

14 Dec 90 -- Armed Forces Epidemiological Board met to consider the use of antibiotics as an adjunct in countering the threat of inhalation AX. 8 Mar 91 -- CENTCOM Surgeon msg (081808ZMar91), ... Also indicated vaccination programs for AX and Bot T discontinued due to diminished threat."

[16] Ezell JW, Abshire T. In Vitro Analysis of Michigan Department of Public Health Human Anthrax Vaccine, U.S. Army Medical Research Institute of Infectious Diseases, 25 Oct 1990, (unpublished)

[17] Form FDA 483 dated 4 May 1993.

[18] Friedlander AM, Brachman PS, "Vaccines", ed. Plotkin and Mortimer, 1994 edition chapter 26.

[19] Form FDA 483 dated 3 June 1994.

[20] Is Military Research Hazardous to Veterans' Health? Lessons Spanning Half a Century. S. Prt. 103-97, 8 December 1994.

[21] Form FDA 483 dated 23 April 1995.

[22] FDA letter to Michigan Department of Public Health, dated 31 August 1995.

[23] SAIC Corporation plan, 29 Sep 1995, enclosure to memorandum from Dr. Anna Johnson-Winegar (US Army) to Dr. Robert Myers (MDPH), US Army Medical Research and Material Command, Fort Detrick, Frederick, MD

[24] LTC David Danley, "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", held on 20 Oct 1995 meeting; Joint Program Office for Biological Defense memorandum, 13 Nov 1995.

[25] Kenimer Associates report to SAIC on trip to MDPH dated 6 February 1996.

[26] Michigan Biologic Products Institute application to Dr. K. Zoon, Director, Center For Biologics Evaluation and Research, dated 20 September 1996.

[27] Form FDA 483 dated 18 November 1996.

[28] NOIR letter from FDA to Michigan Biologic Products Institute dated 11 March 1997, available at http://www.fda.gov/cber/infosheets/mich-inf.htm

[29] http://www.defenselink.mil/pubs/prolif97/secii.html.

[30] 21 CFR 10.85, "Advisory Opinions" -- See: http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=21&PART=10&SECTION=85&YEAR=1999&TYPE=TEXT -- "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 Sec. 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 FDA, and does not bind or otherwise obligate or commit the agency to the views expressed."

[31] 13 March 1997 memo from FDA's Dr. Friedman to DoD's ASD/HA Dr. Joseph.

[32] Industrial Capabilities Assessment, Summary Report for the Production of Anthrax Vaccine, Preliminary report prepared by the Joint Program Office for Biological Defense, Falls Church, VA, December 1997.

[33] Memorandum from Jeanne Novak (DVRPA) to M. Carolyn Hardegree (CBER) dated 10 December 1997.

[34] See supra note 20.

[35] Form FDA 483 dated 4 February 1998.

[36] http://www.defenselink.mil/other_info/burrows.html, http://www.anthrax.osd.mil/resource/qna/ind_rev.asp#11, http://www.af.mil/news/Apr1998/n19980416_980507.html, http://www.defenselink.mil/news/Aug1998/t08171998_t814ntrx.html,

[37] http://www.house.gov/reform/ns/hearings/testimony/cain4-30.htm

[38] SecArmy Memorandum of Decision, dated 3 September 1998.

[39] Friedlander AM, Brachman PS, "Vaccines", ed. Plotkin and Mortimer, 1999 edition chapter 24.

[40] 10 U.S.C § 1107, TITLE 10, Subtitle A, PART II, CHAPTER 55, Sec. 1107

[41] Unwin C, et al. Health of UK Servicemen Who Served in Persian Gulf War. The Lancet. Vol. 353 pp 169-178.

[42] IND 6847 update to FDA dated January 29, 1999 -- block 7 specifically and exclusively reads: "Indication(s) (covered by this submission) Inhalation Anthrax"

[43] 1999 hearings:

24 March – Subcommittee on National Security, Veterans Affairs and International Relations; Oversight of the AVIP.

2. 22 April – Subcommittee on National Security, Veterans Affairs and International Relations; Implementation of the Persian Gulf War Veterans' Act of 1998.

3. 29 April - Subcommittee on National Security, Veterans Affairs and International Relations; Anthrax II – Efficacy of the Mandatory Vaccine

4. 30 June - Subcommittee on National Security, Veterans Affairs and International Relations; Oversight of the DOD Sole Source Procurement.

5. 21 July - Subcommittee on National Security, Veterans Affairs and International Relations; Anthrax Vaccine Adverse Reactions

6. 29 September - Subcommittee on National Security, Veterans Affairs and International Relations; Impact of the AVIP on Reserve and Guard Units

7. 30 September – House Armed Services Committee; DOD and the AVIP

8. 12 October – Government Reform Committee; Defense Vaccines: Force Protection or False Security?

9. 9 November - Subcommittee on National Security, Veterans Affairs and International Relations; Force

Protection – Improving Safeguards of IND Drugs.

[44] GAO Reports from 1999 are available at www.gao.gov or NSIAD-99-5, NSIAD-99-148, NSIAD-99-214, NSIAD-99-226, NSIAD-00-48, NSIAD-00-36

[45] Nass M. Anthrax Vaccine-Model of a Response to the Biologic Warfare Threat. Infectious Disease Clinics of North America. Vol 13. No. 1 pp 187-208

[46] Army Times, April 5, 1999.

[47] May 3, 1999 – email exchange between JPOBD BG Eddie Cain and Col John Wade, reference 29 APR 99 Congressional testimonies and an ongoing Congressional investigation of the AVIP.

[48] https://www.denix.osd.mil/denix/Public/Legislation/EO/note54.html

[49] http://www.fda.gov/cber/rules/lethtox.pdf;

[50] 21 CFR 314.126

[51] 1. 2 February - Subcommittee on National Security, Veterans Affairs and International Relations; Gulf War Veterans Illnesses – The Current Research Agenda

2. 13 April – Senate Armed Services Committee; Review of the DOD AVIP

3. 14 April - Senate Armed Services Committee; DOD's anti-biowarfare vaccine acquisition program

4. 24 May – Subcommittee on National Security, Veterans Affairs and International Relations; DOD Chemical and Biological Defense Program . Management and Oversight.

5. 21 June - Subcommittee on National Security, Veterans Affairs and International Relations; Force Protection –Current individual protective equipment.

6. 12 July - Senate Armed Services Committee; AVIP- The Threat, Effectiveness, Safety and Supply

7. 13 July – House Armed Services Committee; DOD and the AVIP

8. 27 September - Subcommittee on National Security, Veterans Affairs and International Relations; Gulf War Veterans-Linking Exposure to Illnesseses

9. 3 October – Committee on Government Reform; AVIP-What Have We Learned

10. 11 October – Committee on Government Reform; AVIP-What Have We Learned

[52] GAO Reports available at www.gao.gov or NSIAD-00-157, NSAID-00-140, NSIAD-00-138, NSIAD-00-97, GAO-01-92T, GAO-01-21,

[53] The Department of Defense Anthrax Vaccine Immunization Program - Unproven Force Protection. House Report 106-556. Available at House Report 105-556

[54] Institute of Medicine Letter Report to MGen West on 30 March 2000 available at: http://www.nap.edu/html/anthrax_vaccine/

[55] HHS letter from Melinda K. Plaisier to Representative Metcalf, 20 March 2000.

[56] Turnbull PCB. Current status on immunization against anthrax: old vaccines may be here to stay for a while. Current Opinion in Infectious Diseases, Vol. 13, No. 2 pp 113-120.

[57] May 5, 2000; Canada News Briefs By The Associated Press -- Judge Agrees Anthrax Vaccine Unsafe; Halts Court Martial, WINNIPEG, Manitoba.

[58] SecDef Cohen announcement available at http://www.defenselink.mil/news/Jul2000/n07112000_20007114.html

[59] Steele L. Prevalence and Patterns of Gulf War Illness in Kansas Veterans: Association of Symptoms with Characteristics of Person, Place, and Time of Military Service. American Journal of Epidemiology, Vol. 152, No. 10 pp 992-1002.

[60] Hughes JM, Cohen ML. Use of the Anthrax Vaccine in the United States-Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000;49(No. RR-15).

[61] GAO Reports available at GAO-01-13, GAO-01-915, GAO-02-38, GAO-02-181T, GAO-02-219T , GAO-02-445

[62] Letter provided by Senate Majority Leader's office staffer Mr. Randy DeValk.

[63] DOD announcement available at: http://www.defenselink.mil/news/Jun2001/n06112001_200106112.html

[64] DoD memo to SECDEF Rumsfeld dated 10 August 2001.

[65] http://www.washingtonpost.com/wp-dyn/articles/A42952-2001Sep28.html

[66] A Citizen Petition on lack of data and unapproved manufacturing changes – docket #01p-0471: http://www.fda.gov/ohrms/dockets/dailys/01/Oct01/101501/101501.htm#_Toc527850400; This Citizen Petition PDF can be reviewed at the following link: http://www.fda.gov/ohrms/dockets/dailys/01/Oct01/101501/cp00001.pdf

[67] Compliance Policy Guides Manual, Sec. 400.200, titled -- "Consistent Application of CGMP Determinations (CPG 7132.12), http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg400-200.html" which states: "*CGMP deficiencies supporting a regulatory action also support decisions regarding non-approval of drug marketing applications, government purchasing contracts, candidates for MAC, etc. Therefore, the issuance of a warning letter or initiation of other regulatory action based upon CGMP deficiencies must be accompanied by disapproval of any pending drug marketing application, or government contract for a product produced under the same deficiencies*."
Note: The FDA issued a Warning Letter to the anthrax vaccine manufacturer on August 31, 1995, and a Notice of Intent to Revoke (NOIR) their license on March 11, 1997. A subsequent FDA inspection, conducted between February 4th and 19th of 1998, found that the previous deficiencies had not been corrected; all three inspections documented violations of current good manufacturing practices (cGMPs) required under federal law. These regulatory actions, until corrected, made the manufacturer subject to the restrictions contained in this government policy. On September 3, 1998, the FDA informed the new owner of the anthrax vaccine manufacturing facility, BioPort Corporation, that "the Notice of Intent to Revoke issued to MBPI on March 11, 1997 would effectively transfer with the issuance of the license to BioPort and would remain in effect until all compliance issues had been satisfactorily resolved." These deficiencies have still not officially been resolved, and most certainly were not when the DoD contracted for Anthrax Vaccine in 1998. These discrepancies are available at the following link:
FDA Warns Michigan Biologic Products Institute of Intention to Revoke License:
http://www.fda.gov/cber/infosheets/mich-inf.htm

[68] http://www.defenselink.mil/pubs/chem_bio_def_program/2001_CBDP_Annual_Report.pdf -- "***ISSUE:* DoD does not have a current approved mechanism for licensure of chemical and biological defense medical products *(i.e.*, drugs and vaccines) because legal and ethical constraints prevent adequate full testing in humans. *SOLUTION:* The FDA and DoD are working together to amend**

the Code of Federal Regulations to allow animal efficacy data to be used in lieu of large-scale human clinical efficacy trials. This mechanism of licensure is vital to provide military service personnel with licensed products. This rule will also establish requirements for licensure and allow the DoD to plan and conduct the appropriate studies to obtain approval for the products planned for production and licensing. Requests for approval of each medical product will be reviewed on an individual basis."

[69] McCarthy M. Early and aggressive treatment saves US anthrax victims. The Lancet, Vol. 358 pp 1703

[70] Munro R. When Immunity may not be safe. Nursing Times, Vol. 97, No. 44 pp 10-11

[71] Pittman PR et al. Anthrax vaccine: short-term safety experience in humans. Vaccine, Vol. 20 pp 972-978.

[72] See supra note 34.

[73] Asa PB et al. Antibodies to Squalene in Recipients of Anthrax Vaccine. Experimental and Molecular Pathology, Vol. 73 pp 19-27.

[74] http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107_house_hearings&docid=f:82953.wais

[75] See supra note 3.

[76] Geier DA et al. Anthrax vaccination and joint related adverse reactions in light of biological warfare scenarios. Clinical and Experimental Rheumatology, Vol. 20, No. 2 pp 217-220

[77] Schumm WR et al. Self-Reported Changes in Subjective Health and Anthrax Vaccination as Reported by over 900 Persian Gulf War Era Veterans. Psychological Reports, Vol. 90 pp 639-653.

[78] Geier DA et al. Smallpox and Anthrax in the United States. Mealey's Emerging Drugs & Devices, Vol. 7, No. 8 pp 26-30

[79] See supra note 5.

[80] DoD IG complaint #84142, POC -- Mr. Trahan, 800-424-9098.

[81] Schumm, Webb, Jurich, Bollman, Kansas State University. Psychological Reports, Volume 91, 2002, 187-191, "Comments on the Institute of Medicine's 2002 Report on the Safety of the Anthrax Vaccine."

[82] http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/091102/80027a9f.pdf

[83] http://www.anthrax.mil/media/pdf/AFPlan.pdf.

[84] GAO-02-445, Report to Congressional Requesters, United States General Accounting Office, September 2002 ANTHRAX VACCINE GAO*s Survey of Guard and Reserve Pilots, and Aircrew - http://frwebgate.access.gpo.gov/cgi-bin/useftp.cgi?IPaddress=162.140.64.21&filename=d02445.txt&directory=/diskb/wais/data/gao.

[85] United States District Court for the District of Colorado Civil Action No. 00-N-1022, 2 FEB 2003; Jemekiah Barber vs. the United States Army, et al. The Court: *"... the issues in this case are beyond the purview of the federal judiciary and that the Court must decline review because the Department of Defense has wide latitude over military personnel decisions. ... The courts have little competence in the complex decisions as to the control of a military force, and such professional military judgments are more properly subject to civilian control of the Legislative and Executive Branches, which are directly responsible for the people ... the defendants concede that the plaintiff has sufficiently alleged that she suffered the deprivation of a constitutional right or that the military violated federal statutes for its own*

regulations..."