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Drugs and Vaccines for the Common Defense: Refining FDA Regulation to Promote the Availability of Products to Counter Biological Attacks

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DRUGS AND VACCINES FOR THE COMMON DEFENSE: REFINING FDA REGULATION TO PROMOTE THE AVAILABILITY OF PRODUCTS TO COUNTER BIOLOGICAL ATTACKS

*Gail H. Javitt**

"Biological terrorism is more likely than ever before and far more greatly to be feared than explosives or chemicals."

- D.A. Henderson[1]

I. INTRODUCTION

The 1991 Gulf War heightened military concerns about biological warfare. As a result of intelligence gained regarding Iraq's biological weapons stockpile and research program, as well as information obtained about the former Soviet Union's clandestine bioweapons program, the Department of Defense (DOD) began to intensify its focus on biowarfare defense. DOD was particularly concerned about protecting the U.S. military from exposure to biological agents, and in 1997 former Secretary of Defense Cohen ordered the vaccination of all troops against anthrax.

Domestically, however, little attention was paid to the possibility of a bioterrorist attack against U.S. cities until very recently.[2] In the last few years of his administration, President Clinton made combating

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1. Ruth SoRelle, *U.S. Lacks Preparation to Battle Biological Terrorism, Expert Says*, HOUS. CHRON., Mar. 11, 1998, at A8.

2. David R. Franz & Russ Zajtchuk, *Biological Terrorism: Understanding the Threat, Preparation, and Medical Response*, 46 Disease-a-Month 125 (2000).

bioterrorism a top administration priority.[3] Action on his initiatives was limited, however, because of opposition from Congress[4] and questions regarding the significance of the threat being addressed.[5] The government also appeared ill-prepared to counter the effects of a bioterrorist event, as evidenced by a 1999 report by the General Accounting Office criticizing several governmental agencies for mismanaging the medical stockpiles developed to protect the public from biological weapons.[6]

In the wake of the World Trade Center and Pentagon attacks of 9/11 and the distribution of anthrax-laden letters to the U.S. Congress and several news organizations, the threat of biological attacks against both military and civilian targets is widely acknowledged as significant, and one that the United States may at present be inadequately equipped to meet. While the biowarfare threat faced by the military and the bioterrorism concern faced by the civilian population have several distinct characteristics, they share a common irreducible element: the need for safe and effective prophylactic treatments and antidotes.

In the United States, the Food and Drug Administration (FDA) is charged with ensuring the safety and effectiveness of the therapeutic arsenal, which comprises drugs, medical devices and vaccines and other biological products. FDA approval is required before such products may be commercially distributed in interstate commerce, regardless of whether their intended recipients are military personnel or civilians. In addition,

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3. *See e.g.*, Laurie Garrett, *Plan to Fight New Terrorism*, NEWSDAY, Jan. 23, 1999, at A4; James Benet, *Clinton Tells of Antiterrorism Plans*, N.Y. TIMES, May 23, 1998, at A12.

4. For example, in 1999 the Clinton administration asked Congress to require U.S. laboratories to list all their dangerous biological agents, including anthrax, with the federal government, but the proposal failed because of fears that it would inhibit medical research. Aaron Zitner, *Clinton's 1999 Proposal That Labs Be Required to List All Their Dangerous Agents Failed to Win Congress' OK*, L.A. TIMES, Oct. 18, 2001, at A13.

5. *See e.g.*, Daniel S. Greenberg, *The Bioterrorism Panic*, J. COM., Mar. 23, 1999, at 5A; Anthony Shadid, *Funding on Rise for Research into Bioterrorism*, BOSTON GLOBE, Aug. 29, 2001, at A1 (noting that "critics have questioned such a substantial investment in a public health threat that . . . remains, by most accounts, highly unlikely"); Neil C. Livingstone, *Clinton Anti-Terror Plan is Correct*, NEWSDAY, Feb. 3, 1999, at A37 (noting that the Administration's proposals "have been criticized as unnecessary and too costly, designed to frighten the public and usurp traditional civilian authority.").

6. U.S. GEN. ACCOUNTING OFFICE, GAO/HEHS/AIMD-00-36, COMBATING TERRORISM: CHEMICAL AND BIOLOGICAL MEDICAL SUPPLIES ARE POORLY MANAGED (1999).

FDA authorization is necessary before products under development may be tested on humans for their potential therapeutic effect.

In light of FDA's central regulatory role, the agency is integral to any national preparedness strategy for military and homeland defense against biological agents. However, FDA has not traditionally viewed its primary role as protection of national security, nor do its statutory authorities explicitly contemplate this function. Moreover, FDA-DOD interactions during the Gulf War raised concerns about whether FDA had sacrificed the safety of military personnel for the benefit of military objectives. The recent concerns over the availability of the anthrax vaccine have revealed longstanding vulnerabilities in the U.S. vaccine industry – vulnerabilities to which FDA may have been insufficiently prepared to respond. Given the circumstances now facing the nation, it is critical to examine the impact that FDA requirements exert on military and homeland security efforts to combat bioterrorism and to determine whether changes in these requirements could facilitate military and homeland defense needs.

This article discusses FDA's role in regulating products to counter biological attacks. It explores FDA requirements pertaining to these products, and the impact of these requirements on product availability. It reviews historical difficulties —legal, ethical and scientific—surrounding the availability and provision of products to counter bioterrorism to those at risk. It also discusses previous efforts by FDA to change its regulatory requirements and expedite product availability in response to emerging threats, as well as the way in which these changes can be applied to products to counter bioterrorism.

This article identifies and briefly describes five areas in which FDA should develop new initiatives to foster the availability of products for military and homeland defense, including those to counter biological attacks. First, FDA should establish a new office of products for military and homeland defense, to review and approve new products for this purpose. Second, FDA should create a new interim category of product approval for products for military and homeland defense use. Third, FDA should expand the applicability of its fast track approval process to include products for military and homeland defense. Fourth, FDA should impose time limits on Investigational New Drug (IND) applications to encourage the filing of new product applications and prevent products from remaining in a perpetually investigational status. Finally, FDA should deem products for military and homeland defense eligible for orphan drug designation in order to encourage the development of new products unlikely to be commercially viable.

II. DIMENSIONS OF THE THREAT

A. Background: CDC List of Biological Agents

The Federal Centers for Disease Control and Prevention (CDC) maintain a list of biological agents and associated diseases categorized by level of threat. Agents in category A are considered to pose a significant threat to national security because they: (1) can be easily disseminated or transmitted from person to person; (2) result in high mortality rates and have the potential for a major public health impact; (3) might cause public panic and social disruption; and (4) require special action for public health preparedness. Agents currently included in category A are: (1) anthrax (*bacillus anthracis*); (2) botulism (botulinum toxin); (3) plague (*Yersinia pestis*); (4) smallpox (*Variola major*); (5) tularemia (*Francisella tularensis*); and (6) viral hemorrhagic fevers (e.g., filoviruses such as Ebola and Marburg, and arenaviruses such as Lassa and Machupo).[7] Category B agents are considered to be the second highest priority because they: (1) are moderately easy to disseminate; (2) result in moderate morbidity rates and low mortality rates; and (3) require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance.[8] Finally, Category C agents have the third highest priority and represent emerging pathogens that could be engineered for mass dissemination in the future because of their (1) availability; (2) ease of production and dissemination; and (3) potential for high morbidity and mortality rates and major health impact.[9]

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7. CENTERS FOR DISEASE CONTROL AND PREVENTION, Public Health Emergency Preparedness, and Response, Biological Diseases/Agents Listing, Category A, *available at* http://www.bt.cdc.gov/Agent/Agentlist.asp#categorya-diseases (last visited June 25, 2002).

8. *Id.* The following agents are currently included in Category B: "(1) Brucellosis (*Brucella* species); (2) Epsilon toxin of *Clostridium perfringens*; (3) Food safety threats (e.g., *Salmonella* species, *Escherichia coli*, *Shigella*); (4) Glanders (*Burkholderia mallei*); (5) Melioidosis (*Burkholderia pseudomallei*); (6) Psittacosis (*Chlamydia psittaci*); (7) Q fever (*Coxiella burnetii*); (8) Ricin toxin from Ricinus communis (castor beans); (9) Staphylococcal enterotoxin B; (10) Typhus fever (*Rickettsia prowazekii*); (11) Viral encephalitis (alphaviruses, e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis); and (10) Water safety threats (e.g., *Vibrio cholerae, Cryptosporidium parvum*)." *Id.*

9. *Id.* The following agents are currently included in Category C: "Emerging infectious disease threats such as Nipah virus and hantavirus." *Id.*

B. Agents at Issue and Treatments Available

1. Anthrax

Anthrax is caused by the spore-forming bacterium *Bacillus anthracis (B. Anthracis)*. *B. anthracis* occurs naturally in the soil, where it can remain viable for many years. It is primarily a disease of animals (cattle, sheep and other herbivores), and prior to the events of October 2001, the disease was typically contracted by persons in frequent contact with animals through work in agriculture, the wool trade or laboratory research. Anthrax can be contracted through skin contact, ingestion or inhalation. Inhalational anthrax is the most serious form of the disease, causing respiratory failure and death in almost all untreated cases. Inhalational anthrax is also least common in nature and had become extremely uncommon in any form in the United States, until the intentional mailings of anthrax spores caused an outbreak in the autumn of 2001 that resulted in five deaths from the inhalational form of the disease.[10]

> *B. anthracis* is considered one of the most likely biological warfare agents because of the ability of *B. anthracis* spores to be transmitted by the respiratory route, the high mortality of inhalation anthrax, and the greater stability of *B. anthracis* spores compared with other potential biological warfare agents. Anthrax has been a focus of offensive and defensive biological warfare research programs for approximately 60 years. The World Health Organization estimated that 50 kg of *B. anthracis* released upwind of a population center of 500,000 could result in 95,000 deaths and 125,000 hospitalizations.[11]

A licensed vaccine for anthrax is currently marketed in the United States, but it is not available for the general public. As discussed below, there have been significant problems in the manufacturing of this vaccine in addition to concerns about its safety. The vaccine is approved only to prevent anthrax; its effectiveness when used for post-exposure prophylaxis is currently being investigated.[12]

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10. *See* INST. OF MED., THE ANTHRAX VACCINE: IS IT SAFE? DOES IT WORK? 41-42 (Lois M. Joellenbeck, Lee L. Zwanginger, Jane S. Durch, Brian L. Strom, eds., 2002) [hereinafter IOM Report]; *See also Use of Anthrax Vaccine in the United States Recommendations of the Advisory Committee on Immunization Practices*, 49 MORBIDITY & MORTALITY WKLY. REP. 1-3 (2000).

11. *Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices*, 49 MORBIDITY AND MORTALITY WKLY. REP. at 2.

12. *Id.* at 13.

Recently, much has been learned about the effectiveness of antibiotic treatment for inhalational anthrax following exposure. CDC currently recommends treatment with ciprofloxacin or doxycycline. Both have been approved by FDA for this purpose, although FDA notes that "no controlled trials in humans have been performed to validate current treatment recommendations for inhalational anthrax."[13] These antibiotics are also considered first-line therapy for cutaneous anthrax.

2. Botulism

Botulism is caused by botulinum toxin, which is made by *Clostridium botulinum*, a group of spore-forming bacteria commonly found in soil. There are three main kinds of botulism: food borne botulism, caused by consuming foods containing the botulism toxin; wound botulism, caused by toxin produced from a wound infected with *Clostridium botulinum*; and infant botulism, caused by consuming the spores of the botulinum bacteria (e.g., in dirt), which then grow in the intestines and release the toxin. All forms are potentially fatal. About 110 cases are reported each year in the United States.[14]

Botulinum toxin is the "the single most poisonous substance known."[15] It inhibits the neurotransmitter acetylcholine, causing muscle paralysis and respiratory failure. This toxin poses a major bioweapons threat because of its extreme potency and lethality, its ease of production, transport and misuse and the potential need for prolonged intensive care in affected persons.[16]

No approved therapy exists for botulism. CDC holds an IND for an antitoxin to botulinum toxin, which has been used as a vaccine in

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13. *Update: Investigation of Bioterrorism-Related Anthrax and Interim Guidelines for Exposure Management and Antimicrobial Therapy*, 50 MORBIDITY AND MORTALITY WKLY. REP. at 916 (2001). Other antibiotics that may be used in conjunction with ciprofloxacin or doxycycline include rifampin, vancomycin, imipenem, chloramphenicol, penicillin and ampicillin, clindamycin and clarithromycin; but "other than for penicillin, limited or no data exist regarding the use of these agents in the treatment of inhalational B. *anthracis* infection." *Id.*

14. DIVISION OF MYCOTIC AND BACTERIAL DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION, Disease Information, Botulism, *available at* http://www.cdc.gov/ncidod/dbmd/diseaseinfo/ botulism_g.htm (last visited June 25, 2002) [hereinafter CDC, BOTULISM INFORMATION].

15. CENTER FOR CIVILIAN BIODEFENSE STRATEGIES, Botulinum Toxin, *available at* http://www.hopkins-biodefense.org/pages/agents/agentbotox.html (last visited June 25, 2002).

16. *Id.*

occupational settings for workers in agricultural occupations and was administered to some military personnel during the Gulf War.[17] Patients who experience respiratory failure and paralysis may require a ventilator for several weeks, after which the paralysis may improve. Good supportive care in a hospital is the mainstay of therapy for all forms of botulism.[18]

3. Plague

Plague is caused by *Yersinia pestis (Y. pestis)*, a bacterium found in rodents and their fleas in many areas around the world.[19] There are three forms of plague: bubonic, septicemic and pneumonic.[20] Bubonic plague is transmitted from the bite of an infected flea or through broken skin. It is not contagious.[21] It can be fatal if left untreated. Septicemic plague occurs when the bacteria invades the bloodstream, either as a complication of the other two forms of plague or from another source.[22] Pneumonic plague is airborne and can be transmitted from person to person. Without early treatment, pneumonic plague usually leads to respiratory failure, shock and rapid death. [23]

Bacteria introduced in an aerosolized form in a bioterrorist attack would cause pneumonic plague. A 1970 World Health Organization (WHO) assessment asserted that, in a worst-case scenario, a dissemination of fifty kilograms of *Y pestis* in an aerosol cloud over a city of five million might result in 150,000 cases of pneumonic plague, 80,000-100,000 of which would require hospitalization, 36,000 of which would be expected to be fatal.[24]

A U.S. licensed vaccine exists and, in a pre-exposure setting, appears to have some efficacy in preventing or ameliorating bubonic disease.

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17. RICHARD A. RETTIG, MILITARY USES OF DRUGS NOT YET APPROVED BY THE FDA FOR CW/BW DEFENSE: LESSONS FROM THE GULF WAR, 6-7 (1999).

18. CDC, BOTULISM INFORMATION, *supra* note 14.

19. See CENTER FOR CIVILIAN BIODEFENSE STRATEGIES, Plague, *available at* http://www.hopkins-biodefense.org/pages/agents/agentplague.html (last visited June 25, 2002); *See also* CENTERS FOR DISEASE CONTROL AND PREVENTION, Public Health Emergency Preparedness and Response, Facts About Pneumonic Plague, *available at* http://www.bt.cdc.gov/DocumentsApp/FactSheet/Plague/About.asp (last visited June 25, 2002); Franz & Zajtchuk, *supra* note 2, at 150.

20. *See* CENTER FOR CIVILIAN BIODEFENSE STRATEGIES, *supra* note 19.

21. *Id.*

22. *Id.*

23. *Id.*

24. *Id.*

Research and development efforts for a vaccine that protects against inhalationally acquired pneumonic plague are ongoing. Several antibiotics are effective against bubonic plague and, if administered soon after the onset of symptoms, can be effective against pneumonic plague as well.[25]

4. Smallpox

Smallpox is caused by the variola virus. It is transmitted from one person to another through face-to-face exposure and could also be transmitted through contact with contaminated clothing or sheets. Death occurs in thirty percent of patients, and survivors may experience serious scarring. Naturally occurring smallpox was declared eradicated by the World Health Assembly in 1980.[26] Smallpox represents one of the most serious bioterrorist threats to the civilian population because it is highly contagious and causes significant mortality, and treatment of smallpox is currently limited to supportive therapy and antibiotics as required to treat secondary bacterial infections. The only commercially approved smallpox vaccine available in the United States is Wyeth Dryvax. The vaccine was prepared using traditional methods, in which animals were infected with vaccinia (cowpox) and the animal lymph was extracted and prepared.[27] The facilities, expertise and infrastructure required for producing the virus in this way are no longer available, as Wyeth Laboratories discontinued distribution of the smallpox vaccine to civilians in 1983.[28] The current U.S. stockpile contains 15.4 million doses of the Dryvax vaccine, and approximately sixty million doses of vaccine exist worldwide.[29] The government has contracted with several companies to produce additional

25. *Id.*

26. CENTER FOR CIVILIAN BIODEFENSE STRATEGIES, Smallpox, *available at* http://www.hopkinsbiodefense.org/pages/agents/agentsmallpox.html (last visited Nov. 12, 2002).

27. CENTER FOR CIVILIAN BIODEFENSE STRATEGIES, *supra* note 19.

28. Steven R. Rosenthal et al., *Developing New Smallpox Vaccines*, 7 EMERGING INFECTIOUS DISEASES 920 (2001).

29. James W. LeDuc and John Becher, *Current Status of Smallpox Vaccine* (letter to the editor), 5 EMERGING INFECTIOUS DISEASES 593 (1999). In November, 2002, FDA granted a license for the 15.4 million doses of the Dryvax vaccine. Ceci Connolly, *FDA Grants License for Smallpox Vaccine; Debate Continues on How Much of U.S. Population Should Be Innoculated*, WASH. POST., Nov. 2, 2002, at A13.

vaccines, but production is expected to take at least a year.[30] The question of whether, when and to whom the vaccine should be administered, has been the subject of much debate and scientific uncertainty.[31] No antiviral agents have proven effective against smallpox, although research in this area is active.[32]

5. Tularemia

Tularemia is caused by the bacterium *Francisella tularensis (F. tularensis)*, which is widespread in animals, particularly rodents, rabbits, and hares. Approximately 200 cases of tularemia in humans are reported annually in the United States, mostly associated with the bites of infective ticks and biting flies or with the handling of infected rodents, rabbits or hares. It is not transmissible from person to person. It can cause a variety of symptoms, including respiratory problems. At least forty percent of persons with the lung and systemic forms of the disease may die if they are not treated with the appropriate antibiotics.

F. tularensis is one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as ten organisms to cause disease. It is considered to be a dangerous potential biological weapon because of its extreme infectivity, ease of dissemination and substantial capacity to cause illness and death. A WHO expert committee reported in

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30. In November 2001, U.S. Dept. of Health & Human Services awarded a $428 million contract to the British-based Acambis PLC to produce 155 million doses of the vaccine by Fall 2002. The government had previously contracted with Acambis to produce fifty-four million doses. Liz Kowalczyk, *A Deterrent to Terrorism: HHS Awards Contract to Make Smallpox Vaccine*, BOSTON GLOBE, Nov. 29, 2001, at C1. In 2000, CDC awarded a $343 million contract to Oravax, the U.S. subsidiary of the British-based Peptide Therapeutics Group PLC, to develop and stockpile forty million doses of smallpox vaccine, with deliveries scheduled to start in 2004. Ronald Rosenberg, *Oravax in $343M Contract to Develop Smallpox Vaccine for Government*, BOSTON GLOBE, Sept. 21, 2000, at C1. Oravax, in turn, has subcontracted with the Rockville, MD-based BioReliance to produce the vaccine, and BioReliance also has contracts with the U.S. military to produce the vaccine for military personnel. Julie Bell, *BioReliance to Make Smallpox Vaccine for Civilians: Rockville Company is Expected to Produce at Least 40 Million Doses*, BALTIMORE SUN, Sept. 21, 2000, at 3C.

31. *See e.g., The Many Variables of Smallpox Debate: Uncertainty Muddles Decision on Vaccine*, WASH. POST, June 6, 2002, at A3; Susan Okie, *Studies Cite Smallpox Vaccine Tradeoff; Mass Inoculation Might Kill Hundreds, Save Thousands*, WASH. POST , May 8, 2002, at A3.

32. James W. LeDuc & Peter B. Jahrling, *Strengthening National Preparedness for Smallpox: an Update*, 7 EMERGING INFECTIOUS DISEASES 155, 156 (2001).

1970 that if fifty kilograms of virulent *F. tularensis* was dispersed as an aerosol over a metropolitan area with a population of five million, there would an estimated 250,000 incapacitating casualties, including 19,000 deaths.[33]

CDC holds an IND for a vaccine against tularemia, which has been used to protect laboratory personnel routinely working with the agent. Given the short incubation period of the disease and the incomplete protection of current vaccines against inhalational tularemia, vaccination is not recommended for post-exposure prophylaxis. After exposure or diagnosis, early antibiotic treatment is recommended. With appropriate therapy, overall mortality is two percent.

6. Viral hemorrhagic fevers

The term viral hemorrhagic fever (VHF) refers to a group of illnesses that are caused by several distinct families of viruses. While some types of hemorrhagic fever viruses can cause relatively mild illnesses, many of these viruses cause severe life-threatening diseases.

Viruses associated with most VHFs naturally reside in an animal host (e.g. rodents, arthropods). Ticks and mosquitoes serve as vectors for some of the illnesses. However, the hosts of some viruses, such as Ebola and Marburg, remain unknown.

In general, therapy is limited to supportive care, as neither prophylactic nor post-exposure treatments exist for most VHFs.[34]

III. BECOMING A DRUG OR VACCINE: THE FDA APPROVAL PROCESS

A. The Statutes

As a federal administrative agency, FDA is governed and constrained in its actions by statutes enacted by Congress. Roughly a century ago, Congress passed two statutes that have set the framework for FDA's regulatory authority over drugs, medical devices and biological products, including vaccines. These statutes are the Federal Food, Drug, and

33. CENTER FOR CIVILIAN BIODEFENSE STRATEGIES, Tularemia, *available at* http://www.hopkinsbiodefense.org/pages/agents/agenttularemia (last visted Nov. 12, 2002).

34. A licensed vaccine has greatly reduced the risk of yellow fever, and a vaccine developed by the U.S. Army and currently under an IND for Argentine hemorrhagic fever has effectively reduced the incidence of that disease. Franz & Zajtchuk, *supra* note 2, at 159.

Cosmetic Act (FD&C Act)[35] and the Public Health Service Act (PHS Act)[36] (originally the Biologics Control Act). This section will briefly discuss the history of these statutes and the nature of the authority they confer on FDA.

Congressional efforts to protect the public from unsafe medicines date back to the turn of the 20th century. In the late 1800s and early 1900s, Congress became increasingly concerned about the sale of dubious "patent medicines" that were at best a waste of consumers' money and at worst a serious threat to health. Even products containing opium, morphine, heroin or cocaine were sold without restrictions.[37] This, combined with serious concerns about the lack of food sanitation, led Congress to pass the 1906 Pure Food and Drugs Act.[38] The law prohibited the interstate shipment of "adulterated" or "misbranded" food and drug products and empowered FDA—then called the Bureau of Chemistry—to go to court to stop the distribution of these products.[39] However, the law was fairly weak in that it did not provide affirmative requirements for drug safety, such as premarket testing, and did not require ingredient labels or warnings. Moreover, the government could not prohibit product claims unless they could be shown to be both false and fraudulent.[40] Thus FDA could take action only after a product was marketed, and only if FDA

35. 21 U.S.C. § 301 (2000).

36. Biologics Control Act, Pub. L. No. 57-244, 32 Stat. 728 (1902).

37. WALLACE F. JANSSEN, *The Story of the Laws Behind the Labels, Part I*, FDA CONSUMER (1981), *available at* http://vm.cfsan.fda.gov/~lrd/history1.html-#toc (last visited June 25, 2002).

38. Federal Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906).

39. *Id.* The Bureau of Chemistry, under the U.S. Department of Agriculture, enforced the 1906 law until 1927 when it was reorganized. Law enforcement functions were separated from agricultural research in order to emphasize and secure better funding for the latter. The Food, Drug, and Insecticide Administration was formed, to be renamed in 1931 as the Food and Drug Administration. In 1940, to prevent recurring conflicts between producer and consumer interests, FDA was transferred from the U.S. Department of Agriculture to the Federal Security Agency, which, in 1953, became the Department of Health, Education, and Welfare -- now the Department of Health and Human Services. *Id.*

40. Richard A. Merrill, *Symposium on Regulating Medical Innovation: The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1761 (1996) (discussing 1906 Act).

could show actual knowledge by the seller that the claims it made were false.[41]

Since 1906, Congress has incrementally strengthened FDA's authority over medicines. The 1938 Federal Food, Drug, and Cosmetic Act created the statutory entity of "new drug" and required any manufacturer of a new drug to notify FDA prior to marketing.[42] FDA was granted the authority to review the safety of new drugs and to prohibit unsafe products from being marketed.[43] FDA was also empowered to obtain injunctions against manufacturers to inspect manufacturing facilities.[44] FDA was also no longer required to prove intentional falsity in order to remove a product containing false claims.[45]

The 1938 Act was nevertheless limited in that it put the burden on FDA to affirmatively challenge a product to prevent its future marketing. The Act also did not give the agency authority to oversee drug efficacy. The 1962 Amendments to the Act[46] introduced three fundamental changes to the law and thereby launched the "modern U.S. drug regulatory system."[47] First, the Amendments changed the new drug review system from one of premarket notification, under which the maker of a new drug could begin marketing after 180 days unless FDA challenged its safety, to a premarket approval regime, under which the manufacturer could not begin marketing until agency officials approved the product.[48] This change gave FDA "an effective veto" over products for which it had concerns.[49] Second, the Amendments explicitly directed FDA to review new drugs for both safety and effectiveness. Finally, the 1962 Amendments expanded FDA's authority over the design and conduct of clinical trials of new drugs and specified that the effectiveness of a drug must be demonstrated by

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41. *Id.*

42. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-117, 52 Stat. 1040 (1938).

43. Merrill, *supra* note 40, at1761-1762.

44. Wallace F. Janssen, The Story of the Laws Behind the Labels, *Part II: 1938 – The Federal Food, Drug, and Cosmetic Act*, FDA CONSUMER, June 1981, *available at* http://www.cfsan.fda.gov/~lrd/hitorla/html (last visited November 14, 2002).

45. *Id.*

46. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified in various sections of 21 U.S.C.).

47. Merrill, *supra* note 40, at 1764.

48. *Id.* at 1764-1765 (discussing the Drug Amendments of 1962(*see supra* note 46)).

49. *Id.* at 1765.

"substantial evidence."[50] The Amendments also gave FDA explicit authority to establish standards under which experimental drugs may be shipped to investigators who agree to conduct clinical trials.[51] These two grants of authority have made FDA the "ultimate arbiter of how clinical trials should be designed."[52]

Since 1962, the statute has been amended more than twenty four times. Significant changes occurred in 1976, when Congress granted FDA formal jurisdiction over medical devices.[53] Another significant change occurred in 1992, when Congress passed the Prescription Drug User Fee Act (PDUFA).[54] The statute authorized FDA to assess fees from manufacturers of drugs or biological products and directed FDA to use these fees to hire personnel and carry out activities related to the review and approval of product applications.[55] The statute was reauthorized in 1997 for an additional five years as part of the Food and Drug Administration Modernization Act (FDAMA).[56] The user fee act was set to expire in September 2002, but was reauthorized as part of bioterrorism legislation enacted in June 2002.[57]

Biological products came to be regulated through a different historical and statutory pathway. Four years before the enactment of the first law to regulate food and drugs, Congress passed the Biologics Control Act of 1902, "an Act to regulate the sale of viruses, serums, toxins, and analogous products."[58] The Act was passed in direct response to the deaths of several

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50. 21 U.S.C. § 355(d) (2000).

51. Merrill, *supra* note 40, at 1767 (citing 21 U.S.C. § 355(i)).

52. *Id.* at 1767.

53. Medical Device Amendments of 1976, Pub.L. No. 98-21, 90 Stat. 539 (1976).

54. Prescription Drug User Fee Act, Pub. L. No. 102-571, 106 Stat. 4491 (1992) (codified as amended at 21 U.S.C. § 379(g)-379(h) (2000)).

55. *Id. See also* Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 93, 117-118 (1999).

56. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C. (2000)).

57. On June 12, 2002, President Bush signed into law the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, 116 Stat 594 (2002). Title V of the Act, subtitled the Prescription Drug User Fee Amendments of 2002, reauthorized PDUFA for five years.

58. Biologics Control Act of 1902, Pub. L. No. 57-243, 32 Stat. 728 (July 1, 1902).

children from diphtheria antitoxin that was contaminated with tetanus.[59] More generally, the Act was intended to prevent loss of consumer confidence in the emerging medical treatment called "serum therapy," which was being used successfully to treat diphtheria, smallpox and other infectious diseases.

The 1902 Act established a board comprising the Surgeons General of the Army and Navy and the Supervising Surgeon General of the Marine Hospital Service. The board was given authority to promulgate regulations for licensing establishments engaged in the sale and preparation of viruses, serums, toxins, antitoxins and analogous products in interstate or foreign commerce.[60] The Act made it unlawful to transport or sell products not prepared at a licensed establishment and not carrying the name and license number of the manufacturer and a date beyond which the contents could not be expected to yield "their specific results"--in other words, beyond which they would no longer be potent.[61] The Public Health Service, the successor to the Marine Hospital Service,[62] was given power to inspect the premises of any establishment manufacturing these products and to issue sanctions for violations.[63]

Initially, tests of products and inspections of establishments were carried out by scientists in the Hygienic Laboratory, Division of Pathology and Bacteriology, which was under the direction of the Public Health Service.[64] The Ransdell Act of 1930 changed the name of the Hygienic Laboratory to the National Institute of Health, and increased its functions.[65] In 1937, the biologics control program was assigned to the

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59. In the fall of 1901, 13 children in St. Louis died after receiving diphtheria antitoxin contaminated with tetanus. The serum had been obtained from a horse infected with tetanus. During the same time period, nine children in New Jersey died from tetanus thought to be associated with a smallpox vaccine, although it was later determined that the vaccine was not the cause. Ramunas A. Kondratas, *Biologics Control Act of 1902*, *in* THE EARLY YEARS OF FEDERAL FOOD AND DRUG CONTROL, 14,16 (American Institute of the History of Pharmacy ed., 1982).

60. *Id.* at 16.

61. Biologics Control Act, *supra* note 58.

62. *See* Ramunas Kondratas, *Images From the History of the Public Health Service: A Photographic Exhibit* (providing a photographic history of the U.S. Public Health Service), *at* http://www.nlm.nih.gov/exhibition/phs_history/preface.html (last visited June 14, 2002).

63. Kondratas, *supra* note 59, at 16.

64. These scientists also carried out research, including original scientific work to establish the American standard of potency for diphtheria antitoxin and other vaccines. Kondratas, *supra* note 59, at 19.

65. Randsell Act, Pub. L. No. 71-251, 46 Stat. 379 (1930).

newly established Division of Biologics Control. In 1944, the Division was redesignated the Biologics Control Laboratory. In 1955, it was detached from the Institute and expanded into a separate Division of Biological Standards. In 1972, the organization was transferred from the Institute to FDA jurisdiction and renamed the Bureau of Biologics. During the 1980s, the drug and biologic divisions of FDA were briefly joined, but were later severed again into two independent centers: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

The 1902 Act did not require a demonstration of product effectiveness.[66] Nor did the 1944 Public Health Service Act (PHS Act)[67] which superseded the 1902 Act and required manufacturers of biological products to demonstrate that they were "safe, pure, and potent" as a condition of licensing.[68] Nevertheless, in practice, a demonstration of effectiveness has historically been imposed. For example, in 1934, the National Institute of Health promulgated a regulation formalizing this requirement, which provided that "licenses for new products shall not be granted without satisfactory evidence of therapeutic or prophylactic efficiency."[69] In addition, in 1972 FDA explicitly stated in regulations that biological products were also subject to the drug provisions of the FD&C Act.[70] This understanding was formally codified in legislation under FDAMA.[71] Thus, in practice, the requirement of safety, purity and potency has come to be understood as parallel to safety and effectiveness. The manner in which FDA has chosen to ensure the safety and effectiveness of vaccines will be discussed in subsection C below.

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66. JOHN SWANN, *Public Policy on Drug Efficacy*, *in* THE INSIDE STORY OF MEDICINES: A SYMPOSIUM, at 228 (Gregory J. Higby and Elaine C. Stroud, eds., 1997).

67. 42 U.S.C. § 1201(2000).

68. 42 U.S.C. § 262(a)(2)(B)(i)(I) (2000).

69. Swann, *supra* note 66, at 230.

70. *See* 37 Fed. Reg. 4004 (Feb. 25, 1972); *See also* 37 Fed. Reg. 16679 (Aug. 18, 1972); 38 Fed. Reg. 4319 (Feb. 13, 1973).

71. 21 U.S.C § 355 (2000) states:

> The Federal Food, Drug, and Cosmetic Act (21 U.S.C. §301) applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such act.

B. The Process of Drug Approval

The FD&C Act prohibits the interstate distribution of any "new drug," i.e., any drug that is "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof."[72] Section 505 of the FD&C Act provides that a person seeking to market a new prescription drug must file a new drug application (NDA) with the Secretary of Health and Human Services,[73] containing:

> (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (F) specimens of the labeling proposed to be used for such drug.[74]

Information concerning a drug's safety must be derived from "adequate tests by all methods reasonably applicable."[75] The NDA also must contain "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."[76]

The 1962 Amendments to the FD&C Act defined substantial evidence as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under

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72. 21 U.S.C. § 321(p)(1) (2000).

73. Although the text of the statute confers the authority on the Secretary of Health and Human Services, the authority has been delegated to the FDA Commissioner. Delegations from the Secretary of Health and Human Services to the Commissioner of Food and Drugs, 21 C.F.R. § 5.10 (2002).

74. 21 U.S.C. § 355(b)(1) (2000).

75. *Id.* § 355(d).

76. *Id.*

> the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.[77]

The text of the statute provides only a spare outline of the requirements for drug approval. Through the development and issuance of regulations—as well as more informal communications such as guidance documents—FDA has put "flesh on the bones" of the statutory requirements to provide additional specification and clarity regarding the types and number of studies that are generally required as a condition of approval.

At the heart of FDA's requirements for drug approval is the clinical trial. The "history of the effectiveness requirement in drug regulation is inextricably linked to the advent of the randomized, controlled clinical trial as the cornerstone of medical research."[78] The phrase "randomized controlled clinical trial" (RCT) refers to studies in humans in which participants (typically called "subjects") are randomly assigned to receive the drug under investigation or a "control," i.e., another substance such as a placebo or an approved drug for the same disease or condition.[79] RCT's are typically also "double-blinded," meaning that neither the subject nor the investigator knows to what group the subject has been assigned.[80] Within the scientific community, the RCT is generally considered to provide an accurate, objective and scientific assessment of a drug's safety and effectiveness.[81] It is premised on the assumption that randomization increases the comparability between the groups and decreases any potential bias, thereby increasing the generalizability of the results to patients outside the test groups.[82] FDA's regulations therefore incorporate the principles of RCTs, including randomization, control, double-blinding and determination of minimum sample size.[83]

Before beginning to test a drug in humans, however, the "sponsor" of that drug must submit an IND application to the agency.[84] The IND is

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77. *Id.*

78. Jennifer Kulynych, *Will FDA Relinquish the "Gold Standard" for New Drug Approval? Redefining "Substantial Evidence" in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L. J. 127, 131 (1999).

79. *Id.*

80. *Id.*

81. *Id.*

82. *Id.*

83. Id. at 129 (citing 21 C.F.R. § 314.126 (2002)); See also, FOOD AND DRUG ADMIN., U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES, *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications* (1988).

84. 21 U.S.C. § 355(i) (2000).

intended to protect human subjects by ensuring that unapproved products are not administered absent some basis, gleaned through laboratory and animal testing, upon which to assess the safety and potential usefulness of the drug. Thus, the statute provides that the IND application must contain information regarding the "design of the investigation and adequate reports of basic information . . . necessary to assess the safety of the drug for use in clinical investigation" and "adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies."[85] FDA's concerns regarding the pre-clinical studies are threefold: (1) animal studies should be reasonable predictors of a drug's pharmacological activity; (2) toxicity studies should be undertaken so as to reveal potential adverse reactions in humans; and (3) laboratories undertaking non-clinical toxicity testing should conform to good laboratory practices.[86]

FDA regulations also mandate that the research that is the subject of the IND be reviewed and approved by an institutional review board (IRB).[87] FDA regulations set standards for IRBs reviewing clinical investigations to support new product applications to FDA,[88] and authorize FDA inspection of IRB records[89] and the imposition of sanctions for failure to comply with FDA regulations.[90] In practice, however, FDA has a "very limited ability to inspect and evaluate the work of IRBs,"[91] and leaves oversight responsibility largely to the IRB and its governing institutions.[92]

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85. 355 U.S.C. § 355(i)(2)(A), (B) (2000).

86. RICHARD A. MERRILL, *FDA Regulation of Clinical Drug Trials*, *in* THE HANDBOOK OF PSYCHOPHARMACOLOGY TRIALS: AN OVERVIEW OF SCIENTIFIC, POLITICAL, AND ETHICAL CONCERNS 68 (Marc Hertzman & Douglas E. Feltner, eds., 1997).

87. 21 C.F.R. § 56 (2002).

88. *Id.*

89. 21 C.F.R. § 56.115(c) (providing that the "Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.").

90. 21 C.F.R. § 56.120-124. (Sanctions include disqualification of the IRB and/or the institution at which the IRB operates).

91. Sharona Hoffman, *Continued Concern: Human Subject Protection, the Institutional Review Board, and Continuing Review*, 68 TENN. L. REV. 725, 734 (2001). For example, although there are between 3,000 and 5,000 IRBs in the United States, FDA is able to inspect only a few hundred each year.

92. *Id.* at 769. According to a recent Federal Register notice, FDA intends to issue a proposed rule that would require all IRBs to register with the agency, in

FDA considers the administration of an IND to a human being to constitute research. Notwithstanding exceptions to be discussed later in this paper, FDA, in general, authorizes the administration of an investigational product only in the context of a clinical research trial. Furthermore, because the subjects of the trial are being asked to participate in an endeavor in which the prospect of direct therapeutic benefit is uncertain and will likely entail risk—which in some cases may be greater than standard treatment—the statute requires that the sponsor obtain their consent.[93]

The manner in which consent must be obtained and documented is specified in FDA regulations.[94] The statute provides for exceptions to the consent requirement "where it is not feasible or it is contrary to the best interests of such human beings."[95] As discussed below, the circumstances under which exceptions to the consent requirement are legitimate became a contentious issue following the Gulf War. Exception to consent remains of significant concern where drugs to counter bioterrorism are at issue.

Unless FDA objects, clinical trials may begin thirty days after the IND is received by FDA.[96] Thereafter, they may proceed unless FDA places a "clinical hold" on the IND. The statute authorizes this action upon a determination that the drug involved "represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation."[97]

The clinical trial process is typically described as consisting of three pre-approval phases. During Phase I, the drug is tested on a small number of patients or healthy volunteers, usually 20 to 80, to study how the drug is tolerated, metabolized and excreted. Phase I studies are not generally designed to assess drug efficacy although they may provide some initial evidence in this regard.[98] Phase II studies are larger, generally comprising

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order to facilitate FDA inspection of and communication with IRBs. The proposed rule would require IRBs to provide FDA with the name of the institution operating the IRB and the names of the senior officer of the institution and IRB chair, along with their contact information, the range of active protocols (small, medium, or large) involving FDA-regulated products reviewed in the previous calendar year and a description of the types of FDA-regulated products reviewed. 67 Fed. Reg. 33039, 33063 (May 13, 2002).

93. 21 U.S.C. § 355(i)(4) (2000).

94. 21 C.F.R. §§ 50.20, 50.25, 50.27 (2002).

95. 21 U.S.C. § 355(i)(4) (2000).

96. 21 U.S.C. § 355(i)(2) (2000).

97. 21 U.S.C. § 355(i) (2000).

98. 53 Fed. Reg. 41516, 41518 (Oct. 21, 1988).

of 50 to 200 patients, and it is the first time when both safety and effectiveness are evaluated.[99] Finally, Phase III trials may include between 200 and 1,000 patients or more, and are intended to confirm and expand upon the safety and efficacy data obtained from the first two phases.[100] These phases are not statutorily required, and they are by no means absolute: indeed, some officials within FDA have tried to get away from the "phase I, II, III" terminology because of concerns that it conveys an unduly "mechanistic" description of the process.[101] Nevertheless, the terminology appears to remain the standard in the scientific and legal literature, common parlance and FDA's own regulations.[102]

The statute does not mandate any particular number of clinical trials that must be performed to satisfy the requirement for "substantial evidence," but merely requires "adequate and well-controlled clinical investigations."[103] Historically, based on the use of the plural "investigations," FDA required at least two studies demonstrating effectiveness.[104] Critics of this two trial "gold standard" have argued that it is inefficient and unnecessary in light of modern drug development methods, and needlessly adds to the cost and time of drug development.[105] FDA has, in recent years, signaled its willingness to consider approval based on one pivotal phase III clinical trial under certain circumstances. FDAMA explicitly authorized FDA to accept, as substantial evidence, data from only one clinical trial upon a determination that "data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness."[106] The agency's 1998 guidance addressing FDAMA's amendment to the law specifies the conditions under which FDA may be willing to approve a drug or biological product based on fewer than two effectiveness trials.[107] These are when: (1) effectiveness

99. *Id.*

100. *Id.*

101. For example, a 1997 Guidance Document suggested that a Phase II study be referred to as "therapeutic exploratory" and a Phase III study be referred to as "therapeutic confirmatory." Kulynych, *supra* note 78, at 143, (citing Food and Drug Admin., International Conference on Harmonization; Guidance on General Considerations for Clinical Trials, 62 Fed. Reg. 66, 113 (Dec. 17, 1997)).

102. 21 C.F.R. § 312.21 (2002).

103. 21 U.S.C. § 355(d) (2000).

104. Richard A. Merrill, *supra* note 86, at 84.

105. Kulynych, *supra* note 78, at 130.

106. 21 U.S.C. § 355(d).

107. *Id.*

can be adequately demonstrated using existing studies of another claim or dose (e.g., approval for pediatric use on the basis of studies in adults); (2) a controlled trial of a specific new use is supported by evidence from adequately controlled trials from related uses, dosages or endpoints; and (3) a single multicenter trial provides statistically convincing and clinically meaningful evidence of effectiveness, supported by confirmatory research.[108]

It has always been possible for sponsors to meet informally with agency officials before beginning the clinical trial to discuss study design and methodological issues.[109] However, prior to 1997, there could be no guarantee that, after the trials were conducted, an FDA reviewer would not impose additional requirements. FDAMA provided a specific right to meet with FDA officials to negotiate specifications for the effectiveness trials and to obtain a written agreement as to these specifications.[110] The written agreement becomes part of the administrative record and may not be augmented by FDA unless substantive scientific or safety issues arise.[111]

In addition to ensuring safety and effectiveness, clinical trials also serve a "weeding out" function. According to a recent study of approval success rates for investigational drugs, the approval success rate for new chemical entities for which INDs were filed between 1990 and 1992 (the latest time period analyzed) was only 17.3 percent.[112] Economic considerations (e.g., limited commercial market, insufficient return on investment) and difficulty demonstrating efficacy were cited as reasons for abandoning research activities on an NCE prior to marketing approval in a significant percentage of cases.[113]

However, the high threshold of proof required for drug approval is not without cost. According to a recent study by the Tufts Center for the Study of Drug Development, the average prescription drug takes twelve

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108. Kulynych, *supra* note 78, at 146, (citing FOOD AND DRUG ADMIN., *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, 5 (May 1998)).

109. 21 C.F.R. § 10.65.

110. Pub. L. No. 105-115, § 119, 111 Stat. 2317 (1997), codified at 21 U.S.C. § 355(b)(4)(C) (2000).

111. 21 U.S.C. § 355(b)(4)(C). *See also* Kulynych, *supra* note 78, at 147.

112. Joseph A. DiMasi, *Risks in new Drug Development: Approval Success Rates for Investigational Drugs*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 297, 300 (2001). (Approval success rates ranged from 12.3 percent for self-originated NCEs to 37.3 percent for acquired NCEs).

113. *Id.* at 304.

years and costs $802 million to bring to market.[114] Particularly when a drug is not expected to reap large profits, the costs of conducting clinical trials may deter a manufacturer from pursuing clinical trials at all, or from organizing the data and undertaking the administrative burden of preparing and submitting an NDA. Drugs may therefore languish in the IND phase for lack of a willing shepherd. This is the case with several vaccines for agents on CDC's bioterrorism list—CDC holds an IND but there is no financial incentive or regulatory pressure to bring them from the investigational to the approved stage. While the Orphan Drug Act, discussed later in this article, has helped provide incentives to produce financially non-remunerative drugs, it has not yet been applied in the bioterrorism context.

Finally, it should be noted that while a product is, from a regulatory standpoint, "investigational" until the moment FDA approves the NDA, what is known about the product's safety and effectiveness is by no means static during the clinical trial process. There is no "magic moment" at which a product changes from being considered completely ineffective and unsafe to clearly safe and effective. Rather, there is a steady accretion of knowledge concerning a product as clinical investigations proceed until the product reaches the threshold set by FDA. As FDA has acknowledged:

> [v]irtually all drugs can be toxic to humans, and no drug is completely free of risk. In approving a new drug for marketing, FDA analyzes benefits and risks, and approves a drug if the benefit outweighs the risks. In general, the more serious the illness and the greater the effect of the drug on that illness, the greater the acceptable risk from the drug. If products provide meaningful therapeutic benefit over existing treatment for a life-threatening disease, a greater risk may also be acceptable.[115]

Thus, there may be, and often are, points before enough data has been accrued to satisfy FDA requirements or to warrant approval for the general population at which there is nevertheless some basis to believe that the product has therapeutic value. That FDA permits the administration of investigational-status products to patients under certain conditions – as will be discussed in section V—is recognition of the fact that a product can simultaneously be investigational and potentially therapeutic. This "gray zone" became a point of contention during the Gulf War and is an impediment to the use of products to counter

114. Robert Pear, *Research Cost For New Drugs Said to Soar*, N.Y. TIMES, Dec. 1, 2001, at C1.

115. 57 Fed. Reg. 13234, 13236 (Apr. 15, 1992).

bioterrorism. As is proposed in section VII, the development of an interim category of product approval, limited to use for military and homeland defense and subject to stringent limitations and requirements, could alleviate the concerns raised by the use of investigational products while fostering wider availability of products to counter bioterrorism.

C. The Process of Vaccine Approval

A biological product, which includes a vaccine, is defined under the PHS Act as:

> a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.[116]

The statute prohibits the distribution of any biological product unless FDA has approved a "biologics license" for that product.[117] The statute states that an application "shall be approved" if the applicant: (1) demonstrates that the biological product is "safe, pure, and potent"; (2) shows that the facility in which the biological product is manufactured, processed, packed or held "meets standards designed to assure that the biological product continues to be safe, pure, and potent"; and (3) consents to the inspection of the facility that is the subject of the application.[118] FDA regulations prescribe the format and content of an application for a biologics license (BLA),[119] which must include (1) data from nonclinical laboratory and clinical studies demonstrating that the manufactured product meets prescribed requirements of safety, purity and potency; (2) a "full description of manufacturing methods;" and (3) data establishing the stability of the product.[120]

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116. 42 U.S.C. § 262(i) (2000).

117. 42 U.S.C. § 262(a).

118. *Id.* § 262(a)(2)(B).

119. Prior to 1999, FDA required a biologics applicant to file two separate applications, a "product license application" addressing the safety, purity and potency of the biological product, and an "establishment license application" addressing the manufacturing facility and methods. In 1999, FDA issued a final rule eliminating the requirement for separate applications and replacing it with the requirement for the submission of a "biologics license application" or BLA. The BLA reduced the amount of information that had been required in the ELA, but did not eliminate it. 64 Fed. Reg. 56441 (Oct. 20, 1999).

120. 21. C.F.R. § 601.2(a) (2002).

The vaccine development and approval process shares many features with that for drugs: animal and laboratory testing begins the research process; clinical trials are almost always needed to establish safety and effectiveness; and an IND is required in order to conduct clinical testing. While the statutory standard under the PHS Act is "safety, purity, and potency," as stated previously, FDA has traditionally interpreted it to require the same amount and type of data as the safety and effectiveness standard applied to drugs.

However, vaccine development has historically differed from drug development, and consequently the manner of regulation has been different as well. Prior to the advent of recombinant DNA technology, vaccines were developed using either whole live attenuated (i.e., weakened) organisms, killed whole organisms, or inactivated toxins.[121] Vaccines were originally prepared in live animals, a method prone to contamination with bacteria and other adventitious agents, and the antigenic and allergenic character of the accompanying animal protein could potentially result in sensitization and allergic reactions.[122] More recently, animal cells grown in culture have been used, which reduce these risks somewhat but do not eliminate them.

As a class, vaccines are distinct from drugs in three principal respects. First, they are difficult to characterize, making it difficult to precisely analyze their molecular composition.[123] Second, as a consequence of the difficulty of characterization, proper evaluation typically requires in vivo testing (i.e., in a living animal or human system). Third, quality cannot be assured from final tests on random samples but rather must be determined from a combination of in-process tests, end-product tests and strict controls of the entire manufacturing process.[124]

These differences mean that the quality of a vaccine is closely linked to the process for its manufacture, which must be rigorously controlled to ensure that batches of vaccines produced on different occasions are of reproducible and consistent quality. Quality is achieved through the application of current good manufacturing practices (GMPs), which are not static but rather evolve as scientific progress, technical development and experience help to identify deficiencies and make improvements

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121. Gregory A. Poland, *Current Paradoxes and Changing Paradigms in Vaccinology*, 17 VACCINE 1605, 1608 (1999).

122. Rosenthal, *supra* note 28, at 921.

123. U.S. GEN. ACCOUNTING. OFFICE, GAO/T-NSIAD-99-148, MEDICAL READINESS: SAFETY AND EFFICACY OF THE ANTHRAX VACCINE 2-3 (1999). [hereinafter GAO REPORT: SAFETY AND EFFICACY OF THE ANTHRAX VACCINE].

124. *Id.*

possible. GMPs apply not only to the manufacturing process but also to the facilities and equipment in which the product is manufactured. In short, FDA regulations and attitudes reflect a much greater concern with the method of vaccine production than with drugs, based on the underlying belief that the "process is the product."

Because regulation of vaccines is tied to advances in technology to an even greater extent than for drugs, FDA regulation of vaccines has become more stringent over time. As technology has permitted greater precision and control in the production process, FDA has demanded higher standards.[125] FDA has in recent years placed particular emphasis on inspection of biologics facilities to review GMP compliance. In 1998, CBER established Team Biologics, a group specifically tasked with conducting post-approval inspections of biologics manufacturing facilities,[126] in order to "focus resources on inspectional and compliance issues in the biologics area."[127] Given this heightened emphasis on process,

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125. A recent report by the RAND corporation describes the way in which the science has changed over time:

> [m]olecular biology has allowed scientists to clone and characterize the molecules that determine virulence and confer immunogenicity and has thus allowed the development of new vaccine strategies. Advances in cell biology have led to a greater understanding of cellular and molecular interactions after infection. The Institute of Medicine cited eight major areas of increased scientific understanding over the past fifteen years: the role of helper T cells in antibody and cell-mediated immunity; mucosal immune system organization; molecular aspects of virulence; design of recombinant protein vaccines; novel vaccine delivery systems; development of novel adjuvants; and vaccine against autoimmune diseases. These scientific advances have led to advanced vaccine target selection, increased ability to characterize vaccines more accurately, greater purity of vaccines, and improved safety and efficacy profiles.

Richard A. Rettig, Jennifer Brower, and Orlie Yaniv, Drugs & Biologics: Development & Acquisition for CW/BW Defense, at 25 (unpublished draft report, on file with author).

126. Team Biologics is a partnership between FDA's Office of Regulatory Affairs and CBER. The goal of Team Biologics is to "ensure the quality and safety of biological products and quickly resolve inconsistencies and bring products into compliance." It is designed to "promote uniformity between CBER and the field and among FDA field components associated with inspections, policy implementation, and current good manufacturing practice interpretation." 63 Fed. Reg. 36699, 36699-36700 (July 7, 1998).

127. CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMIN., *Team Biologics, A Plan For Reinventing FDA's Ability to Optimize*

vaccines approved in past decades would face significantly more difficult requirements if approval were sought today. As will be seen below in the discussion of the anthrax vaccine, this has been a problem for "legacy" vaccines developed through traditional methods.[128]

Finally, vaccines differ from drugs in another crucial respect. The vast majority of drugs are developed to cure or ameliorate existing diseases or conditions. While in recent years more emphasis has been placed on prevention (e.g., lower cholesterol, maintain bone density), even these drugs target known correlates of future disease in the context of diseases whose statistical likelihood is fairly predictable. Thus, whereas the risks of a drug are balanced against the risks of the disease it is treating or preventing, the risks of a vaccine must be weighed against the risk of exposure and risk of harm from the disease in the event exposure occurs. Since vaccines are almost always intended for administration to healthy people, and the risk of exposure can never be predicted with complete certainty, particularly when the risk stems from feared bioterrorist events, it may be much more difficult to decide when exposure to the risk of adverse reactions from the vaccine is warranted. Such decisions can be expected to be fraught with disagreement and controversy.

D. Drugs and Vaccines to Counter Bioterrorism: FDA's Animal Efficacy Rule

Demonstrating the effectiveness of drugs and vaccines to counter bioterrorism is more challenging than for many other products because of ethical constraints on the conduct of clinical trials. The best test of the effectiveness of a vaccine to counter a biological agent would be to vaccinate individuals and then expose them to the agent. Failure to contract the disease would be strong evidence of the vaccine's effectiveness. Similarly, recovery from the disease following administration of an investigational drug would be convincing evidence of the drug's effectiveness. Neither of these trial designs would, however, be ethical, as they would require the administration of a potentially lethal substance to healthy human volunteers in the absence of any proven treatment that could be administered if the vaccine or drug being tested were ineffective.[129]

Compliance of Regulated Biologics Industries, *available at* http://www.fda.gov/cber/genadmin/teambio.htm (last visited June 25, 2002).

128. IOM Report, *supra* note 10, at 182.

129. *Id.* at 61.

In 1999, FDA issued a proposed rule addressing this problem.[130] The proposed rule stated FDA's conclusion that requiring human efficacy studies "has the effect of preventing the development and availability" of drug and biological products "to reduce or prevent serious or life-threatening toxicity resulting from exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances."[131] Thus, to promote the availability of such products, FDA proposed to eliminate the requirement for efficacy data derived from human studies and to instead grant marketing approval for a new drug or biological product on the basis of adequate and well-controlled animal trials under certain conditions.

On May 31, 2002, nearly three years after it first proposed the rule, FDA issued a final rule authorizing FDA to base a determination of effectiveness for drugs and biological products used to reduce or prevent the toxicity of chemical, biological, radiological or nuclear substances solely on data derived from animal studies.[132] The rule is intended to address those situations in which "adequate and well-controlled efficacy studies cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers" and field trials prior to approval are not feasible.[133] FDA specified four criteria that must be met in order to base a determination of effectiveness on animal studies.[134] In

130. 64 Fed. Reg. 53960 (Oct. 5, 1999).

131. *Id.* at 53963.

132. 67 Fed. Reg. 37988 (May 31, 2002). Interestingly, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, 116 Stat. 594 (2002) which was signed into law on June 12, 2002, imposed a 90-day deadline on FDA to complete the rulemaking process for the animal efficacy rule. It is unclear whether awareness of this impending deadline spurred FDA's completion of the rulemaking process.

133. *Id.* at 37989.

134. *Id.* at 37995-37997 (to be codified at 21 C.F.R. pts. 314.610(1)-(4), 601.91a(1)-(4)(2002)) ("(1) There is a reasonably well-understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product; (2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a single well-characterized animal model (meaning the model has been adequately evaluated for its responsiveness) for predicting the response in humans; (3) The animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and (4) The data or information on the

addition, approval pursuant to the new rule is subject to three requirements. First, the manufacturer must conduct postmarketing safety and clinical benefit studies, to the extent such studies are feasible and ethical, i.e., in the event of an exposure or possible exposure to a lethal or potentially disabling substance.[135] Applications for approval must include a plan for postmarketing studies. Second, FDA approval will be conditioned on "such postmarketing restrictions as are needed to ensure safe use of the drug product."[136] Finally, patient labeling for the products must state that the drug's approval was based on efficacy studies conducted in animals only, in addition to providing information typically included in patient labeling, such as foreseeable risks, potential adverse reactions and contraindications.[137] Notably, the rule does not impose an absolute requirement that labeling be provided to patients prior to the administration of the product, but states that this must be done "if possible."[138]

The rule became effective as of July 1, 2002. It is therefore too soon to determine whether it will result in greater availability of products to counter biological attacks. This will depend in large measure on the manner in which it is applied by FDA to particular products (e.g., the number of animal species from which FDA requires data, the length of time for which tests must be conducted).[139] Similarly uncertain is the degree to which pharmaceutical companies will choose to take advantage of the new rule. As has been noted, drugs to counter bioterrorism have

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pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well-understood to allow selection of an effective dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.").

135. *Id.* (to be codified at 21 C.F.R. pts. 314.610(b)(1), 601.91(b)(1)).

136. *Id.* (to be codified at 21 C.F.R. pts. 314.610(b)(2), 601.91(b)(2)). (These conditions could include restricting distribution to specially trained personnel, requiring particular medical procedures to be performed, such as medical followup, and requiring compliance with specified recordkeeping obligations).

137. *Id.* (to be codified at 21 C.F.R. pts. 314.610(b)(3), 601.91(b)(3)).

138. *Id.*

139. FDA estimates that the rule will be applied infrequently, probably once every three years. 64 Fed. Reg. at 37994. Janet Woodcock, the Director of FDA's Center for Drug Evaluation and Research, stated her view that the rule is "narrowly drawn," that it will usually require two or more animal tests, and that it could be invoked only when all other FDA testing standards are inappropriate. Marc Kaufman, *FDA Acts To Speed Bioterror Medicines*, WASH. POST, May 31, 2002, at A1.

historically constituted a "niche" market with limited profits,[140] and the extent to which 9/11 and its aftermath have caused substantive alterations in this market remains to be seen. It should also be noted that the ability to use animal data exclusively applies only to the effectiveness requirement; safety must still be demonstrated using human subjects. It is unclear how extensive FDA's safety testing requirements will be for these products, and therefore how long product approval will require. Notwithstanding these concerns, the new rule is a necessary—but likely insufficient—step toward increasing the availability of products to counter bioterrorism.

IV. HISTORICAL REASONS FOR CONCERN

The purpose of this paper is to examine FDA's role in regulating products to counter biological attacks and to suggest changes that could facilitate the development and approval of new products for this purpose. The topic under consideration necessarily presupposes, however, that there are reasons for concern regarding FDA's influence on the availability of products and that things "could be better" than they are, for reasons both internal and external to FDA. This section examines the bases for such concerns, some of which are related to specific events and others that relate to the perceived "culture" of FDA.

A. DOD and FDA: The Troubling Gulf War Legacy

1. Background

In Operation Desert Storm, the U.S. military faced the frightening possibility that Saddam Hussein would use chemical or biological weapons against U.S. troops; indeed he was known to have used chemical agents against his own population, and available intelligence indicated he might also have biological weapons capability. The chemical threats of particular concern were nerve agents, i.e., chemicals that inhibit the enzyme acetylcholinesterase, a key regulator of cholinergic neurotransmission. Agents in this class include the gases sarin, soman and tabun, and the liquid VX.[141] Biological threats viewed most significant

140. Andrew Pollack and William J. Broad, Traces of Terror: *Bioterrorism; Antiterror Drugs Get Test Shortcut*, N.Y. TIMES, May 31, 2002, at A1.

141. Rettig, *supra* note 17, at 2.

were the microorganism *Bacillus anthracis* (anthrax) and botulinum toxin, produced by the bacterium *Clostridium botulinum*.[142]

Thus, the military sought to protect its personnel through any available means, including both physical (e.g., protective equipment), and chemical/biological (e.g., drugs and vaccines). However, while there existed a FDA-licensed vaccine to protect against anthrax exposure, no agents had been approved by FDA specifically for the purpose of preventing harms from exposure to nerve agents or botulinum toxin. The military therefore sought to administer investigational products—i.e., products for which an IND had been filed with FDA but for which no NDA or BLA had yet been issued—to troops facing potential exposure. Specifically, the military sought to administer the drug pyridostigmine bromide (PB) as a pre-treatment against nerve agent exposure, and botulinum toxin (BT) vaccine to protect against botulism. PB is approved by FDA for treatment of myasthenia gravis and for use in reversing some effects of certain anesthetics. DOD had filed an IND for PB as a pretreatment to nerve agent exposure in 1984.[143] BT vaccine, which had been used for over a decade by individuals in certain agricultural occupations at risk for botulism, was the subject of an IND held by the CDC.

To accomplish its objectives, DOD's Assistant Secretary for Health Affairs submitted a letter to FDA in which it requested the authority to administer products under an IND to troops. The letter detailed the Department's belief that "the best preventive or therapeutic treatment calls for the use of products now under investigational new drug (IND) protocols of the FDA."[144] Further, DOD requested that FDA provide a

142. *Id.*

143. Rettig, *supra* note 17, at 6.

144. 55 Fed. Reg. 52814 (Dec. 21, 1990). The letter further stated, in part:

> [t]hese are not exotic new drugs; these drugs have well-established uses (although in contexts somewhat different from our requirements) and are believed by medical personnel in both DOD and FDA to be safe. For example, one product consists of a very commonly used drug packaged in a special intramuscular injector to make it readily useable by soldiers on the battlefield. Another example involves a vaccine long recognized by the Centers for Disease Control as the primary preventive treatment available for a particular disease, but the relative infrequency of its use has slowed the accumulation of sufficient immunogenicity data to yet support full licensing of the product. Still another example involves a drug in common use at a particular dosage level, but to preserve alertness of the soldiers, we prefer a lower-dosage tablet, which is not an FDA approved product. FDA personnel have been extremely cooperative and

mechanism to waive the requirement of informed consent "in cases in which it is established that military combat exigencies make that necessary."[145]

The considerations underlying DOD's decision to request FDA authorization have never been publicly articulated. It is worth a few moments reflection on the usually unquestioned assumption that DOD was legally required to seek FDA's approval before administering these products to troops facing combat. Notwithstanding a memorandum of understanding (MOU) between FDA and DOD concerning clinical testing of investigational products by the military,[146] DOD could have taken the

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supportive in reviewing our proposed protocols for these products, quickly providing favorable responses to all of our submissions to date.

Id.

145. *Id.* at 52815. The letter further articulated the rationale justifying DOD's request:

> FDA assistance is also needed on the issue of informed consent. Under the Federal Food, Drug and Cosmetic Act, the general rule is that, regardless of the character of the medical evidence, any use of an IND, whether primarily for investigational purposes or primarily for treatment purposes, must be preceded by obtaining informed consent from the patient. The statute authorizes exceptions, however, when the medical professionals administering the product "deem it not feasible" to obtain informed consent.
>
> Our planning for Desert Shield contingencies has convinced us that another circumstance should be recognized in the FDA regulation in which it would be consistent with the statute and ethically appropriate for medical professionals to "deem it not feasible" to obtain informed consent of the patient -- that circumstance being the existence of military combat exigencies, coupled with a determination that the use of the product is in the best interest of the individual. By the term "military combat exigencies", we mean military combat (actual or threatened) circumstances in which the health of the individual, the safety of other personnel and the accomplishment of the military mission require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or for some alternative treatment.

Id. at 52814-52815.

146. 52 Fed. Reg. 33472, 33473 (Sept. 3, 1987) provides:

The FDA and the DOD agree that:

> A. Clinical testing of investigational drugs, biologics, or medical devices under programs sponsored by the DOD and conducted either by the DOD within its own research facilities, or for the DOD by a contractor or grantee will follow the provisions of 21 CFR Part 312 or 21 CFR Part 812 governing the investigational use of new drugs and medical devices in

position that neither FDA's governing statutes nor the MOU were intended to apply to the administration of unapproved products for therapeutic purposes under conditions of imminent combat. For example, DOD could have, if challenged, asserted that distribution of drugs under these circumstances does not constitute distribution in "interstate commerce" within the meaning of the FD&C Act. Furthermore, a court might have determined that the decision to administer products, considered investigational by FDA for the purpose of force protection, was within the sole discretion of the military and therefore nonjusticiable.[147]

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human beings, and FDA's informed consent and Institutional Review Board regulations (21 CFR Part 50 and 21 CFR Part 56).

B. They will continue to cooperate in meeting the requirements of the Federal Food, Drug, and Cosmetic Act and its implementing regulations without jeopardizing the mission of the DOD. To accomplish this goal, they agree that an expeditious review of special DOD requirements to meet national defense considerations will be carried out by FDA. This review would consist of an FDA review of available data on a drug, biological, or device under IND or IDE to determine if stockpiling for future use, or use in an expanded military population is appropriate. When necessary, special reporting requirements would also be established by FDA.

C. It is the general policy of the DOD not to classify medical research and development. However, should it become necessary to classify for reasons of national security the clinical testing of a drug, biologic, or medical device that would normally fall under the provisions of 21 CFR Parts 312 or 812, these studies will be handled under the special provisions of this MOU. The DOD will be solely responsible for determining the security classification of such research projects. If classified studies are required DOD will submit a classified IND or IDE application to be reviewed by appropriate FDA personnel who hold the required security clearances. It will be the responsibility of the FDA to maintain an appropriate cadre of personnel who have security clearances. In the event that a request is made under the Freedom of Information Act for records concerning the research DOD has classified, FDA will refer such requests to DOD for processing and response under DOD regulations.

147. Doe v. Sullivan, 756 F. Supp. 12 (D.D.C. 1991), *aff'd* 938 F.2d 1370 (D.C. Cir. 1991) (rejecting a service member's challenge to Interim Rule 50.23(d) on the basis that the military's decision to administer unapproved drugs to troops was "precisely the type of military decision that courts have refused to second-guess" *Id.* at 15. While the appellate court reversed the lower court's finding on reviewability because it construed the petitioners' challenge as being to FDA, and not DOD's, authority, it did not refute the lower court's assertion that the underlying decision whether or not to administer the drugs was within the sole discretion of the military.).

The point of this thought experiment is not to suggest that DOD's decision to involve FDA was mistaken. Indeed, putting aside the question of uncertain applicability of FDA regulations and the MOU to combat conditions, there are several policy justifications that could be proffered to support at least some degree of dialogue between DOD and FDA concerning the administration of unapproved products under these circumstances. At the very least, recent events have demonstrated that drugs whose initial foreseeable use is uniquely military may rapidly be needed to protect at least some sectors of the civilian population. Thus, there is merit to involving FDA at an early stage of product development. Nevertheless, it is at the same time true that DOD's decision to engage FDA has led to a complex and delicate dance for which both partners were arguably ill-prepared and in which both, at least initially, stumbled.

Although it might have taken another position, DOD acceded to FDA's jurisdiction and requested the authority to administer IND drugs to military personnel. Such a request was not unprecedented; indeed, as will be discussed in greater detail in section V, FDA had expanded and formalized the circumstances under which investigational products could be administered outside the context of a research protocol. What was without precedent, however, was DOD's request that FDA waive the requirement for informed consent that some would argue is a non-waivable prerequisite for clinical use of unapproved products. While FDA's informed consent regulations contain exceptions to the general requirement for informed consent in cases where consent was "infeasible," this exception had previously been narrowly limited to cases of clear incapacity under emergent conditions.[148] FDA ultimately acceded to DOD's interpretation of "infeasibility" that encompassed competent military personnel. As set forth in the waiver request submitted to FDA by the Assistant Secretary of Defense (Health Affairs), DOD believed

148. 21 C.F.R. § 50.20 1990 (providing that "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative." Prior to the Interim Rule, section 50.23(a) provided that consent "shall be deemed feasible" unless both the investigator and a non-participating physician certify in writing that: "(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article. (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject. (3) Time is not sufficient to obtain consent from the subject's legal representative. (4) There is available no alternative method of approved or generally recognized therapy that provides equal or greater likelihood of saving the life of the subject.").

that refusal by individual military personnel of therapies that, while from a regulatory perspective investigational, nevertheless constituted the best available treatment, would constitute an unacceptable threat to other personnel and to combat objectives.[149] Furthermore, notwithstanding the investigational status of the products, DOD viewed their administration as therapeutic, that is, for the purpose of protecting troops from the chemical and biological threats they could potentially encounter. Thus, DOD concluded that their use did not constitute "research involving a human being as an experimental subject" within the meaning of DOD regulations governing human subjects research.[150] And, unlike civilians, the consent of

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149. The Assistant Secretary's request stated:

> [i]n all peacetime applications, we believe strongly in informed consent and its ethical foundations. In peacetime applications, we readily agree to tell military personnel, as provided in FDA's regulations, that research is involved, that there may be risks or discomforts, that participation is voluntary and that refusal to participate will involve no penalty. But military combat is different. If a soldier's life will be endangered by nerve gas, for example, it is not acceptable from a military standpoint to defer to whatever might be the soldier's personal preference concerning a preventive or therapeutic treatment that might save his life, avoid endangerment of the other personnel in his unit and accomplish the combat mission. Based on unalterable requirements of the military field commander, it is not an option to excuse a non-consenting soldier from the military mission, nor would it be defensible militarily -- or ethically -- to send the soldier unprotected into danger.

55 Fed. Reg. 52814, 52815 (Dec. 21, 1990) (regulations repealed).

150. At the time of the Gulf War, DOD's governing statute, 10 U.S.C. § 980, provided that funds appropriated to the Department of Defense could not be used for research involving a human being as an experimental subject unless the informed consent of the subject was obtained in advance, or, in the case of "research intended to be beneficial to the subject," the "informed consent of the subject or a legal representative of the subject" was obtained in advance. When faced with the issue of administering IND drugs to military personnel, Robert Gilliat, the Assistant General Counsel of DOD concluded in a memorandum that "the proposed uses of the drugs in question are, in fact, primarily treatment uses, not uses primarily for investigational or research purposes." Additionally, the memorandum stated:

> [i]n connection with the potential need in Operation Desert Shield for certain treatment uses of the several drugs classified as INDs, it is clear that very unusual circumstances are present. The drugs have all progressed through FDA's IND process sufficiently to establish a high level of confidence on the part of the DOD medical community; the potential effects of the chemical and biological weapons widely reported as available to the Iraqi military are deadly; and the proposed uses, if

military personnel is not required to administer standard medical treatments.[151]

In December 1990, FDA issued Interim Rule 50.23(d) granting the Assistant Secretary's request, but simultaneously imposed several conditions.[152] First, any request for waiver was "limited to a specific military operation or the immediate threat of combat,"[153] and time-limited to twelve months, and any determination that obtaining consent was not feasible was similarly limited. Second, requests were required to include written justification supporting the conclusions of the military physician and investigator identified in the IND that:

> a military combat emergency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate the accomplishment of the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or some alternative treatment.[154]

Third, the requests were required to include a statement that an IRB had reviewed and approved the use of the investigational product without consent.[155] The FDA Commissioner could grant the request "only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy."[156] In making the determination, the Commissioner would consider (1) the

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> approved by the FDA, will reflect the best scientific and medical judgment of the U.S. Government.

Rettig, *supra* note 17, at 21, *quoting* Robert L. Gilliat, Memorandum for the Assistant Secretary of Defense (Health Affairs), "Applicability of Human Subject Research Restrictions to Potential Medical Treatments in Connection with Operation Desert Shield," September 14, 1990.

In 2001, Congress amended 10 U.S.C. § 980 to include a new subsection (b), which provides: "The Secretary of Defense may waive the prohibition in this section with respect to a specific research project to advance the development of a medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws." 10 U.S.C. § 980(b) (2000).

151. Army Regulation 600-20, 5-4 (2002).

152. 55 Fed. Reg. 52814, 52817 (Dec. 21, 1990)(regulations repealed).

153. *Id.*

154. Army Regulation 600-20, 5-4. .

155. *Id.*

156. *Id.*

extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use; (2) the context of the drug's administration, e.g., battlefield, hospital setting or self-administration; (3) the nature of the disease or condition for which the preventive or therapeutic treatment was intended; and (4) the nature of the information to be provided to the recipients of the drug concerning the potential benefits and risks of taking or not taking the drug.[157]

FDA also exempted DOD from many of the record-keeping requirements usually mandated for administration of IND products.[158] DOD contended that detailed record keeping regarding what products were administered, when, and to whom, were not possible under conditions of battle. [159] FDA agreed to waive or reduce some of the record-keeping requirements, and DOD appears to have agreed, before the fact, to conduct some degree of record keeping. Notwithstanding prior agreements, however, DOD was later faulted for its inadequate record keeping, which impeded the ability to study the possible health-effects experienced by veterans.[160]

DOD also requested a waiver from the labeling requirements for IND products. Such products ordinarily must contain language stating "Caution: New Drug—Limited by Federal (or United States) law to investigational use."[161] DOD argued that this language would undermine soldiers' confidence in the product and even encourage non-use.[162] FDA therefore permitted different labeling that stated "FOR MILITARY USE AND EVALUATION."[163]

Following the issuance of the Interim Rule, DOD submitted, and FDA granted, specific waiver requests for PB and BT.[164]

2. Analysis

FDA's waiver of the informed consent requirement generated significant controversy as well as criticism of the agency, and ultimately led to changes in military policy that reverberate to this day. Although the

157. *Id.*

158. 55 Fed. Reg. 52814, 52816 (Dec. 21, 1990)(regulations repealed).

159. Rettig, *supra* note 17, at 17-19.

160. Rettig, *supra* note 17, at 36 (discussing Presidential Advisory Committee report).

161. 21 C.F.R. § 312.6 (1991).

162. Rettig, *supra* note 17, at 17.

163. 64 Fed. Reg. at 54184 (Oct. 5, 1999)(regulations repealed).

164. Rettig, *supra* note 17, at 26-28.

decision was upheld by the U.S. Court of Appeals for the D.C. Circuit as a proper exercise of the agency's authority,[165] many viewed FDA as having been complicit in serious ethical violations perpetrated by DOD against its personnel. Criticism was fueled, in part, by the widespread reports by veterans of an unexplained constellation of debilitating symptoms—what has come to be known as Gulf War Syndrome. While no single definitive cause of Gulf War Syndrome has been identified, PB has been identified as a possible contributor to the development of at least some of the illnesses reported by Gulf War veterans.[166]

Most critics have reflexively taken the position that the lack of informed consent was a clear violation of the Nuremberg Code.[167] This Code, which was promulgated by the tribunal that presided over the trial of the Nazi doctors at Nuremberg in 1947, specifies ten principles that should govern all experiments conducted with human research subjects.[168] The first of these principles – and the one that historically has received the most attention – provides that the "consent of the human subject is absolutely essential."[169] This consent, furthermore, must be voluntary, competent, informed and comprehending.[170]

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165. Doe v. Sullivan, 938 F.2d 1370 (D.C. Cir. 1991).

166. *See e.g.*, BEATRICE ALEXANDRA GOLOMB, A REVIEW OF THE SCIENTIFIC LITERATURE AS IT PERTAINS TO GULF WAR ILLNESSES VOLUME II: PYRIDOSTIGMINE BROMIDE, 1999.

167. *See* George J. Annas, *Protecting Soldiers from Friendly Fire: The Consent Requirement for Using Investigational Drugs and Vaccines in Combat*, 24 AM. J. L. AND MED. 245 (1998); *See also* Claire Alida Milner, *Gulf War Guinea Pigs: Is Informed Consent Optional During War?*, 13 J. CONTEMP. H. L. & POL'Y 199 (1996); Robyn Pforr Ryan, *Should Combat Troops Be Given the Option of Refusing Investigational Drug Treatment?*, 52 FOOD DRUG L.J. 377 (1997); Suzanne B. Seftel, *Justiciability: Waiving for the Flag: Should Informed Consent Rules Apply in the Context of Military Emergencies?*, 60 GEO. WASH. L. REV. 1387 (1992).

168. TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, VOL. 2, 181-182 (1949) [herinafter NUREMBERG MILITARY TRIBUNALS].

169. *Id.* The complete text of the Nuremberg Code provides:

> 1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there

While it is often assumed that the Nuremberg Code is universal in its scope and application, in reality the drafters focused narrowly on what is generally termed as "nontherapeutic" research- that species of research

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should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability or death to the experimental subject.

170. RUTH R. FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT 155 (1986).

that is without potential therapeutic value or purpose for the particular subjects of the research.[171] Such research is ethically suspect because it uses the individual solely as a means to an end completely unrelated to that person's well being.[172] Specifically, non-therapeutic research seeks to use an individual's physical and/or mental capacities solely for purposes not intended or expected to be directly beneficial to that person. While such information may ultimately lead to the development of new therapies, the immediate endpoint of interest is knowledge. Consent is therefore intended to ensure that the subject is a knowing and voluntary participant in this quest for knowledge, has a full appreciation of the risks involved, as well as the fact that there is no expectation of personal benefit.

The other provisions of the Nuremberg Code seek to ensure that the research itself stays within acceptable bounds, i.e., that the research for which consent is being sought is within ethical limits, recognizing that people may, through coercion, ignorance or other factors, agree to participate in research that is inherently morally objectionable.[173]

That the drafters of the Nuremberg Code were directed to nontherapeutic research is logical, given that the Nazi experiments were "willfully harmful," using unwilling captive research subjects to explore physiological effects of, for example, ingesting poisons, infection with various diseases and intravenous injections with ice water--interventions that were clearly not intended to confer any benefit on the subjects.[174] This limited scope of the Nuremberg Code may explain, in part, why many physicians and investigators in the United States after World War II did not view the Code as applicable to their clinical treatment and research activities. They perceived themselves as focused on patient care and on developing interventions with the potential to alleviate their patients' suffering.[175] While this type of research, usually termed "therapeutic" or

171. *Id.* at 156.

172. In developing a moral paradigm for the duties owed to research subjects, Western bioethical thought has relied in part on the writings of the 18th century German philosopher Immanuel Kant. Kant expressed the view that autonomous individuals possess intrinsic value that is independent of external circumstances that confer value. Therefore, autonomous persons are "ends in themselves, determining their own destiny, and are not to be treated merely as means to the ends of others." Faden & Beauchamp, *supra* note 170, at 8.

173. NUREMBERG MILITARY TRIBUNALS, *supra* note 168.

174. Faden & Beauchamp, *supra* note 170, at 153.

175. *Postwar Professional Standards and Practices for Human Experiments*, *in* FINAL REPORT, ADVISORY COMMITTEE ON HUMAN RADIATION 130-170 (1995).

"clinical", also raises ethical concerns, it does so in a quite different context. The Declaration of Helsinki, issued in 1964 by the World Medical Association, explicitly distinguished nontherapeutic from therapeutic research, and sought to develop ethical principles to govern these distinct settings.[176] Like the Nuremberg Code, the Declaration of Helsinki made consent a "central requirement of ethical research." Unlike the Nuremberg Code, however, the Helsinki Declaration recognizes that, in the context of therapeutic research, it may be ethically permissible for the physician conducting the clinical investigation to refrain from obtaining informed consent.[177]

Critics of FDA's grant of a waiver to DOD appear to have taken the position that the administration of a drug classified by FDA as investigational is categorically non-therapeutic research, and that the failure to obtain consent is therefore a *per se* violation of the Nuremberg Code. As George Annas, one of the Interim Rule's most prominent critics, has stated:

> [i]t would seem that the only justification a physician could have for participating in the administration of experimental or investigational agents without consent is that the physician sincerely believes that the agents are therapeutic under combat conditions. This is a difficult position to defend, because *war does not change the investigational nature of a drug or vaccine. (emphasis added)*[178]

Thus, Annas appears to take the position that the regulatory status of a product as investigational is also incontrovertible evidence that the product is non-therapeutic, and therefore failure to obtain consent is a *per se* violation of the Nuremberg Code. Similarly, bioethicist Arthur Caplan, a member of the President's Advisory Committee on Gulf War Veterans'

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176. WORLD MEDICAL ASSOCIATION, DECLARATION OF HELSINKI, (1964) (as amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, and the 35th World Medical Assembly, Venice, Italy, October 1983), *available at* http://ohsr.od.nih.gov/helsinki.php3 (last visited July 10, 2002). The Declaration of Helsinki provides:

> [i]n the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

177. *Id.* §II (5) ("If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.").

178. Annas, *supra* note 167, at 257.

Illnesses, stated that "[t]he use of unapproved, unlicensed agents was clearly understood by FDA and DOD to be research inasmuch as both agencies recognized the need to seek waivers from prevailing informed consent requirements."[179]

It is no doubt true that the doctrine of informed consent "enjoys talismanic – if not sacramental – status in modern life and thought."[180] Consent's resonance stems in part from the real and unfortunate abuses of human subjects that were perpetrated not only by the Nazis, but also by our own government. Examples include the Cold War radiation experiments,[181] the Tuskegee syphilis experiments[182] and the army's experimental administration of LSD to military personnel.[183] The requirement of consent also implicates core Western values of liberty, autonomy and self-determination. Removal of consent invariably and unavoidably raises the specter of a totalitarian regime that seeks to subjugate individual free will and well being for the larger goals of the state.

But an ethical analysis that focuses solely on consent, to the exclusion of other issues, may mask deeper and more troubling concerns. This is particularly the case with the use of investigational products for protection of military personnel and for homeland defense. While there are troubling aspects of both the substance and process of the interaction between FDA and DOD that led to the decision to administer PB and BT during the Gulf War, the single-minded focus on consent has unfortunately served to deflect a thoughtful analysis of these more fundamental issues and to impede regulatory improvements that could avoid similar problems in the future.

At the heart of the decision to administer investigational products to troops is the question of what is the appropriate balance of risks and benefits. There has been no suggestion by even the critics of the Interim Rule, that DOD sought to use PB and BT for other than the direct

179. Rettig, *supra* note 17, at 56.

180. Richard W. Garnett, *Why Informed Consent? Human Experimentation and the Ethics of Autonomy*, 36 CATH. LAW. 455, 456 (1996).

181. U.S. government-sponsored radiation experiments were documented in Final Report, Advisory Committee on Human Radiation Experiments, *supra* note 175.

182. *See* JAMES HOWARD JONES, BAD BLOOD: THE TUSKEGEE SYPHILIS EXPERIMENT 1 (1993).

183. *See e.g.*, Ted Gup, *The Coldest Warrior*, WASH. POST, Dec. 16, 2001, (Magazine) at W9; *see also*, Stanley v. United States, 786 F.2d 1490, 1492 (11th Cir. 1986).

protection of military personnel. In other words, there has been no claim that military personnel were serving as "healthy volunteers," who receive investigational products knowing that they face risk in the absence of potential benefit, in order that scientists may obtain knowledge of general applicability that can potentially be of benefit to others.

Given that the primary purpose of administering these products during the Gulf War was to protect the health of the military forces, the appropriate calculus to use in judging the appropriateness of the decision is one in which the risks to recipients are weighed against potential benefits to these recipients. In this context, if the risk of using an investigational product outweighs its possible benefit, no amount of informed consent can or should justify its use. Conversely, if there is a general scientific consensus that the potential benefit of these products is greater than their potential side effects, then their use is clearly justified. Withholding such use would be unethical, and the consent of military personnel would be unnecessary according to current military rules.

However, the regulatory category of "investigational," in reality, encompasses a lengthy continuum that spans from the first use of a new agent in humans (i.e., Phase I trials), to the decision by FDA to approve an application to market the new product, be it NDA or BLA. Many pitfalls, both scientific and non-scientific, can derail or impede progress along this continuum. Moreover, there is no regulatory distinction within this continuum between substances about which much is presently known from already-existing uses, and those whose safety and effectiveness profile is a blank slate. There is also no official recognition of the fact that, at some point along the continuum, investigational products may have demonstrated therapeutic benefit, at least for some populations under some circumstances, despite their officially investigational status. While FDA has taken steps to examine the different stages along the continuum and to permit the broader use of investigational products in particular circumstances, none of these exceptions apparently were considered appropriate for Gulf War combatants.

Thus, when faced with the task of determining whether it was appropriate to permit the administration of PB and BT to military personnel, FDA found itself with the need to fit a proverbial square peg into a round hole. While neither FDA nor DOD considered the proposed use to be research in the conventional sense, FDA had conferred only "investigational status" on the product. This necessitated following the provisions suitable to research subjects. In other words, because it had no alternative regulatory paradigm – i.e., one that acknowledged the different stopping points along the investigational continuum – all of the

deliberating about informed consent of necessity took place within the confines of the human subject provisions.

FDA was therefore left open to the charge that it had inappropriately manipulated regulations designed to protect research subjects to advance military objectives at the expense of the rights, dignity and safety of military personnel. In reality, however, FDA's actions are more appropriately characterized as permitting the use of less-than-fully approved treatments for a particularly high-risk population in a non-traditional setting, and, moreover, a setting in which military regulations already require soldiers to submit to medical care under certain conditions.[184]

The task facing FDA was to determine whether the risks inherent in the particular use of PB and BT was justified by the potential benefit to soldiers, i.e., whether the risk of untreated exposure to chemical and biological agents was greater than the potential side effects of these products. The purpose of assessing the risks and benefits was to determine the best therapeutic approach for the soldiers, and was not to answer a research question.

The lack of an appropriate regulatory paradigm also led FDA to reinterpret its existing regulations governing human subject protection in a manner that could have had troubling ethical ramifications in the future, had they not been revoked. FDA interpreted "infeasible" to include, for the first time, considerations external to the recipient of the investigational product. The implications of such an interpretation could have proved difficult to constrain. For example, could such an interpretation include the use of an investigational vaccine on prisoners without their consent to prevent an outbreak of infectious disease within the prison? Arguably, it would be infeasible to obtain consent in a prison population because refusal of any one prisoner could endanger the entire prison population. The same might be true of an infectious disease outbreak among institutionalized children. Indeed, there are many potential circumstances where public health objectives are at odds with individual preferences. While decisions that promote the former at the expense of the latter, such as the decision to waive informed consent requirements, may be ethically defensible, it is not because consent in such cases is "infeasible," but rather because we place a higher value in those circumstances on the attainment

184. Army Regulation 600-20, 5-4 (2002) (stating: "A soldier on active duty or active duty for training will usually be required to submit to medical care considered necessary to preserve his or her life, alleviate undue suffering, or protect or maintain the health of others.").

of public health than on the honoring of individual preferences. To decide such cases on the grounds of infeasibility conflates quite different situations. Infeasibility should be limited to those circumstances wherein is truly not possible to obtain consent from the individual because of that individual's incapacity, physical or mental, but where it is believed that the intervention is in the individual's best interest. Decisions made on public health protection and/or national security grounds, including protection of other members of the military, should be made under a basis different from infeasibility, one that recognizes that sometimes tensions exist, perhaps unavoidable ones, between protecting individuals and protecting the public.

Another troubling reality brought to light by the Gulf War experience is what may be termed the "orphan IND by 1990, both BT and PB had been under an IND for a fairly long period of time; the IND for PB was filed by DOD in 1984 and the IND for BT was filed by CDC in 1965.[185] Yet neither product had progressed beyond the IND stage. The reasons for this are unclear, but likely relate, at least in part, to the lack of a commercial market for these products, and therefore a lack of incentive on the part of the sponsors to seek approval of the product. In addition, in the case of drugs to prevent illness from exposure to life-threatening chemical or biological agents, there are ethical restrictions that prevent testing the effectiveness of these agents in humans, which has traditionally been a requirement before FDA will approve these products. However, regardless of the reasons that some INDs become stuck during their journey, the consequence of the failure to progress to final product approval is that the investigational product is frozen along the continuum, and is at a perpetually ambiguous status. As a result, when the products are needed for therapeutic purposes, concerns necessarily arise over their use. It is unclear how many INDs are currently languishing in this developmental phase, but as the Gulf War experience suggests, it is counterproductive to leave products in a perpetually investigational phase, and the rights conferred by the granting of an IND should also entail a responsibility to shepherd the IND diligently along the path to approval.

A final troubling aspect of the Gulf War experience is that it required complex risk-benefit decisionmaking to be conducted within an extremely short time frame. Policy-making in the shadow of military conflict is not conducive to a reflective and deliberative approach. DOD approached FDA regarding the use of PB and BT on October 30, 1990, and FDA

185. Rettig, *supra* note 17, at 6.

issued its decision on December 21, 1990.[186] FDA was no doubt keenly aware that war was imminent and that its decision could mean life or death for thousands of military personnel. In light of this pressure, FDA used the regulatory tools at its disposal, however awkward and ill-fitting, to achieve objectives it believed were in the interest of both individual military personnel and national security. It also appears to have granted considerable deference to DOD in terms of following the record-keeping and information-providing requirements of the IND--agreements that DOD appears to have been unable to fulfill.[187] Ideally, deliberations on such matters should be conducted before crises arise, and agreements worked out without the press of imminent war. Such prospective decision-making can better ensure that all the relevant factors and concerns are addressed.

3. Consequences

Following the Gulf War, it was expected that FDA would finalize the Interim Rule. This, however, did not happen. The reasons are unclear, and could reflect internal ambivalence over the rule, external criticism of FDA for adopting it or simply the press of more immediate business (or some combination of these three). The Presidential Advisory Committee on Gulf War Veterans' Illnesses, which operated from 1995 until 1997, recommended that FDA complete the rulemaking process it had begun.[188] In response, FDA published a request for comments on the merits of finalizing, modifying or revoking the Interim Rule.[189] The overwhelming majority of comments FDA received opposed the interim rule and argued that informed consent is essential for military personnel.[190]

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186. 55 Fed. Reg. 52814 (Dec 21, 1990) (regulations repealed).

187. Rettig, *supra* note 17 at 33-34.

188. Rettig, *supra* note 17, at 35-38, (citing Presidential Advisory Committee on Gulf War Veterans' Illnesses, *Interim Report*, February 1996 and Presidential Advisory Committee on Gulf War Veterans' Illnesses, *Final Report*, December 1996).

189. 62 Fed. Reg. 40996 (July 31, 1997).

190. 64 Fed. Reg. 54180 (Oct. 5, 1999). According to FDA, the agency received 134 comments on whether it should revoke or amend the Interim Rule, 119 of which opposed the rule and recommended revocation:

> Most of these comments opposed the agency's continued use of the interim rule after the experience of the Persian Gulf War. Many thought it should never have been used. Specifically, 114 comments stated that informed consent was absolutely essential and that military personnel, like other nonmilitary citizens, should receive adequate information about an investigational product before its use and have the right to refuse to

By mid-1998, it was known that FDA was leaning towards revoking the Rule, despite DOD's objections. Legislation adopted in October 1998, effectively mooted the issue. Known as the Byrd Amendment, the legislation vested the authority to grant waivers of informed consent for the use of an IND product solely in the President of the United States, based on criteria to be established by FDA.[191] Thereafter, FDA formally revoked the Interim Rule and issued the criteria to be used by the President in reviewing waiver requests.[192]

Since the enactment of the Byrd Amendment, there have been no requests to waive consent. The result of the Amendment appears to have been to deter DOD from using products that have not yet been licensed.[193] While some may applaud this move as affording greater protection to military personnel, it has limited DOD's options when faced with possible chemical or biological threats. In addition, the failure of the military to pursue approval of investigational products for which they are the sponsor could be detrimental to homeland security if terrorists widen the scope of biological agents to include civilian targets.

B. BioPort and the Continuing Controversy over the Anthrax Vaccine

During the Gulf War, DOD was also concerned about the potential exposure of troops to anthrax, to which Saddam Hussein was believed to have access. DOD therefore ordered the vaccination of approximately

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receive it. Seventeen comments stressed the need for followup of possible adverse reactions to investigational products, and 15 comments indicated that DOD could not fulfill its responsibilities even if FDA required adequate followup and other requirements as part of a new regulation. Five comments stated that DOD had shown itself to be incapable of adequate oversight and recordkeeping and three comments noted that the interim rule had not been implemented by DOD as had been intended. Several comments suggested that if the rule were to be used again, there must be an independent board of medical and ethical experts, there must be an institutional review board independent of DOD, and there must be proper monitoring that could only be done by non-DOD personnel.

Id. at 54181.

191. 10 U.S.C. § 1107(f)(2000).

192. FDA issued an Interim Final Rule describing these criteria in 1999. 64 Fed. Reg. 54180 (Oct. 1999). More recently, the agency announced its intention to issue a final rule by July 2002. Semiannual Regulatory Agenda, 67 Fed. Reg. 33039 (May 13, 2002).

193. Rettig et al., *supra* note 125, at 15.

150,000 troops going to the Gulf.[194] However, because a vaccine for anthrax had previously been licensed by FDA, neither FDA nor DOD considered it to be an investigational product.[195] For this reason the anthrax vaccine was not included in DOD's waiver request to FDA.

The lack of controversy was, however, short-lived. Following the war, U.N. inspectors confirmed that Iraq had produced and weaponized anthrax.[196] Following several years of internal debate, in December 1997, the Pentagon announced that all troops and reservists would be vaccinated against anthrax.[197] This decision was made in response to "heightened

194. Bradley Graham, *Pentagon Plans to Inoculate Troops Against Anthrax Bacteria*, WASH. POST, Dec. 16, 1997, at A23.

195. Some critics have erroneously argued that the administration of AVA for prophylaxis against inhalational anthrax is "investigational" because the labeling for AVA does not explicitly include inhalational anthrax as an indication for use. See Randall D. Katz, *Friendly Fire: The Mandatory Military Anthrax Vaccination Program*, 50 DUKE L.J. 1835, 1859-1861 (2001). This claim erroneously conflates the category of "investigational" with the "off-label" administration of an approved product. A product is investigational -- within the meaning of the FD&C Act and FDA regulations --only if it is the subject of an IND. An IND, in turn, is required of an approved product only if it is administered in the context of a clinical study protocol. On the other hand, a product that has been approved for one indication by FDA and is subsequently administered for a use not explicitly indicated in its labeling may constitute an off-label use. FDA has long taken the position that the decision to administer a product for indications not included in labeling is within the scope of medical practice and constitutes a clinical judgment, and is therefore not appropriately within the purview of FDA regulations. See, FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS, 1998. Update, *available at* http://www.fda.gov/oc/ohrt/irbs/offlabel.html (last visited July 8, 2002). Thus, while the administration of AVA for inhalational anthrax may arguably constitute an off-label use, it is not correct to characterize the vaccine as investigational for this purpose.

196. The seriousness of the Iraqi threat was confirmed by written evidence from within the regime when Saddam Hussein's son-in-law, Hussein Karnel Hassan, defected in 1995, carrying documents demonstrating that the Iraqis's had stockpiled 8,000 liters of anthrax spore suspension and 20,000 liters of botulinum toxin, and had also armed SCUD missiles with 400 pounds of biological warheads with a range of 300 to 600 kilometers. Philip M. Polgreen and Charles Helms, *Vaccines, Biological Warfare, and Bioterrorism*, 28 PRIMARY CARE: CLINICS IN OFFICE PRACTICE 807, 809 (2001).

197. Steven Lee Myers, *U.S. Armed Forces to be Vaccinated Against Anthrax*, N.Y. TIMES, Dec. 16, 1997, at A1.

Pentagon concern about the prospect of biological attack,"[198] based on information that "Iraq, Russia and as many as 10 other countries [had] ... the capability to load spores of anthrax into weapons."[199] DOD's decision created a significantly increased demand for the vaccine. Indeed, DOD estimated the need for 2.4 million troop equivalent doses.[200] To fulfill its requirements, DOD turned to the sole U.S. manufacturer of the vaccine, BioPort.[201]

This company, however, had a rather convoluted and financially troubled history with a record of repeated non-compliance with FDA requirements, as will be described in this section.

The currently marketed product, anthrax vaccine adsorbed (AVA), is manufactured using "old-fashioned" laboratory methods, in which the part of the toxin produced by the *anthrax bacillus* known as "protective antigen," is isolated, purified, and prepared for administration to humans.[202] Data demonstrating the safety and effectiveness of the current vaccine was derived from research conducted at Fort Detrick (then Camp Detrick) in the 1950s to develop methods to grow the bacteria in a laboratory, and to concentrate, stabilize and purify protective antigen.[203] Researchers at Merck, Sharpe and Dohme developed a vaccine that was tested by Brachman, et. al. in field trials conducted from 1955-1959 in goat

198. Bradley Graham, *Military Chiefs Back Anthrax Inoculations; Initiative Would Affect All of Nation's Forces*, WASH. POST, Oct. 2, 1996, at A1.

199. *Id.* Other events also contributed to the increased concern regarding bioterrorism. These included the release of Salmonella by the Rajneesh cult in The Dalles, Oregon in 1984 and the release of sarin gas by the cult, Aum Shinrikyo, in Tokyo, Japan in 1995. *See also*, JUDITH MILLER, STEPHEN ENGELBERG, AND WILLIAM BROAD, GERMS: BIOLOGICAL WEAPONS AND AMERICA'S SECRET WAR 15-33, 151-164 (2001).

200. Meyers, *supra* note 197. A troop equivalent dose, or TED, represents the number of shots required to achieve immunization multiplied by the number of troops to be immunized.

201. *Id.*

202. "The [anthrax] toxin has three major components: protective antigen, lethal factor and edema factor. When the toxin is released in the body," the protective antigen binds to the surface of target cells in a manner that allows the other two components to infiltrate and destroy the cell. The vaccine is designed to stimulate the production of antibodies against protective antigen, in order to prevent it from binding to cells. Thomas H. Maugh, II, *Anthrax and Smallpox Shots Present Manufacturing Problems and Dangerous Side Effects*, L.A. TIMES, Oct. 29, 2001, at A14.

203. IOM Report, *supra* note 10, at 48.

hair-processing plants in the eastern United States.[204] This was the only randomized, controlled clinical trial conducted with a protective antigen-containing vaccine.[205] It demonstrated efficacy against cutaneous anthrax.[206] Because the number of individuals who contracted anthrax by inhalation was so small, it was not possible to assess the vaccine's efficacy against this form of the disease.[207]

In 1966, the CDC submitted an IND for AVA to the Bureau of Biologics, which at that time was under the jurisdiction of the NIH.[208] The Michigan Department of Public Health (MDPH) developed this vaccine, at the request of the federal government.[209] The MDPH vaccine differed from the Merck vaccine in several respects.[210] Nevertheless, both the MDPH vaccine and the Merck vaccine were used in industrial settings (e.g., textile mills) during the 1960s, and FDA relied on data generated from both vaccines when evaluating the safety and effectiveness of AVA.

In 1970, the Bureau of Biologics granted a license for AVA to the MDPH.[211] The approved indication was "only for certain occupational groups with a risk of uncontrollable or unavoidable exposure to the organism,"[212] and MDPH produced the vaccine primarily for veterinary, laboratory and industrial workers. The license did not specify the form of anthrax for which it was indicated, and the vaccine has been used to protect those at risk from all forms of the disease, notwithstanding the lack of human clinical evidence. Evidence from animal studies supports the view that the vaccine is protective against inhalational anthrax as well, but the relevance of this data to humans is limited.[213] The vaccine was approved as a series of six shots over eighteen months, with an annual

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204. GAO REPORT: SAFETY AND EFFICACY OF THE ANTHRAX VACCINE, *supra* note 123, at 5.

205. *Id.*

206. *Id.*

207. *Id.*

208. IOM Report, *supra* note 10, at 136.

209. Merck apparently lost interest in developing the vaccine because of its small market, and no other company was willing to produce it. Mike Toner, *Anthrax Vaccine Mired in Red Tape*, ATLANTA J. CONST., Nov. 11, 2001, at 1B.

210. Among other differences, the AVA and Merck vaccines used a different strain of the *anthrax bacillus*, different purification and concentration procedures, and a different adjuvant and preservative. IOM Report, *supra* note 10, at 137.

211. IOM report, *supra* note 10, at 136.

212. *Id.* at 84.

213. GAO REPORT: SAFETY AND EFFICACY OF THE ANTHRAX VACCINE, *supra* note 123, at 5-6.

booster, although no studies have been done to determine the optimum number of doses of the vaccine.[214]

Prior to recent concerns about bioterrorism, the anthrax vaccine had a very small market. Only 68,000 doses were distributed by MDPH between 1974 and 1989,[215] and the MDPH consistently lost money.[216] In 1996, Michigan Governor John Engler provided the impetus for the creation of a new governmental corporation, the Michigan Biologics Products Institute (MBPI), comprising what had formerly been the vaccine production unit of the MDPH.[217]

In 1998, Michigan transferred ownership and licenses of MBPI to BioPort, a newly formed corporation.[218] At the time of the transfer, the FDA had already cited MBPI for failure to comply with various FDA requirements, in particular with its GMP requirements, among others.[219] FDA issued several warning letters to the company, including one stating its intent to revoke the facility's license if corrective actions proved

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214. U.S. GEN. ACCOUNTING OFFICE, GAO/T-NSIAD-99-226, MEDICAL READINESS: ISSUES CONCERNING THE ANTHRAX VACCINE 1 (1999) [hereinafter GAO REPORT: ISSUES CONCERNING THE ANTHRAX VACCINE]. In 1998, BioPort submitted an IND to FDA for a study to determine whether the number could be reduced from six shots to five. *Id.* at 2.

215. U.S. GEN. ACCOUTING OFFICE, GAO/T-NSIAD-00-48, ANTHRAX VACCINE: SAFETY AND EFFICACY ISSUES 5 (1999) [hereinafter GAO REPORT: SAFETY AND EFFICACY ISSUES].

216. Judith Miller, *Company Led By Top Admiral Buys Michigan Vaccine Lab*, N.Y. TIMES, July 8, 1998, at A19.

217. History of BioPort Corporation, *at* http://www.bioport.com/AboutBioPort/BioPortHistory/History_BioPort-Corporate.asp (last visited November 13, 2002).

218. Partners in the corporation were Admiral William J. Crowe, Jr., former Chariman of the Joint Chiefs of Staff, and former U.S. Ambassador to Britain, Fuad El-Hibri, German national who previously privatized the British Government's vaccine production plant, the Neogen Corporation, and MBPI. Id. Financial backing for BioPort came from a Netherlands Antilles investment company owned by El-Hibri's father, Ibrahim Hibri. Bradley Graham, *Anthrax Vaccine Firm in Trouble; Pentagon's Innoculation Program Supplier Near Bankruptcy*, WASH. POST, July 1, 1999, at A27.

219. For example, a 1997 report by FDA criticized the company's "failure to establish and/or follow written procedures for product and process controls designed to assure that products have the identity, strength, quality, and purity they purport or represent to possess." Thomas D. Williams, *Reports Criticize Anthrax Vaccine's Manufacturer; Federal Inspections Find Quality-Control Problems at Firm*, HARTFORD COURANT, May 22, 2000, at A1. *See also*, IOM Report, *supra* note 10, at 190-193.

inadequate.[220] MBPI also failed to follow required reporting procedures. For example, in the early 1990s, MBPI changed the filters it had been using to manufacture the vaccine without notifying FDA.[221] Upon taking ownership of MBPI in 1998, BioPort did not validate the filters to demonstrate consistency of the end product.[222] Studies by DOD indicated that the composition of the vaccine changed after the filters were replaced, but studies have not been conducted to evaluate if these changes affected the safety or effectiveness of the vaccine.[223] FDA was apparently unaware of the filter changes until the GAO issued a report in late 2001.[224] FDA was not granted access to inspect the facility prior to 1993 because "its inspectors had not been vaccinated against anthrax."[225]

FDA's faultfinding continued after MBPI was transferred to BioPort, and FDA inspectors repeatedly found violations such as lot contamination and substantial deviations from GMPs.[226] BioPort, in turn, looked to DOD, its main customer, for a major infusion of capital it claimed it needed to continue producing the vaccine.[227] DOD, facing a significant demand and perceiving no other alternatives, more than doubled the amount it had contracted to pay BioPort for the vaccine,[228] and advanced

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220. IOM Report, *supra* note 10 at 190-193.

221. GEN. ACCOUNTING OFFICE., GAO-02-181T, ANTHRAX VACCINE, CHANGES TO THE MANUFACTURING PROCESS 5-7 (2001) [hereinafter GAO Report: Changes to the Manufacturing Process].

222. *Id.*

223. *Id.*

224. *Id.* FDA reviewed its potency data results and stated that it did not detect any changes in potency testing results throughout the time period in which filters were changed. Sabin Russell, *Anthrax Vaccine Report Shows Spikes in Potency*, S.F. CHRON., Nov. 2, 2001, at A1.

225. GAO REPORT: SAFETY AND EFFICACY OF THE ANTHRAX VACCINE, *supra* note 123, at 6.

226. Rich Hein, *Anthrax Shot Fears Rise; More Troops Refusing Order to be Vaccinated*, CHICAGO SUN-TIMES, Nov. 4, 1988, at 3.

227. GEN. ACCOUNTING. OFFICE., GAO/T-NSIAD-99-214, CONTRACT MANAGEMENT: OBSERVATIONS ON DOD'S FINANCIAL RELATIONSHIP WITH THE ANTHRAX VACCINE MANUFACTURER 2 (1999) [hereinafter GAO REPORT: OBSERVATIONS ON DOD'S FINANCIAL RELATIONSHIP WITH THE ANTHRAX VACCINE MANUFACTURER].

228. Bradley Graham, *Anthrax Vaccine Firm in Trouble; Pentagon's Innoculation Program Supplier Near Bankruptcy*, WASH. POST, July 1, 1999, at A27; Steven Lee Meyers, *U.S. Doubles Payment to Sole Source of Anthrax Vaccine*, N.Y. TIMES, Aug. 6, 1999, at A16.

the company millions of dollars.[229] In 1998, BioPort shut down the facility for more than a year to conduct extensive renovations, during which time no new vaccine was produced.[230] In November 1999, FDA inspectors identified about thirty deficiencies in the new, larger plant that precluded licensure of the new facility or the vaccine produced therein.[231] The following year, "FDA inspectors cited BioPort for 18 violations of manufacturing procedures."[232] The violations included a lack of consistency in the manufacturing process and problems with sterility, packaging and filling procedures.[233] Inspectors also cited BioPort for failing to properly track and investigate reports of serious adverse reactions by people who received the vaccine.[234] FDA did not permit BioPort to release lots of the vaccine until January 31, 2002, after approving a supplement to the BLA to have the vaccine filled by another laboratory.[235]

In December 1997, Secretary Cohen announced plans to vaccinate all military personnel with the anthrax vaccine.[236] The Pentagon subsequently had to scale back and postpone the vaccination program, known as the Anthrax Vaccine Immunization Program (AVIP), after it became clear that BioPort's problems would create a significant shortage of the

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229. In 1999, DOD provided an interest-free advance payment of $18.7 million. In 2000, DOD provided an additional thirteen million dollars to BioPort's contract, in part to hire technical assistance in obtaining FDA approval. DOD also extended the schedule for BioPort to repay its interest-free advance and returned $7.4 million that the company had repaid for the $18.7 million advance. GEN. ACCOUNTING. OFFICE., GAO/T-NDIAD-00-140, CONTRACT MANAGEMENT: DOD'S ANTHRAX VACCINE MANUFACTURER WILL CONTINUE TO NEED FINANCIAL ASSISTANCE 1 (2000).

230. Keith Bradsher, *A Nation Challenged: The Supplies; The Only U.S. Laboratory for the Anthrax Vaccine Says Production Will Be Delayed*, N.Y. TIMES, Nov. 12, 2001, at B7.

231. Bradley Graham, *Pentagon Anthrax Program Suffers Setback; New Manufacturing Plant Fails FDA Inspection; Inoculation Expansion Delayed*, WASH. POST, Dec. 14, 1999, at A12.

232. Thomas D. Williams, *Vaccine Maker Again Gets Low Grades From U.S. Inspectors*, HARTFORD COURANT, Oct. 31, 2000, at A6.

233. *Id.*

234. Thomas D. Williams, *Vaccine Manufacturer Faulted; FDA Cites Failure to Track Effects of Anthrax Inoculation*, HARTFORD COURANT, Nov. 11, 2000, at A14.

235. Justin Gillis, *FDA Releases Anthrax Vaccine to Military, Approves More*, WASH. POST., Feb. 1, 2002, at A17.

236. Graham, *supra* note 194.

vaccine.[237] Following the initial vaccination order, several soldiers refused orders to be vaccinated because of concerns regarding possible side effects of the vaccine, concerns which stemmed in part from the possibility that the vaccine was responsible for ailments experienced by some Gulf War veterans.[238] The military instituted various disciplinary measures, on an individual basis, for such refusals, including discharge from military service.[239] Overall, as many as 400 active service members have resigned or been court martialed for refusing the vaccine.[240] In addition, an unknown number of National Guard and reserve personnel chose to leave rather than be vaccinated.[241] A GAO report criticized DOD for inadequate monitoring of adverse reactions to the vaccine,[242] and noted the limitations of using a "passive" monitoring system.[243]

Most recently, following the intentional distribution of anthrax through the U.S. mail, the CDC began offering the anthrax vaccine to those

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237. Eliot Marshall, *DOD Retreats on Plan for Anthrax Vaccine*, 289 SCIENCE 382, 382-383, July 21, 2000.

238. Anita Manning, *Anthrax Vaccine Injects Anger into Military Fearing Reactions, Troops Quit the Service*, USA TODAY, Oct 19, 1999, at 8D.

239. Jim Ritter, *Anthrax Shot Fears Rise; More Troops Refusing Order to be Vaccinated*, CHICAGO SUN-TIMES, Nov. 4, 1988, at 3.

240. Maugh, *supra* note 202, at 14.

241. In 2000, the GAO conducted a survey of 1,253 randomly selected Guard and Reserve Pilots and other aircrew members to assess attitudes about AVIP. The survey found that anthrax was a key reason that participants cited for leaving the military or changing their military status. GEN. ACCOUNTING OFFICE, GAO-01-92T, ANTHRAX VACCINE: PRELIMINARY RESULTS OF GAO'S SURVEY OF GUARD/RESERVE PILOTS AND AIRCREW MEMBERS (2000).

242. GEN. ACCOUNTING OFFICE, GAO/NSIAD-00-36, MEDICAL READINESS: DOD FACES CHALLENGES IN IMPLEMENTING ITS ANTHRAX VACCINE IMMUNIZATION PROGRAM (1999) [hereinafter GAO REPORT: DOD FACES CHALLENGES IN IMPLEMENTING ITS ANTHRAX VACCINE IMMUNIZATION PROGRAM]; Thomas D. Williams, *Military's Anthrax-Vaccination Program Criticized; Watchdog Agency Lists Deficiencies*, HARTFORD COURANT, Oct. 29, 1999, at A8.

243. DOD uses the Vaccine Adverse Event Reporting System (VAERS), established in 1990 and administered by FDA and CDC. The system relies on vaccine recipients and health care providers to report adverse events. This form of surveillance detects only a small fraction of adverse events. In contrast, an active surveillance system, in which health care workers monitor vaccine recipients to find out if they have had adverse reactions, is a more reliable indicator of a vaccine's safety. GAO REPORT: ISSUES CONCERNING THE ANTHRAX VACCINE, *supra* note 214, at 3-4; GAO REPORT: SAFETY AND EFFICACY ISSUES, *supra* note 215, at 5.

already exposed. Because the original license for the vaccine did not include post-exposure prophylaxis, the administration of the vaccine is being conducted under an IND. Thus far, 192 people have chosen to participate,[244] which represents only a small fraction of those potentially exposed.[245]

The controversy over the vaccine's safety, effectiveness and manufacturing, led to several government-sponsored analysis efforts. Between 1999 and 2001, the GAO issued several reports concerning the vaccine.[246] These studies noted a lack of data on long-term safety and efficacy and that the limited data regarding short-term adverse reactions suggested a higher rate of adverse reactions in women.[247] They also cited several disadvantages with the method of production, such as the inability to measure the amount of protective antigen precisely, variation between lots of the product, and evidence suggesting diminished efficacy against certain virulent strains of anthrax.[248]GAO noted the advantages of developing a "second generation recombinant vaccine ... [using] a process that ... [can be] fully defined, quantified, and controlled."[249]

In March 2002, the Institute of Medicine released a report in which it concluded that AVA is both effective against all forms of anthrax and reasonably safe. Specifically, the report found that the rate of adverse reactions, both local and systemic, was comparable to other adult vaccines,[250] and that while data is limited there was "no convincing

244. IOM Report, *supra* note 10, at 50.

245. Sheryl Gay Stollberg, *A Nation Challenged: Steps Against Anthrax; Civilians Are Reluctant to Join U.S. Test of Anthrax Vaccine*, N.Y. TIMES, Jan. 8, 2002, at A13; Ceci Connolly, *Workers Exposed to Anthrax Shun Vaccine; Low Participation Is Blamed on Confusing Signals From U.S. Health Authorities*, WASH. POST, Jan. 8, 2002, at A6.

246. GAO REPORT: SAFETY AND EFFICACY OF THE ANTHRAX VACCINE, *supra* note 123; GAO REPORT: ISSUES CONCERNING THE ANTHRAX VACCINE, *supra* note 214; GAO REPORT: DOD FACES CHALLENGES IN IMPLEMENTING ITS ANTHRAX VACCINE IMMUNIZATION PROGRAM, *supra* note 242; GAO REPORT: SAFETY AND EFFICACY ISSUES, *supra* note 215; GAO Report: Changes to the Manufacturing Process, *supra* note 221; GEN. ACCOUNTING OFFICE, GAO/T-NSIAD-00-157, DOD Continues to Face Challenges in Implementing Its Anthrax Vaccine Immunization Program (2000).

247. *Id.*

248. *Id.*

249. GAO REPORT: ISSUES CONCERNING THE ANTHRAX VACCINE, *supra* note 214, at 10.

250. IOM Report, *supra* note 10, at 12.

evidence at this time [of] elevated risk of later-onset [adverse] events."[251] Nevertheless, the Committee concluded that reliance on the current vaccine was "far from satisfactory," and that there is a "need for research toward the development of a different and better anthrax vaccine, as well as a need for improvements in monitoring the safety of the current vaccine."[252]

The history of the anthrax vaccine exposes a number of troubling realities. First, it is clear, in retrospect, that DOD did not appreciate the substantial hurdles BioPort faced in achieving FDA compliance or the significance of FDA's regulatory role. Lacking this awareness, DOD made decisions, such as the decision to vaccinate all troops, without assessing the capability of BioPort to produce sufficient vaccine, particularly in light of BioPort's ongoing difficulties in complying with FDA requirements. For example, the renovations conducted by BioPort to modernize its facilities, while necessary, also meant that the company, in essence, needed FDA to re-approve the vaccine, since FDA considers the facility in which a vaccine is produced to be an integral component of the vaccine's overall safety and effectiveness. Additionally, it appears that DOD did not, until recently, perceive the need to take a leading role in developing alternate anthrax vaccines through means of biotechnology, which presumably would be less subject to the production difficulties faced by legacy vaccines, such as the BioPort vaccine. Notably, although the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) developed a recombinant vaccine in 1995, it did not conduct clinical trials to test safety because it considered further development of the vaccine to be an "unfunded requirement."[253] More recently, however, DOD has begun collaborating with the National Institutes of Health (NIH) to develop a recombinant vaccine,[254] and has

251. *Id.* at 14.

252. *Id.* at 15. Specifically, the IOM found that "[t]he current anthrax vaccine is difficult to standardize, is incompletely characterized, and is relatively reactogenic. . . and the dose schedule is long and challenging. An anthrax vaccine free of these drawbacks is needed, and such improvements are feasible. *Id.* at 20.

253. GAO REPORT: ISSUES CONCERNING THE ANTHRAX VACCINE, *supra* note 214, at 10.

254. Dave Eberhart, *Anthrax Vaccine? No, Not Yet*, NEWSMAX.COM, Oct. 29, 2001, *at* http://www.newsmax.com/archives/articles/2001/10/28/210212.shtml (last visited August 2, 2002).

also begun collaborating with private firms to develop new prevention and treatment methods.[255]

Second, it is similarly apparent that FDA historically did not take an active role in trying to bring BioPort into compliance. Inspectors repeatedly found violations, but it is unclear how much follow-up or assistance was provided to the company. Ordinarily, perhaps, this would be the desirable course. Arguably, the appropriate role of the regulatory agency is to identify regulatory deficiencies and permit the private company to correct them or suffer the consequences. Furthermore, given limited resources, a vaccine serving only a small number of people, as was historically the case with the anthrax vaccine, should perhaps not be the agency's highest priority. However, when the context becomes national security and broad-based public health protection, it is insufficient simply to identify problems periodically and hope they are corrected. Rather, more active intervention is required, stemming from the awareness that the product at issue is vital, and a safe, effective and stable supply must be maintained.

Related to this second concern, BioPort is a stark example of the fragility of the U.S. vaccine industry generally, and particularly in the context of vaccines likely to be employed in a biological attack. Vaccines are a small, and not very profitable, segment of the U.S. pharmaceutical industry, representing only one or two percent of global pharmaceutical sales.[256] As a consequence, there are few major pharmaceutical firms involved in their production—primarily in the childhood vaccine market—and many vaccines are manufactured by only one manufacturer. Indeed, of the ten leading pharmaceutical companies in terms of sales, only four produce vaccines.[257] Thus, there is little redundancy in the system, and production problems by one manufacturer have had resounding effects

255. "For example, army researchers are working with EluSys Therapeutics Inc., a small New Jersey company, to develop an early monoclonal antibody treatment for soldiers when they are first exposed to anthrax." Ronald Rosenberg, *Shot Against Bioterrorism: US Companies Like Oravax in Cambridge Are Producing New Smallpox, Anthrax, and Other Vaccines for Soldiers And Civilians, But Are We Stockpiling Enough Drugs to Meet the Threat?*, BOSTON GLOBE, Oct. 4, 2000, at D4. *See also*, Marsha Austin, *Better Anthrax Vaccine Claimed Denver Company Ready for Fast Track*, DENVER POST, Nov. 2, 2001, at C1; Thomas D. Williams, *Anthrax: Safe, Effective Vaccine Proves Elusive; Responding to Terrorism*, HARTFORD COURANT, Nov. 6, 2001, at A1.

256. Donald S. Burke, Vaccine Vuneralibility: National Security Dimension, Address at Johns Hopkins Bloomberg School of Public Health Society of Alumni Event (March 21, 2002).

257. *Id.*

throughout the population. This was clearly evident in the fall of 2001, when shortages occurred with a number of childhood vaccines, and delays occurred in the distribution of several others.[258] Overall, of twenty-three licensed vaccines, three were withdrawn because of safety concerns, delays in supply have occurred with four, the supply of three was insufficient, and seven, although currently in stable supply, are produced by only a single manufacturer.[259]

Lack of profitability and redundancy are an even greater concern for vaccines for national security, as "military vaccines represent a highly specialized niche market of minimal commercial interest to the pharmaceutical industry."[260] The manufacturers of vaccines for agents likely to be used in biological attacks have largely been small, unknown and sometimes offshore entities, rather than well-known U.S. companies with a proven track record. Notably, all three vaccines manufactured for biodefense—anthrax, plague and smallpox—are manufactured by only a single source that does not have sufficient capacity to produce them.[261] Although the events of 9/11 may have led to an increased interest by big firms because of the increased financial incentives to develop these vaccines, they still cannot compete with "blockbuster" drugs. Nevertheless, ensuring their availability is as vital to the national defense and public health as is the military, emergency services and roads. This is particularly true, since the anthrax vaccine experience demonstrates that vaccines considered to be solely a military need may quickly become needed for the broader population. Thus, like other common goods, vaccines must not be permitted to fall victim to what has traditionally been termed the "tragedy of the commons," but must be supported so that their availability can be assured.

The BioPort experience may serve as an opportunity to improve the availability of vaccines in the future. As will be discussed in greater detail in part VII, FDA can take several concrete steps to help ensure the availability of safe, and effective vaccines for military and homeland defense.

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258. Robert Pear, *Shortage of Juvenile Vaccines Worries Doctors and Officials*, N.Y. TIMES, Dec. 2, 2001 at 38. Jonathan Bor, *Shortages Hamper Children's Vaccination; Doctors Fear U.S. Could Lose Ground in Fighting Illnesses*, BALTIMORE SUN, Mar. 23, 2002, at 1A.

259. Burke, *supra* note 256.

260. Rettig et al., *supra* note 125, at 3.

261. Donald S. Burke, *supra* note 256.

C. Organizational Considerations

A third reason for concern regarding the impact of FDA requirements on the availability of products to counter bioterrorism stems not from any particular event or episode, but rather from a much more intangible, but no less influential factor, namely, the "culture" of FDA. In trying to describe FDA culture or to ascribe it practical significance, a few caveats are in order. First, it would be incorrect to ascribe a single, unified and static culture to the agency as a whole. FDA comprises several independent centers, each with its own director and staff, and each with different institutional histories. Thus the culture of those tasked with regulating drugs may be quite different from that of biological products, which may in turn be quite different from that of medical devices. Second, the culture of any agency is necessarily influenced by who is at the helm, and FDA is no exception. The Commissioner of Food and Drugs is appointed by the President and is often selected because of the views possessed by or ascribed to that individual, both about particular controversial issues (e.g., abortion) and more generally about the proper role of an administrative agency. Finally, formal historical analyses of FDA's culture are sparse, and much of the information resides in the minds of agency officials and former officials who have lived through various periods, making it an elusive topic for description.

Nevertheless, certain attitudes and beliefs that have been woven into the fabric of FDA's regulatory culture, stemming in part from the agency's historical mandate and from particular episodes in the agency's history, may present challenges to efforts to redirect FDA activities in the service of national security objectives. Richard Merrill, in discussing the challenges of mutual recognition agreements, has described three key features of this culture: (1) a "strong tradition of tough-minded regulation"; (2) the "widely-held conviction . . . that the Agency is over-extended and under-resourced"; and (3) a tradition of paternalism, manifested in the agency's view of itself as "having responsibility to protect citizens of other countries as well as citizens of our own."[262]

Another consistent description of the FDA's culture and core beliefs comes from former Commissioner Jane Henney:

> [a] public health regulatory agency like FDA must define and maintain strong values in order to sustain consumer confidence in FDA's commitment to protect and promote public health. There are three such values that have been and should continue

262. Richard A. Merrill, *The Importance and Challenges of Mutual Recognition Agreements*, 29 SETON HALL L. REV. 736, 742-746 (1998).

> to be FDA's bedrocks: credibility, integrity, and independence. Credibility – the agency's credibility must be sound to fulfill its mission. This includes scientific skill and knowledge, as well as FDA's commitment to meeting society's need for public health protection. Integrity—people working at FDA and those who serve on its behalf must act and take actions that are above reproach. FDA can ill-afford to have any questions raised regarding its intent or any assertions made about potential or real conflicts. Independence—a strong regulatory agency must be able to exhibit and exert its independence free from undue influence or conflicts of interest by any parties involved. These values help to guide the agency in the right direction and help shape the culture of an organization. Thus the workforce of FDA, at any point in its almost one hundred year history, has been guided by these values and committed to the protection of the public health, using scientifically rigorous methodology to underpin its decision.[263]

Several key themes emerge from Merrill and Henney's descriptions. First, the FDA culture is one that views as paramount the responsibility to protect the public's health, by protecting consumers from dangerous products. This view has been fostered in part by the legislative history of its governing statutes and by the fear of the consequences of being "wrong," i.e., of approving a product that later turns out to cause unanticipated adverse effects. Second, the agency has an unassailable commitment to "science," and specifically, to a particular view of science that strictly adheres to the randomized clinical trial as the *sine qua non* of safety and effectiveness. This process views clinical trial design and data collection as paramount, and necessarily accepts that the process is time-consuming, slow and not readily susceptible to strict timetables. A third, and related theme is that the constraints of low resources and multiple demands has led to an acceptance of the fact that not all areas within the agency's jurisdiction will receive the same amount of attention as others, and that certain subjects must remain on the back burner of the agency's priorities. Finally, the agency's culture of independence, described by Henney, in addition to signifying the agency's desire not to be perceived as "beholden" to either the regulated industry or to other governmental entities, also connotes an attitude that the agency need not accommodate other interests, and rather that all those subject to FDA's authority must adhere equally, without exceptions or alterations, to the agency's rules, expectations and manner of conducting business.

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263. Jane E. Henney, *Remarks of the Commissioner of Food and Drugs*, 55 FOOD DRUG L.J.1, 3 (2000).

How then, might FDA's culture and values conflict with national security objectives? First, there is reason for concern that FDA's traditional conception of public health protection may miss an essential dimension in its failure to pay sufficient attention to the risks associated with not approving products because of concerns about inadequate safety or effectiveness. This concern exists regarding all diseases—indeed, studies have estimated the loss of life caused by delays in failing to approve such drugs as streptokinase (a blood-clot dissolving agent) and beta blockers.[264] Pharmacologists William Wardell and Louis Lasagna noted, almost thirty years ago, that whereas the introduction of a new drug that produced significant fatalities "would be regarded as a major disaster" the "occurrence of deaths through failure to introduce a drug has so far gone unremarked."[265] Nevertheless, the failure to factor in the other side of the public health equation in the national security context has even more chilling ramifications since the objective of biological warfare and bioterrorism is to incapacitate military forces and destabilize civilian society. It is, therefore, more than a simple matter of excess deaths.

Second, where national security is concerned, time is often "of the essence" in a way not typical of products for other uses. The timing of military campaigns is unpredictable (or not subject to disclosure) and may occur on short notice. Similarly, information concerning possible bioterrorist threats may be obtained with very little lead-time for preparing the civilian population. As FDA's actions during the Gulf War illustrate, decision-making under threat of war is less than ideal for reflective deliberation. Furthermore, as seen with the length of time it took FDA to promulgate a new regulation for the use of animal data – more than two and a half years – FDA's timetable is somewhat longer than might be optimal in the military context. Thus, mechanisms must be in place both to expedite products and regulations in the service of national security and to resolve new regulatory concerns in a manner that avoids precipitous action with potentially far-reaching implications.

Third, availability of drugs and vaccines needed for national security cannot be subject to shifting FDA priorities and resource constraints. Rather, they require a consistent and vigilant level of regulatory oversight to ensure that they are available, if needed, and that any problems that arise during development or production are resolved expeditiously.

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264. Elizabeth C. Price, *Teaching the Elephant to Dance: Privatizing the FDA Review Process*, 51 FOOD & DRUG L. J. 651, 654-655 (1996).

265. *Id.* at 655 (quoting WILLIAM M. WARDELL & LOUIS LASAGNA, REGULATION & DRUG DEVELOPMENT 73 (1975)).

Currently, however, drugs and vaccines proceed through the same regulatory channels as all other products, and thus are subject to the same vagaries of the administrative process.

Finally, positive and effective communications must be ensured between FDA and those who produce, as well as purchase, drugs and vaccines for national security. While FDA has a long tradition of interacting with commercial sponsors, its history with DOD is less frequent and has, at times, been awkward. Yet DOD, in addition to conducting research to develop drugs and vaccines to meet specific military needs, has been the largest and sometimes the only "customer" for these products. DOD is unlike most sponsors and customers in that it is like FDA, a federal executive branch agency charged with protecting the public. Some attention must therefore be given to the unique relationship between FDA and DOD and the ways in which this relationship may differ in relevant respects from the typical FDA-sponsor interaction.[266]

V. LESSONS FROM THE PAST: HOW FDA AND CONGRESS HAVE ADAPTED TO CHANGED CIRCUMSTANCES

While there are reasons for concern, there are also reasons to be optimistic that FDA has sufficient authority and flexibility to fine-tune its procedures to better meet national security needs. This section describes several regulatory changes within FDA that began in the mid 1980s and that have potential relevance to the agency's ability to facilitate the availability of drugs and vaccines to counter biological attacks.

A. The Rutherford Era

Over the past two decades, FDA has evolved from a "one-size-fits-all" regulatory strategy to one that recognizes that the agency's statutory and regulatory authorities can, and must be, applied flexibly to accommodate individual circumstances. This has been the case, in particular, with drug development for life-threatening illnesses. Through a combination of factors, including sometimes-confrontational episodes with patient advocacy groups and pressure from industry, FDA has begun to recognize that those suffering from life-threatening diseases, and facing imminent death, may have different risk-benefit preferences from those of the general population, and that such preferences are legitimate and should be given credence in the form of accelerated approvals and greater access to unapproved products. This section discusses FDA's regulatory changes, some of which were subsequently codified by Congress as amendments to

266. *See generally*, Rettig et al., *supra* note 125.

the (FD&C Act),[267] with particular attention to the lessons applicable to the bioterrorism context.

Prior to the 1980s, FDA provided a single route to drug approval: IND, Phase I, Phase II and Phase III. Furthermore, the "gold standard" for successfully completing Phase III was, almost without exception, the completion of two independently conducted "adequate, well-controlled clinical trials."[268] In addition, investigational products could generally not be given to patients, except in limited circumstances.[269]

FDA's exclusive authority to require approval as a condition of marketing, and its concomitant authority to prohibit distribution of any unapproved product—even for dying patients—was confirmed by the Supreme Court in the 1979 case, *United States* v. *Rutherford.*[270] In that case, terminally ill cancer patients and their families challenged FDA's injunction against the distribution of Laetrile, an unapproved cancer therapy.[271] FDA contended that this product was a "new drug" within the meaning of the FD&C Act, and therefore an application for approval must be submitted, and approval granted by FDA, prior to distribution in interstate commerce.[272] Since no application had been submitted for Laetrile, FDA held the distribution of the drug to be unlawful.[273] The patients argued, and the lower courts agreed, that the safety and effectiveness requirements for new drugs had "no reasonable application to terminally ill cancer patients."[274] Further, since these patients would

267. 21 U.S.C §301 (2000).

268. Kulynych, *supra* note 78, at 129.

269. Prior to 1987, FDA had permitted a compassionate use IND exemption on a case-by-case basis, but only at the request of the patient's primary care physician and provided that the pharmaceutical company was willing to supply the investigational drug at no charge. Both of these requirements made the theoretical possibility of an exemption insufficient to meet the demands of most persons with AIDS. Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL'Y 295, 315-316 (1999/2000); *See also* Richard J. Nelson, *Regulation of Investigational New Drugs: "Giant Step for the Sick and Dying"?*, 77 GEO. L.J. 463, 471 (1988) (noting that the use of the compassionate IND was "largely ad hoc and not widely publicized."). FDA also allowed a personal use import exemption, which permitted individual citizens to import limited quantities of unapproved drugs for their personal medical use. *See* Greenberg at 316.

270. United States v. Rutherford, 442 U.S. 544 (1979).

271. *Id.*

272. *Id.* at 549-550.

273. Rutherford v. United States, 438 F. Supp. 1287, 1289-90 (D. Ok. 1977).

274. Rutherford, 442 U.S. at 551 (discussing lower court holdings).

likely die of their illness regardless of the therapy used, there were "no realistic standards against which to measure the safety and effectiveness of a drug for that class of individuals."[275] The Supreme Court unanimously reversed, holding that the safety and effectiveness provisions applied to all products, regardless of the illness they were intended to treat.[276] Furthermore, the Court disputed the rationale of the lower courts, stating that even patients suffering from potentially fatal diseases could be harmed by unproven products if the use of such products caused them to reject conventional therapy.[277]

The Supreme Court's validation of FDA's rigorous, cautious and uniform approach to product approval should not be surprising. Indeed, the history of the FD&C Act amply demonstrates that its consumer-protection motivations are embedded in its origins. Each step in Congress' incremental strengthening of FDA authority was made in response to consumer deaths from dangerous products: elixir sulfanilamide, thalidomide and the Dalkon Shield being a few of the more prominent examples.[278] Thus, the entrenched tradition has been to keep unsafe products out of the marketplace, and to protect vulnerable patients from "quack" therapies, not to facilitate the entrance of risky but potentially beneficial products into the marketplace.

B. AIDS and the Waning of Rutherford

The *Rutherford* decision marked the high water mark in FDA's unquestioned status as the exclusive final arbiter of safety and effectiveness. Only a short time later, the emergence of the AIDS epidemic challenged the agency's core identity as public health protector and its long-held assumptions about the proper ratio of risk to benefit in drug development, and ushered in a dramatic shift in the agency's regulatory perspective. Indeed, the epidemic "marked a seminal event in the evolution of new drug approval policy at the FDA."[279]

With the emergence of the AIDS epidemic, FDA was faced with a highly organized, articulate and politically savvy advocacy community. FDA was also faced with a highly motivated patient body that perceived

275. *Id.* at 551.

276. *Id.* at 551-552.

277. *Id.* at 558-559.

278. FOOD AND DRUG ADMINISTRATION, Milestones in U.S. Food and Drug Law History, *at* http://www.fda.gov/opacom/backgrounders/miles.html (last visited October 24, 2002).

279. Greenberg, *supra* note 269, at 296.

itself as literally having nothing to lose by trying unproven therapies. Frustrated by the Reagan administration's seeming indifference, and by the apparent slow pace of approval for new drugs, AIDS activists employed a variety of strategies to advance their agenda. In an unprecedented demonstration of grassroots protest against the agency, FDA's Rockville, Maryland headquarters were picketed by protestors, a thousand strong and many suffering from AIDS, who chanted for hours demanding faster drug approval.[280] Protesters also took more subtle, and potentially more damaging, measures to demonstrate their unwillingness to accept the established clinical trial system as a means to drug approval. For example, one AIDS activist group established a method by which patients could have their clinical trial drug supply analyzed, thus definitively un-blinding the study.[281] Patients receiving active treatment shared their drugs with those receiving placebos.[282] Patients also adjusted their doses and added treatments prohibited by the protocol.[283] Finally, an "underground" distribution network developed for drugs being tested in clinical trials.[284] The availability of investigational drugs outside the clinical trial setting impeded efforts to recruit patients to serve in supervised clinical trials.[285]

It appears that patients and activists undertook such efforts in the belief that they would maximize not only individual well being, but also patient well being as a whole. It is unclear how widespread such actions were, but

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280. Paul Duggan, *1,000 Swarm FDA's Rockville Office To Demand Approval of AIDS Drugs*, WASH. POST, Oct. 12, 1988, at B1.

281. Nancy K. Plant, *Food Allergy and the Health Care Financing Administration: A Story of Rage: Adequate Well-Controlled Clinical Trials: Reopening the Black Box*, 1 WID. L. SYMP. J. 267, 286 (1996).

The term "blinding" refers to procedures that prevent participants in a clinical trial from knowing whether they are receiving the drug being investigated or some other substance (e.g., placebo).

282. *Id.*

283. *Id.*

284. *Id.*

285. In addition, the lack of availability of investigational drugs opened the door to the use of "untested compounds for which there were anecdotes or rumors in support of efficacy" and the development of black market buying clubs for drugs that were available overseas. This occurred "in an environment where good information about the effectiveness of treatments was unavailable because the treatments had emerged entirely outside the regulatory purview of the FDA" leading to "initial desperate enthusiasm for the newest treatment fad [that] would die down as evidence accumulated to suggest its inefficaciousness." Greenberg, *supra* note 269, at 311.

even if only on a small scale, they posed a symbolic challenge to the supremacy of the double-blind, placebo-controlled clinical trial. It is difficult to quantify the extent to which the efforts of AIDS activists led to FDA's willingness to consider changes to the status quo. Certainly the testimony of impassioned, terminally ill individuals arguing for the autonomy to accept greater risks must have been compelling to at least some regulators. Moreover, both FDA and the research community were no doubt seriously concerned about threats to the integrity of the clinical trial process.[286] As has been noted:

> HIV patients were the first group of patients ever to disobey the system in such an organized and widespread fashion. Their disregard for the traditional drug development system, expressed both from outside the system and as quietly errant cogs in the drug development wheel, drew attention to these issues in a way that had never been done.[287]

Whatever the motivation, FDA made several dramatic regulatory changes to the clinical trial process in the 1980s and early 1990s. While FDA, in the early 1980s, was able to informally improvise strategies to expedite new AIDS drug approvals,[288] ultimately, a more formal enunciation of policy was required. In 1987, after receiving over 300 comments from a wide array of interest groups, FDA issued a final rule specifying the conditions under which investigational new drugs could be administered to patients with severe medical conditions.[289] FDA articulated the purpose of the rule as facilitating "the availability of

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286. Indeed, some of these threats were rather dire: At one FDA Advisory Committee meeting concerning early access, AIDS activist Larry Kramer stated: "If we do not get these drugs you will see an uprising, the likes of which you have never seen before since the Vietnam War in this country. We will sabotage all of your phase I studies." Plant, *supra* note 281 at n.144 (citing Lisa Terrizzi, *The Need for Improved Access to Experimental Drug Therapy: AIDS Activists and Their Call for a Parallel Track Policy*, 4 ADMIN. L. J. 589, 622 (1991)).

287. Plant, *supra* note 281, at 289.

288. While FDA's rapid approval of AZT and pentamidine were initially lauded, critics later found several faults with the research methodology used in these trials. Greenberg, *supra* note 269, at 312-313.

289. 52 Fed. Reg. 19466 (May 22, 1987). According to FDA, comments were received from representatives of "virtually every affected constituency," including consumers, consumer group leaders, health professionals and health care providers, representatives of specific disease and orphan drug organizations, State and local health departments, clinical investigators and research institutions, institutional review boards, pharmaceutical manufacturers and former FDA officials. *Id.*

promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness."[290]

The FDA rule provided that a drug could be used for treatment if: (1) the drug is intended to treat a serious, or immediately life-threatening, disease; [291] (2) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (3) the drug is under investigation in a controlled clinical trial under an IND, or all clinical trials have been completed; and (4) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.[292] Sponsors seeking to use an IND drug for treatment were required to submit a treatment protocol to FDA containing information on the rationale for using the drug, the criteria for patient selection and other information.[293] The sponsor was not required to wait for FDA approval to begin but rather could begin thirty days after submission unless FDA directed otherwise.[294] Another important component of the rule was that FDA permitted a sponsor or investigator to charge for the drug used in a treatment protocol provided that certain conditions were met.[295] This was a departure from the prohibition against charging for investigational products, and provided important incentives to companies to provide their investigational products to patients.

In 1988, FDA again undertook measures intended to expand access to investigational products by issuing an interim rule that provided a mechanism for expediting the development, evaluation and marketing of

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290. *Id.*

291. The rule defined "immediately life threatening" to mean a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. 21 C.F.R. § 312.34(b)(3)(ii) (2002). The preamble to the final rule also provided the following illustrative list of diseases fitting this definition: Advanced cases of AIDS; Advanced congestive heart failure (New York Heart Association Class IV); Recurrent sustained ventricular tachycardia or ventricular fibrillation; Herpes simplex encephalitis; Most advanced metastatic refractory cancers; Far advanced emphysema; Severe combined immunodeficiency syndrome; Bacterial endocarditis; and Subarachnoid hemorrhage. 52 Fed. Reg. 19466, 19467 (May 22, 1987).

292. 21 C.F.R. § 312.34(b)(1)(i)-(iv).

293. 21 C.F.R. § 312.35(a).

294. 21 C.F.R. § 312.35(b).

295. 21 C.F.R. § 312.7(d)(2).

new therapies intended to treat persons with life-threatening[296] or severely debilitating illnesses.[297] The measures were focused especially on those for which no satisfactory alternative therapies existed. The interim rule permitted a departure from the classic Phase I, II III approach. Instead, FDA stated that it would consider approval following phase two investigational studies, without the need for Phase III, which would represent a potentially significant saving of time:

> FDA believes that if sufficient attention is paid to the quality and amount of data obtained in phase 2, it should be possible to identify early those drugs that represent safe and effective treatments for life-threatening and severely-debilitating diseases – and to develop the evidence needed for their marketing – in the course of carrying out the first controlled trials.[298]

This early approval was predicated on early and frequent meetings between sponsors and FDA reviewers to discuss the design of animal and clinical studies. FDA anticipated that sponsors would make use of the treatment protocol provisions established in previous years to administer the drug to patients while preparing the marketing application. Finally, FDA anticipated that post-marketing (Phase IV) studies would be used to obtain additional information about a product's risks, benefits and optimal uses. Underlying these changes was the explicitly articulated premise that a different risk-benefit calculus was appropriate for the agency to use in reviewing product applications intended to treat patients with life-threatening or seriously debilitating illnesses:[299]

> [t]he procedures contained in this rule reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.[300]

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296. The rule defined life threatening diseases as: "(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and (2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival." 21 C.F.R. § 312.81(a) (2002).

297. The rule defined severely debilitating illnesses as: "diseases or conditions that cause major irreversible morbidity." 21 C.F.R. § 312.81(b) (2002).

298. 53 Fed. Reg. 41516 (Oct. 21, 1988) (21 C.F.R. pts. 312 and 314).

299. 53 Fed. Reg. at 41518.

300. *Id.*

In May 1990, the Public Health Service, another agency under the aegis of the Department of Health and Human Services (HHS), published a proposed policy statement specifically aimed at speeding new IND drugs to people with AIDS and HIV-related illnesses.[301] The policy statement, which was issued under the authority of the FD&C Act, proposed to authorize a "parallel track" under which certain individuals with AIDS or HIV could receive investigational products at an earlier stage of development outside the context of a controlled clinical trial.[302] To be eligible, a participant (1) had to have clinically significant HIV-related illness or be an imminent health risk due to HIV-related immunodeficiency, (2) be unable to participate in a controlled clinical trial because of (i) failure to meet entry criteria, (ii) severity of illness, or (iii) full enrollment of the controlled clinical trials; and (3) be unable to take standard treatment because it is contraindicated, cannot be tolerated or is no longer effective.[303]

The new drugs would be made available based on studies without concurrent control groups to monitor drug safety.[304] It was expected that the drugs at issue would be in the very early stages of development, and would only be made available to people with no satisfactory alternative therapy. While data collection was required, the Public Health Service anticipated that most data for marketing would come from controlled clinical trials.[305] The evidence required to administer these drugs to patients would be less than that required for a treatment IND.[306] However, specific criteria to be considered were listed.[307] A final policy statement was issued in April 1992.[308]

In December 1992, FDA issued regulations to accelerate approval of drugs for serious or life-threatening illnesses that contained a significant change to the drug approval process.[309] FDA stated that such products

301. 55 Fed. Reg. 20856 (May 21, 1990). The proposed statement was developed by a working group comprising representatives from NIH, FDA, the Office of the General Counsel and the National AIDS Program Office, as well as community advocates, physicians, clinical researchers and industry representatives.

302. *Id.*

303. *Id.* at 20858-20859.

304. *Id.* at 20857.

305. *Id.*

306. *Id.*

307. *Id.* at 20858.

308. 57 Fed. Reg. 13250 (April 15, 1992).

309. 57 Fed. Reg. 58942. (Dec. 11, 1992) (codified at various sections of 21 C.F.R. §§314, 601 (1992)).

could be approved based on data concerning "surrogate endpoints." Traditionally, FDA had required that if it was claimed that a product caused or prevented a particular outcome (e.g., cause remission, prevent death), that outcome must be demonstrated in clinical trials.[310] However, certain outcomes may take years to demonstrate, increasing the length of time required to demonstrate effectiveness.

By contrast, a surrogate endpoint is a "laboratory measurement or physical sign"[311] that has been shown to correlate with, and be predictive of, the outcome of interest. FDA stated that it would permit approval of drugs to treat serious or life-threatening illnesses "on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit."[312] Products approved based on such data would be required to undergo additional postmarketing studies confirming the clinical benefit of the drug.[313]

Under the new regulation, FDA also stated that it could impose post-marketing restrictions for certain drugs approved under accelerated procedures.[314] FDA stated that certain clinically beneficial drugs, such as those with potential for significant toxicity, could be used safely only if distribution were limited to certain facilities or physicians or in conjunction with ongoing monitoring.[315] Restrictions would be tailored to the specific safety concerns for a particular product.[316]

The foregoing reforms produced a sea change in FDA operations, and, perhaps more significantly, in the agency's conception of its essential mission. Prior to 1980, the virtually unquestioned mission of FDA was public health protection, construed narrowly as protecting consumers from the harmful effects of unsafe products. The AIDS crisis forced both the agency and the broader medical community to reassess the appropriate mission and to reconsider the parameters of the "public health." While the agency always, by the very nature of its mission, had to grapple with the "conflicting objectives of caution and expedience,"[317] AIDS dramatized

310. Greenberg, *supra* note 269, at 323.
311. 57 Fed. Reg. 13234, 13235.
312. *Id.*
313. 21 C.F.R. § 314.510 (2002).
314. 21 C.F.R. § 314.520.
315. *Id.*
316. 57 Fed. Reg. 58942.
317. Salbu, *supra* note 55, at 95.

the conflict in a way that had not been done before and compelled FDA to acknowledge that the public health could be compromised not only through the incautious approval of unsafe or ineffective products but also by the overly cautious withholding of approval. FDA also acknowledged that its "traditional mission neglected the interests of people whose lives were primarily threatened by the absence of treatment, rather than by unidentified harmful side effects of treatment."[318]

In 1997, Congress formally sanctioned FDA's dual role when it legislatively codified FDA's mission as comprising both *protection* of the public health by ensuring the safety and effectiveness of products and the *promotion* of public health, by "promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."[319] At the same time, Congress legislatively codified many of the regulations issued by FDA to accelerate the availability of drugs to seriously ill patients.[320] Significantly, FDAMA contained an explicit provision permitting the products to be designated as "fast track" and eligible for expedited review and approval.[321]

AIDS also effected a change in FDA's assessment of its role *vis-à-vis* the patient and research subject. FDA's regulatory process requires a constant assessment of the appropriate boundaries of tradeoffs between risk and benefit; it is "at its heart an exercise in risk management."[322] Additionally, FDA must choose between substituting its own judgment about appropriate risk thresholds for public protection and allowing the public to make independent choices to assume risk. Baldly stated, requiring a high degree of safety will result in fewer adverse events from the product, but also more morbidity and mortality from the underlying disease. Lowering the risk threshold may lead to more adverse events, including death, but may also prolong some lives and alleviate some morbidity. It is not usually possible to know in advance whether a given shift in the risk/benefit profile will result in a net increase or decrease in morbidity and mortality. Prior to 1980, FDA erred on the side of limiting access to risky products in order to reduce the risks of treatment to the patient. The *Rutherford* decision affirmed FDA's central role of protecting vulnerable patients from the unproven claims of charlatans. However, AIDS activists and other patient advocacy groups urged a shift

318. Greenberg, *supra* note 269, at 328.

319. 21 U.S.C. § 393(b)(1)(2002).

320. Pub. L. No. 105-115, 111 Stat. 2296 (1997).

321. 21 U.S.C. § 356 (2002).

322. Greenberg, *supra* note 269, at 337.

from FDA-centered risk/benefit decision-making to one that included the patient's own risk preferences.

The changes of the late 1980s and 1990s demonstrated FDA's willingness to permit seriously ill people to accept more risk in the interest of obtaining potentially beneficial treatments. This shift was applauded by some, who viewed it as a victory of patient autonomy and individual self-determination over a paternalistic government entity. Others, however, expressed concern that the changes were potentially detrimental to both individual patients and the broader research enterprise. For example, concern was raised that permitting pharmaceutical companies to charge for treatment INDs would limit access to those patients who could afford to pay and would also decrease manufacturers' incentives to seek approval.[323] Some also feared that lowering the standards for approval would compromise overall research quality. Even AIDS activists were publicly divided about whether faster approval was beneficial, with some groups expressing concerns that too many drugs were being made available with too little data about their safety or effectiveness.[324]

The regulatory changes that FDA initiated in response to AIDS—changes that have been broadened to include other serious diseases[325]—raise issues of particular salience to products to counter bioterrorism. The emergence of the bioterrorism threat requires a similar reassessment of the appropriate risk-benefit calculus for optimal military and public health protection. The statutory and regulatory changes initiated in response to AIDS can therefore provide both a conceptual and practical framework for crafting new regulatory mechanisms to better address national security and homeland defense needs.

C. The Orphan Drug Act

The regulatory changes of the late 1980s and early 1990s were aimed at getting therapies already under investigation to the patient more quickly. These changes also indirectly encouraged research and development of new therapeutic entities, but this was not the main focus of advocates of reform.

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323. Nelson, *supra* note 269, at 480-481.

324. *See e.g.*, Gina Kolata, *F.D.A. Debate on Speedy Access to AIDS Drugs Is Reopening*, N.Y. TIMES, Sept. 12, 1994, at A13.

325. In March, 1996, for example, FDA unveiled its "cancer drug initiative," under which it extended many of its AIDS drug policies to cancer drugs. Salbu, *supra* note 55, at 118-119.

For patients suffering from serious illnesses that affect only a small number of people, the existence of a therapeutic vacuum, i.e., the absence of any therapeutic modality, investigational or otherwise, is also a significant concern. This is because pharmaceutical companies typically focus their research and development efforts on diseases and conditions likely to be beneficial for large numbers of people, and thereby to yield the most sales. Thus, potentially therapeutic compounds with a small potentially treatable patient population may languish for lack of a sponsor willing to invest the time and money to conduct clinical trials and shepherd the drug through the approval process.[326]

In order to encourage the development of such "orphaned" products, Congress enacted the Orphan Drug Act in 1983.[327] The Act provided several economic incentives to sponsors of these products, perhaps the most significant being seven years of market exclusivity beginning from the date of FDA approval.[328] This means that FDA cannot approve a marketing application for the same drug approved to treat the same condition for seven years from the approval date of said orphan drug. FDA has provided regulatory definitions to guide exclusivity determinations.[329] Nevertheless, competing sponsors have fiercely contested the precise boundaries of this exclusivity.[330]

To qualify for the incentives provided in the Act, the sponsor must first obtain orphan drug designation from FDA, by demonstrating that the product is intended to treat a rare disease or condition.[331] Initially, the Act defined this category based on the lack of expectation of cost recovery.[332]

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326. *See e.g.*, David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD DRUG L.J. 125, 126 (2000).

327. Pub. L. No. 97-414, 96 Stat. 2049 (1983).

328. 21 U.S.C. § 360cc(a)(2002). The Act also provided (1) a tax credit for fifty percent of "qualified clinical testing expenses," 26 U.S.C. § 45C, (2) the opportunity to obtain written recommendations from FDA regarding the types of investigations that should be conducted, 21 U.S.C. § 360aa, (3) encouragement to conduct "open" protocols in order to get investigational products to patients not enrolled in clinical trials, Id. § 360dd, and (4) federal grants to defray clinical trial expenses, Id. § 360ee.

329. *See*, 21 C.F.R. § 316 (2002).

330. *See e.g.*, Genentech v. Bowen, 676 F. Supp. 301 (D.D.C. 1987) (noting recombinant human growth hormone not the same as cadaver-derived hormone); Berlex Laboratories, Inc. v. FDA, 942 F. Supp. 19 (D.D.C. 1996) (noting clinically superior product for the same disease can receive orphan drug designation).

331. Pub. L. No. 97-114, 96 Stat. 2049 (1983).

332. Orphan Drug Act, Pub. L. No. 97-414, 526(a)(2), 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. 360bb(a)(2) (1994)); *see also* Gary A. Pulsinelli,

This definition required sponsors to submit, and FDA to evaluate, data demonstrating a lack of commercial feasibility.[333] As a result of this cumbersome requirement, few sponsors sought designation.[334] In 1984, Congress amended the Act to provide an additional test based solely on the number of people in the population affected with a disease.[335] The Act defines "rare disease and condition" as:

> any disease or condition which (A) affects less than 200,000 persons in the U.S. or (B) affects more than 200,000 persons in the U.S. but for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug.[336]

FDA issued final regulations in 1992[337] in which it set forth the data required to demonstrate that a drug is unlikely to be profitable, notwithstanding the fact that it affects more than 200,000 people.[338] In practice, however, all sponsors seeking designation have relied on the definition provided in subsection (a).[339]

Since the passage of the Act, FDA has designated 944 products as orphan drugs,[340] and has approved 227 of these products for marketing.[341] The Act has been subject to criticism on the basis that it has been used by some companies as a means to gain the economic benefits of the Act for products that are not truly "orphans," i.e., that are highly profitable. According to critics, this has been accomplished in some cases through the practice of "salami slicing," meaning artificially dividing a disease into arbitrary subsets in order to meet the 200,000 patient limit, and in others through monopolistic pricing.[342] Even drugs that legitimately qualify at the outset may "outgrow" their designation as the incidence of the disease

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The Orphan Drug Act: What's Right With It?, 15 COMPUTER & HIGH TECH. L. J. 299, 307 (1999).

333. Pulsinelli, *supra* note 332.

334. *Id.* at 307; *see also* Rohde, *supra* note 326, at 129.

335. Health Promotion and Disease Prevention Amendments of 1984, Pub. L. No. 98-551, 98 Stat. 2815 (1984).

336. 21 U.S.C. § 360bb(a)(2).

337. 57 Fed. Reg. 62076 (Dec. 29, 1992) (codified at 21 CFR pt. 316).

338. 21 C.F.R. § 316.21(c)(2002).

339. Pulsinelli, *supra* note 332, at 313.

340. FOOD AND DRUG ADMINISTRATION, LIST OF ORPHAN PRODUCT DESIGNATIONS AND APPROVALS, *available at* http://www.fda.gov/orphan/designat/list.htm (last visited July 2, 2002).

341. *Id.*

342. Pulsinelli, *supra* note 332, at 321.

increases in the population. For example, the first drugs approved for AIDS, AZT and pentamidine isethionate, were approved pursuant to an orphan drug designation. While the actual patient population at the time of designation may have been under 200,000, it quickly grew as the number of infected patients, and the number who could potentially benefit from the drug increased.[343] The statute does not provide any mechanism for revoking the orphan drug designation under these circumstances, although such an amendment to the Act has been proposed.[344]

Notwithstanding the flaws that have been identified, some of which may be correctable by legislation or regulation, and others that may be inherent, more products to treat rare diseases and conditions are available as a result of the Act than would otherwise have been the case. Thus, the statute did achieve its goal of correcting a defect of the free market to the benefit of at least a subset of patients.

Like drugs for rare diseases or conditions, products to counter bioterrorism may also be considered therapeutic "orphans." As discussed earlier, the vaccine industry is fragile in part because it is not viewed as an economically fertile ground for product development. The Orphan Drug Act therefore provides a model for promoting innovation that has particular relevance to products to combat bioterrorism. In particular, the inclusion within the statutory framework of products for which there is a lack of expectation of cost recovery would appear to have particular applicability to such products. Thus the Orphan Drug Act, either as written or with targeted legislative amendments or regulatory clarifications, can be an important vehicle to overcome the absence of appropriate treatments and to encourage innovation in this area.

VI. CURRENT INITIATIVES FROM CONGRESS AND FDA

Since October 2001, Congress has introduced numerous bills addressing various aspects of bioterrorism. While some bills have sought additional appropriations to purchase drugs and vaccines,[345] the bills have not sought,

343. *Id.* at 323.

344. *Id.* at 333-337.

345. *See e.g.*, Matt Kelly, *Ganske's Bioterrorism Bill Mirrors Senate's; The Legislation Includes $1.1 Billion to Help Prevent and Respond to Agricultural Terrorism*, OMAHA WORLD-HERALD, Nov. 17, 2001, at 11a; Sheryl Gay Stolberg, *A Nation Challenged: Bioterrorism; Senators Seek $3.2 Billion to Fight Germ Threats, Doubling Bush Plans*, N.Y. TIMES, Nov. 16, 2001, at B8.

for the most part, to directly alter FDA's authority over drugs and vaccines.[346]

One exception has been the Public Health Security and Bioterrorism Preparedness and Response Act of 2002,[347]which was enacted into law on June 12, 2002.[348] As previously mentioned, this law extended PDUFA authorization for an additional five years.[349] In addition, the new law contains provisions intended to spur the development of "priority countermeasures."[350] The law authorizes the Secretary of Health and Human Services to designate a priority countermeasure as a "fast-track" product under the FD&C Act[351] upon request from the product's sponsor.[352] Additionally, the new law mandates annual registration with FDA of foreign manufacturers engaged in the import of drug and device products into the United States and authorizes the exclusion of products from unregistered establishments.[353]

Other bills containing FDA-related provisions are still pending, and are unlikely to pass in the waning days of the 107th Congress. For example, in

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346. Indeed, the only area in which Congress has sought to significantly amend FDA's authority has been with regard to food safety, but these proposed changes have encountered significant resistance by the food industry. *See e.g.*, Robert Pear, *Food Industry's Resistance Stalls Bill to Protect Food* , N.Y. TIMES, Apr. 16, 2002, at A22; Bill Lambrecht, *Safety of Nation's Food Supply is Scrutinized; Bioterrorism Legislation Also May Address Issue of Food-Borne Illnesses*, ST. LOUIS POST-DISPATCH, Nov. 4, 2001, at A1.

347. 21 U.S.C. § 356(a)(1) (2002).

348. Pub. L. No. 107-188,116 Stat 594 (2002).

349. *Id.* at §502(3)(A).

350. The law defines a "priority countermeasure" as "a countermeasure, including a drug, medical or other technological device, biological product or diagnostic test, to treat, identify, or prevent infection by a biological agent or toxin listed pursuant to section 351A(a)(1) of the PHS Act or harm from any other agent that may cause a public health emergency." *Id.* § 125.

351. Section 506 of the FD&C Act directs FDA to conduct expedited review of new product applications for products intended for the "treatment of a serious or life-threatening condition" and that "demonstrate the potential to address unmet medical needs for such a condition." 21 U.S.C. § 356(a)(1)(2002).

352. The law also authorizes the Secretary of HHS to award grants and contracts to facilitate the development of countermeasures for pathogens of potential use in a bioterrorist attack. *Id.*

353. *Id.* § 321. It also directs the Secretary to develop a national stockpile of drugs, vaccines and other products that might be required in the event of a bioterrorist attack. It specifically authorizes the Secretary to carry out activities necessary to ensure the availability of sufficient quantities of smallpox vaccine. Id. § 121.

December 2001, Senator Joseph Lieberman (D-CT) introduced a bill that aims to extend patent terms, provide tax credits and offer indemnification to firms that develop diagnostic and medical countermeasures to agents listed on a "biological and chemical agent research priority list."[354] Entities seeking these benefits would be required to register with FDA, and provide, among other information, the name of the agent or toxin for which products are being developed and a description of the research to be undertaken.[355] In addition, FDA, in consultation with the Director of the Office of Homeland Security, would determine whether the "research to be conducted under such registration is intended to lead to the development of countermeasures." The bill does not in any way, however, address the process by which FDA would review and approve such countermeasures.

Since the events of last fall, FDA has not published any new proposed regulations relating to bioterrorism. Shortly after the intentional release of anthrax, FDA published a notice in the Federal Register clarifying that two generic antibiotics, doxycycline and penicillin G procaine drug products, were approved for use in cases of inhalational exposure to *Bacillus anthracis* and providing dosing regimens for this use.[356] FDA encouraged manufacturers to submit applications to change the labeling of their products to add this new dosing information.[357] FDA took this action in response to concerns about possible shortages of ciprofloxacin, the only antibiotic with labeling explicitly stating that it was effective to prevent and treat inhalational anthrax.[358]

In March 2002, FDA published a draft guidance document for the industry concerning the development of drugs to treat exposure to inhalational anthrax.[359] The draft guidance is "intended to assist applicants who wish to plan, design, conduct, and appropriately monitor the studies,

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354. S. 1764, 107th Cong., 1st Sess. (2001). The bill is titled the "Robert Stevens, Thomas Morris Jr., Joseph Curseen, Kathy Nguyen, Ottilie Lundgren, and Lisa J. Raines Biological and Chemical Weapons Research Act" in commemoration of victims of 9/11 and the intentional distribution of anthrax. *Id.*

355. *Id.*

356. 66 Fed. Reg. 55679 (Nov. 2, 2001).

357. *Id.*

358. Gina Kolata, *A Nation Challenged: The Treatments; 2 Drugs Received Federal Approval Long Ago to Fight Anthrax, Agency Says*, N.Y. TIMES, Oct. 20, 2001, at B8.

359. FDA also issued a guidance concerning assessing donor suitability and blood and blood product safety in cases of possible anthrax exposure. 67 Fed. Reg. 1774 (Jan. 14, 2002).

including clinical studies, for drugs to treat persons exposed to *B. anthracis*."[360] In April 2002, CBER, in cooperation with DOD, held a public workshop to discuss possible strategies for the efficacy testing of investigational anthrax vaccines, including the identification of surrogate markers, in order to expedite the development of new vaccines.[361] Finally, as stated above, in May 2002, FDA issued a final rule permitting a demonstration of effectiveness for drugs and biological products used to reduce or prevent the toxicity of chemical, biological, radiological or nuclear substances to be based solely on data derived from animal studies.[362]

VII. NEW INITIATIVES FOR FURTHER DEVELOPMENT

This paper has identified several impediments to the ability of the United States ability to protect its military and civilians from biological attacks. Some of the problems are clearly beyond FDA's capacity to resolve. For example, FDA cannot require manufacturers to develop or manufacture particular products, or control the pace of research and development efforts. Nor can it allocate money for this purpose; indeed the agency's own budget is dictated by Congress. Nor can FDA intervene in the day-to-day operations of specific manufacturers to prevent their failure to comply with FDA requirements. Rather, the agency is limited to identifying violations through inspection and imposing sanctions if such violations are not corrected.

There are, nonetheless, several steps that FDA could undertake to foster the availability of products needed for national security and homeland defense. Through the development of more transparent and predictable regulatory mechanisms, FDA could create an environment more conducive to well-established manufacturers to develop and produce products for military and homeland defense. Moreover, using already established statutory and regulatory mechanisms, as both a conceptual and practical starting point, to expedite drug approval and to provide economic incentives for product development, FDA can institute initiatives to foster the timely development, review and approval of products to counter bioterrorism. This section identifies five initiatives, some of which specifically target this category of products, others of which may have broader effect on the availability of many different product

360. *Id.*

361. 67 Fed. Reg. 17076 (Apr. 9, 2002) (notice of workshop).

362. 67 Fed. Reg. 37988 (May 31, 2002) (to be codified at 21 CFR pts. 314 and 601).

categories including those for military and homeland defense. The initiatives are presented in broad, conceptual form, and are meant to serve as a template for further discussion and development by policy makers.

A. Establishment of a New Office of Products for Military and Homeland Defense

A new office should be created within FDA, with the primary purpose of reviewing and approving INDs and product applications for new drugs and biological products for military and homeland defense, including those intended to counter biological agents. A separate budget should be allocated for this purpose, so that the mission of the office is not undermined through lack of necessary resources. The new office should also serve as a liaison between FDA and other federal government agencies that oversee military and homeland defense matters.

The office should comprise scientific reviewers from both CDER and CBER, and from CDRH, if needed. These reviewers should receive special training in the scientific issues likely to arise in conducting clinical trials for such products, such as the challenges of demonstrating efficacy, as well as education regarding effective strategies for interaction with DOD. This training would permit reviewers to guide manufacturers through the review and approval process more effectively and to address concerns as they arise.

This new office can be established by FDA, on its own initiative, or by Congressional legislation. However, a direct budgetary appropriation by Congress would help ensure that the office had the necessary personnel and resources to achieve its mission.

B. Creation of a New Interim Category of Product Approval

FDA and/or Congress should develop an interim category of product approval for military and homeland defense use. This interim designation would be intended for products about which insufficient information on safety and effectiveness was available to warrant full approval, but for which the risks were considered justifiable in light of the particular military or homeland defense threats at issue. Products receiving such designation would not be considered investigational. However, such products would be subject to stringent requirements, including tight controls on distribution and diligent surveillance of recipients to identify adverse reactions. The interim designation would be for a specific period of time, during which the sponsor would be required to continue research and surveillance efforts. The sponsor would be required to file periodic reports describing the results of ongoing clinical studies. Recipients would

be required to be informed of the approval status of the product and of the mechanism for reporting adverse reactions.

C. Creation of a Fast Track for Military andHomeland Defense Products

Legislation enacted in 2001 has explicitly authorized the use of FDA's fast track authority for products to counter bioterrorism. The new law gives FDA fairly wide latitude in its implementation. FDA should quickly issue regulations to implement the new law and thereby permit the fast track approval of such products.

D. Imposition of Time Limits on INDs

FDA must take steps to end the problem of "orphan INDs," i.e., products that remain in a perpetually investigational phase. While not all the products in this situation are for military or homeland defense use, the orphan IND problem is particularly acute for this category of products for the reasons previously discussed. FDA can accomplish this by requiring periodic renewal of, and imposing time limits on, INDs to ensure that research is being pursued diligently. Currently, IND holders are required to file annual reports describing the status of research efforts, but the current regulations do not in any way ensure that INDs are progressing towards the NDA/BLA stage. The imposition of time limits would encourage IND holders to file new product applications. While exceptions to such time limits may be required in some cases, as the pace of research is often unpredictable, the imposition of time limits in most cases will encourage IND holders to diligently pursue the investigations that are the subject of the application.

E. Clarification of the Applicability of Orphan Drug Designation to Products for Military and Homeland Defense

FDA should encourage manufacturers of products for military or homeland defense to seek orphan drug designation for these products. Since the foreseeable population for such products is, potentially, the entire country, the usual basis for orphan drug designation (patient population less than 200,000) would be inapplicable. However, for the reasons already discussed herein, there is a good faith basis to believe that there is "no reasonable expectation" that manufacturers of these products will recover the costs of developing these drugs, which is the alternate basis for receiving orphan drug designation. FDA should therefore revise its orphan drug regulations to provide that products whose intended use is solely or primarily for military or homeland defense are automatically

deemed to meet the criteria for orphan drug designation. Alternatively, FDA should provide a simple, clearly understandable and easy to follow method for demonstrating that a particular counter-bioterrorism product does not have a reasonable expectation of cost recovery.

CONCLUSION

All of the above initiatives could be accomplished without the enactment of additional legislation. In other words, FDA currently has sufficient authority to legally accomplish each of these proposals. Nevertheless, the agency may be reluctant to initiate many, if not all, of these efforts, (in the absence of specific direction from Congress or the Executive Branch) particularly those that can be expected to engender controversy or require a reallocation of significant resources. Such direction could arise from (1) an order from the Secretary of Health and Human Services; (2) an Executive Order from the President; or (3) a Congressional amendment to the FD&C Act. To the extent that additional financial resources are required to achieve the above initiatives, an appropriation of funds from Congress may be required.

All the above initiatives would foster the availability of more drugs and biological products to protect the public from biological attack. However, in the final analysis, they are necessary but not sufficient. Ultimately, if FDA is to effectively regulate products for national security, it must, at least in some respects, "think" like a national security agency. This by no means requires any lessening of commitment to the scientific process or to patient safety. It does require a recognition that, just as the presence of unsafe and ineffective products endanger public health, the absence of therapeutic agents to counter biological attacks has significant negative consequences for the health of both the military and civilian populations. Ultimately it requires a commitment to facilitating the timely and expeditious development and manufacture of such products using the best currently available information on safety and effectiveness.