

October 2007

PROJECT BIOSHIELD

Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing the Stockpile of Licensed Vaccine





Highlights of [GAO-08-88](#), a report to congressional requesters

Why GAO Did This Study

The anthrax attacks in September and October 2001 highlighted the need to develop medical countermeasures. The Project BioShield Act of 2004 authorized the Department of Health and Human Services (HHS) to procure countermeasures for a Strategic National Stockpile. However, in December 2006, HHS terminated the contract for a recombinant protective antigen (rPA) anthrax vaccine because VaxGen failed to meet a critical contractual milestone. Also, supplies of the licensed BioThrax anthrax vaccine already in the stockpile will start expiring in 2008. GAO was asked to identify (1) factors contributing to the failure of the rPA vaccine contract and (2) issues associated with using the BioThrax in the stockpile. GAO interviewed agency and industry officials, reviewed documents, and consulted with biodefense experts.

What GAO Recommends

GAO is recommending that the HHS Secretary ensure that (1) for future procurements the concept of use and all critical requirements for medical countermeasures are clearly articulated at the outset, (2) expired stockpile vaccines are destroyed, and (3) the HHS and the Department of Defense (DOD) Secretaries develop an integrated stockpile for BioThrax with rotation based on a first-in, first-out principle.

HHS and DOD generally concurred with GAO's recommendations but identified legal challenges that may require legislative action.

To view the full product, including the scope and methodology, click on [GAO-08-88](#). For more information, contact Keith Rhodes at (202) 512-6412 or rhodesk@gao.gov.

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Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing the Stockpile of Licensed Vaccine

What GAO Found

Three major factors contributed to the failure of the first Project BioShield procurement effort for an rPA anthrax vaccine. First, HHS's Office of the Assistant Secretary for Preparedness and Response (ASPR) awarded the procurement contract to VaxGen, a small biotechnology firm, while VaxGen was still in the early stages of developing a vaccine and had not addressed many critical manufacturing issues. This award preempted critical development work on the vaccine. Also, the contract required VaxGen to deliver 25 million doses of the vaccine in 2 years, which would have been unrealistic even for a larger manufacturer. Second, VaxGen took unrealistic risks in accepting the contract terms. VaxGen officials told GAO that they accepted the contract despite significant risks due to (1) the aggressive delivery time line for the vaccine, (2) VaxGen's lack of in-house technical expertise—a condition exacerbated by the attrition of key company staff as the contract progressed—and (3) VaxGen's limited options for securing any additional funding needed.

Third, important Food and Drug Administration (FDA) requirements regarding the type of data and testing required for the rPA anthrax vaccine to be eligible for use in an emergency were not known at the outset of the procurement contract. In addition, ASPR's anticipated use of the rPA anthrax vaccine was not articulated to all parties clearly enough and evolved over time. Finally, according to VaxGen, the purchase of BioThrax for the stockpile as a stopgap measure raised the bar for the VaxGen vaccine. All these factors created confusion over the acceptance criteria for VaxGen's product and significantly diminished VaxGen's ability to meet contract time lines. ASPR has announced its intention to issue another request for proposal for an rPA anthrax vaccine procurement but, along with other HHS components, has not analyzed lessons learned from the first contract's failure and may repeat earlier mistakes. According to industry experts, the lack of specific requirements is a cause of concern to the biotechnology companies that have invested significant resources in trying to meet government needs and now question whether the government can clearly define future procurement contract requirements.

GAO identified two issues related with the use of the BioThrax in the Strategic National Stockpile. First, ASPR lacks an effective strategy to minimize the waste of BioThrax. Starting in 2008, several lots of BioThrax in the Strategic National Stockpile will begin to expire. As a result, over \$100 million per year could be lost for the life of the vaccine currently in the stockpile. ASPR could minimize such potential waste by developing a single inventory system with DOD—a high-volume user of BioThrax—with rotation based on a first-in, first-out principle. DOD and ASPR officials identified a number of obstacles to this type of rotation which may require legislative action. Second, ASPR planned to use three lots of expired BioThrax vaccine in the stockpile in the event of an emergency. This would violate FDA rules, which prohibit using an expired vaccine, and could also undermine public confidence because the vaccine's potency could not be guaranteed.

Contents

Letter		1
	Scope and Methodology	4
	Results in Brief	5
	Background	8
	Several Factors Contributed to the Failure of ASPR's First Project BioShield Effort for the Production of an rPA Anthrax Vaccine	14
	ASPR Lacks an Effective Strategy to Minimize Waste in the Strategic National Stockpile and Plans to Use Expired Anthrax Vaccine	24
	Conclusions	25
	Recommendations for Executive Action	26
	Agency Comments and Our Evaluation	26
Appendix I	Time Line of Events in the First rPA Anthrax Vaccine Development and Procurement Effort	28
Appendix II	Comments from the Department of Health and Human Services	29
Appendix III	Comments from the Department of Defense	39

Abbreviations

ASPR	Office of the Assistant Secretary for Preparedness and Response
AVA	Anthrax Vaccine Adsorbed
AVIP	Anthrax Vaccine Immunization Program
BARDA	Biomedical Advanced Research and Development Authority
CBER	Center for Biologics Evaluation and Research
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control
cGMP	current Good Manufacturing Practices
DHS	Department of Homeland Security
DOD	Department of Defense
EUA	emergency use authorization
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IND	investigational new drug
IOM	Institute of Medicine
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PHEMCE	Public Health Emergency Medical Countermeasure Enterprise
PTA	population threat assessment
RFI	request for information
RFP	request for proposal
rPA	recombinant protective antigen
TRL	Technology Readiness Level

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United States Government Accountability Office
Washington, DC 20548

October 23, 2007

The Honorable Edward M. Kennedy
Chairman
Committee on Health, Education, Labor and Pensions
United States Senate

The Honorable Joseph I. Lieberman
Chairman
The Honorable Susan M. Collins
Ranking Member
Committee on Homeland Security and Governmental Affairs
United States Senate

The Honorable Richard Burr
United States Senate

The anthrax attacks in September and October 2001 highlighted major gaps in our civilian preparedness to respond to health emergencies that threaten national security. These incidents also led the Congress and the federal government to focus attention on the importance of developing new drugs, vaccines, and therapeutics to protect U.S. citizens.

In 2002, in response to the anthrax attacks, the National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH) launched an effort to rapidly develop a second generation recombinant protective antigen (rPA) anthrax vaccine.¹ While there is already a licensed anthrax vaccine (BioThrax), it is given in six doses over 18 months followed by an annual booster. NIAID wanted to have a vaccine that could be administered in an immunization series of not more than three doses.²

¹ The vaccine based on rPA is often referred to as a second generation anthrax vaccine to differentiate it from BioThrax. Recombinant refers to a product created using a genetic engineering technology in which one or more pieces of DNA are combined together. A protective antigen is a biochemical that produces an immunologic response that then protects animals or humans against challenges from the infectious agent.

² National Institute of Allergy and Infectious Diseases, "Production and Testing of Anthrax Recombinant Protective Antigen (rPA) Vaccine." Request for Proposal (RFP) No. NIH-NIAID-DMID-03-29.

In the late 1980s, Department of Defense (DOD) research identified an rPA anthrax vaccine, created with a process that (1) is fully defined, quantified, and controlled in terms of protective antigens; (2) showed development potential; and (3) required fewer doses. DOD researchers developed a fully defined manufacturing process to produce highly purified rPA. The researchers found that they could protect animals using this rPA with fewer doses than the existing licensed vaccine.³ In 2002, the Institute of Medicine (IOM) stated that although AVA—Anthrax Vaccine Adsorbed, now called BioThrax—is safe and effective for use, “it is far from optimal.”⁴ The IOM supported the development of a new anthrax vaccine. According to the Department of Health and Human Services (HHS), when an rPA vaccine is fully developed, it will address the shortcomings of the AVA vaccine identified in the IOM report.⁵

In 2002 and 2003, NIAID awarded development contracts for rPA vaccines to two companies—VaxGen and Avecia. VaxGen was a small U.S. biotechnology company. According to NIAID, one of the objectives was to demonstrate how manufacturing efforts might be increased to support creation of a national stockpile of medical countermeasures.

The Project BioShield Act of 2004 formalized this initiative and authorized the Secretary of HHS, who in turn entrusted the Office of the Assistant

³ B. Ivins and others, “Immunization Studies with Attenuated Strains of *Bacillus anthracis*,” *Journal of Infection and Immunity*, 52(1986):454-58. B. E. Ivins, “The Search for a New-Generation Human Anthrax Vaccine,” *Clinical Immunology Newsletter*, 9(1988): 30-32; and Y. Singh and others, “Study of Immunization against Anthrax with the Purified Recombinant Protective Antigen of *Bacillus anthracis*,” *Journal of Infection and Immunity*, 66(1998): 3447-48.

⁴ Institute of Medicine, *The Anthrax Vaccine: Is It Safe? Does It Work?* (National Academy Press: Washington, D.C., 2002), p. 20.

⁵ Stewart Simonson, Assistant Secretary, Department of Health and Human Services, Office of Public Health and Emergency Preparedness (now ASPR), testimony before the Senate Committee on Appropriations, Subcommittee on Homeland Security, April 28, 2005.

Secretary for Preparedness and Response (ASPR)⁶ with responsibility for acquiring and ensuring the management of and accounting for a Strategic National Stockpile of medical countermeasures.⁷ It is designed to supplement and resupply state and local public health agencies in the event of a national emergency anywhere and anytime within the United States or its territories. Among other medical countermeasures, this stockpile contained, as of June 2007, about 10 million doses of BioThrax, the licensed anthrax vaccine.⁸ Since doses of BioThrax, like other vaccines, have an expiration date, these doses will be disposed of if they are not used before their expiration date.

The only other large user of BioThrax vaccine is DOD, which has procured its own inventory of the vaccine. DOD has a mandatory Anthrax Vaccine Immunization Program (AVIP) for military personnel, emergency-essential DOD civilians, and contractors, based on defined geographic areas or roles. The policy also allows personnel previously immunized against anthrax, who are no longer deployed to high-threat areas, to receive follow-up vaccine doses and booster shots on a voluntary basis.

In November 2004, ASPR awarded VaxGen a procurement contract for \$877.5 million for the manufacture and delivery of 75 million doses of its rPA anthrax vaccine to the Strategic National Stockpile. Two years later, in December 2006, ASPR terminated VaxGen's contract for failure to meet a critical contractual milestone. The failure of this procurement effort

⁶The Office of the Assistant Secretary for Preparedness and Response (ASPR) is the lead agency within HHS on this issue. These offices have undergone several name changes. ASPR was formerly the Office of Public Health Emergency Preparedness (OPHEP) and was renamed pursuant to Public Law 109-417, the Pandemic and All-Hazards Preparedness Act in December 2006. The name OPHEP was created administratively in August 2004. Prior to that change, the office was called the Office of the Assistant Secretary for Public Health Emergency Preparedness (ASPHEP), pursuant to Public Law 107-188, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. Briefly, before that change, it had been called the Office of Public Health Preparedness, which was created administratively in January 2002. In July 2006, Office of Public Health Emergency Medical Countermeasures (OPHEMC), an office within ASPR, was renamed, replacing the name Office of Research and Development Coordination. ORDC was created administratively within ASPHEP in December 2002. OPHEMC has been renamed Biomedical Advanced Research and Development Authority (BARDA).

⁷The Strategic National Stockpile, formerly known as the National Pharmaceutical Stockpile, contains pharmaceuticals, vaccines, medical supplies, and medical equipment to respond to terrorist attacks and other emergencies.

⁸The Department of Homeland Security provides indemnification to the manufacturer of BioThrax for civilian use of the vaccine.

raised larger questions regarding the country's ability to develop a new anthrax vaccine and a robust and sustainable biodefense medical countermeasure industry by building a partnership between pharmaceutical and biotechnology firms and the government. The biotech industry has raised concerns whether the government can clearly define its requirements for future procurement contracts.

In our May 2006 testimony, we concluded that ASPR's procurement strategy for rPA anthrax vaccine had been very aggressive. We stated that "it is important to understand the unique issues at stake in this early phase of implementation of the biodefense strategy. The rest of the biotechnology sector will be watching to see whether the industry and the U.S. government can make this partnership work. Issues with this contract might have an effect beyond just this individual vaccine procurement. They could have an impact on how the biotechnology industry responds to government overtures in the future for the development and procurement of medical countermeasures for the many biothreat agents still to be addressed."⁹

To assist in ongoing efforts to address these concerns, you asked that we identify (1) factors that contributed to the failure of ASPR's first Project BioShield procurement effort with VaxGen for an rPA anthrax vaccine and (2) issues associated with using the licensed anthrax vaccine, BioThrax, in the Strategic National Stockpile.

Scope and Methodology

To determine what factors contributed to the failure of ASPR's procurement effort with VaxGen, we interviewed officials from HHS's components—ASPR, NIAID, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). In addition, we reviewed documents these agencies provided. We visited and interviewed the officials of the two companies—Avecia and VaxGen—that NIAID contracted with to develop the new rPA anthrax vaccine. We also talked to officials of several biotech companies that are currently working on biodefense medical countermeasures. We consulted with a small group of experts in the manufacturing of biodefense vaccines to ensure that our assessments were accurate. Finally, we reviewed scientific literature on

⁹ GAO, *Anthrax: Federal Agencies Have Taken Some Steps to Validate Sampling Methods and to Develop a Next Generation Anthrax Vaccine*, [GAO-06-756T](#) (Washington, D.C.: May 9, 2006) pp. 20-21.

vaccine development, manufacturing, and safety and efficacy, including regulatory requirements for licensing.

To identify issues associated with using the licensed anthrax vaccine (BioThrax) in the stockpile, we interviewed officials from ASPR, CDC, and DOD. In addition, we reviewed documents these agencies provided and analyzed data on stockpile inventory of the licensed anthrax vaccine. We visited and interviewed officials from Emergent Biosolutions, the company that manufactures the licensed anthrax vaccine. We also talked to officials of several biotech companies that are currently working on biodefense medical countermeasures to obtain their views on ways to minimize waste in the stockpile. We conducted our review from June 2007 through August 2007 in accordance with generally accepted government auditing standards.

Results in Brief

Three major factors contributed to the failure of the first Project BioShield procurement effort. First, ASPR awarded the first BioShield procurement contract to VaxGen when its product was at a very early stage of development and many critical manufacturing issues (such as stability¹⁰ and scale-up production¹¹) had not been addressed. ASPR officials told us that they felt a sense of urgency to demonstrate to the public that a new, improved vaccine was coming; they also stated that at the time of the award, they were 80 percent to 90 percent confident about VaxGen's chances of success. These officials based this confidence level on a subjective assessment and not on objective tools to determine a product's level of maturity. This award—several years before planned completion of earlier and uncompleted NIAID development contracts with VaxGen—preempted critical development work. Similarly, the requirement to deliver 75 million doses of rPA anthrax vaccine was not based on objective data. This requirement, according to the industry experts, would have

¹⁰ Stability refers to the physical, chemical, biological, biopharmaceutical, and microbiological characteristics of a vaccine, during and up to the end of the expiration dating period and storage periods of samples under expected handling and storage conditions. The results of stability studies are used to recommend storage conditions and to establish the shelf life and/or the release specifications.

¹¹ Scale-up production occurs when the decision is made to take a vaccine produced in small amounts in a pilot facility and increase production to commercial levels. This is one of the most difficult, complex, time-consuming, and resource-intensive aspects of vaccine development for manufacturers.

been unrealistic for even a large pharmaceutical firm, given that the product was at an early stage of development.

Second, VaxGen took unrealistic risks in accepting the contract terms. According to VaxGen officials, they understood that their chances of success were limited. Nonetheless, they accepted the contract terms in spite of (1) the aggressive delivery time line, (2) their lack of in-house technical expertise in stability and vaccine formulation—a condition exacerbated by the attrition of key staff from the company as the contract progressed—and (3) their limited options for securing additional funding should the need arise for additional testing required to meet regulatory requirements.

Third, important FDA requirements regarding the type of data and testing required for the rPA anthrax vaccine to be eligible for use in an emergency were not known—to FDA, NIAID, ASPR, and VaxGen—at the outset of the procurement contract. They were defined later when FDA introduced new guidance on emergency use authorization (EUA). In addition, ASPR's anticipated use of the rPA anthrax vaccine was not articulated to all parties clearly enough and evolved over time. Finally, according to VaxGen, the purchase of BioThrax for the stockpile as a stopgap measure raised the requirement for using the VaxGen rPA vaccine. All of these factors created confusion over the acceptance criteria for VaxGen's product and significantly diminished VaxGen's ability to meet contract time lines.

ASPR had announced its intention to issue another request for proposal for an rPA anthrax vaccine procurement in 2007 but had not done so at the time of this report.¹² Since ASPR and other HHS components involved have not completed any formal lessons-learned exercise from the first procurement's failure, they may repeat their mistakes in the absence of a corrective plan. According to industry experts, the lack of clear requirements is a cause of concern to companies asked to partner with the government since they invest significant resources in trying to meet government needs and now question whether the government can clearly define its requirements for future procurement contracts.

We identified two issues related to using the licensed anthrax vaccine, BioThrax, in the Strategic National Stockpile: First, ASPR lacks an

¹² HHS issued a Source Sought Notice in May 2007.

effective strategy to minimize waste.¹³ Vaccine valued at more than \$12 million has already expired and is no longer usable. Without an effective management strategy in the future, over \$100 million per year could be lost for the life of the licensed anthrax vaccine currently in the stockpile. ASPR could minimize such potential waste by developing a single inventory system for BioThrax with DOD, with rotation based on a first-in, first-out principle. DOD and ASPR officials told us that they discussed the rotation option in 2004 but identified several obstacles. Specifically, since the funding to purchase BioThrax comes from DOD and HHS appropriations, respectively, ASPR officials believe funding transfer may be a problem. However, DOD officials told us that funding is not an issue. DOD and ASPR officials told us that they have used different authorities to indemnify the manufacturer against any losses or problems that may arise from use of the vaccine.¹⁴ Finally, since DOD vaccinates its troops at various locations around the world, there may be logistical distribution issues. DOD officials acknowledged that these issues could be resolved.

The second issue related to use of the BioThrax in the Strategic National Stockpile is ASPR's planned use of expired vaccine in violation of FDA's current rules. According to CDC, ASPR told CDC not to dispose of three lots of BioThrax vaccine that expired in 2006 and 2007. ASPR officials told us that the agency's decision was based on the possible need to use these lots of vaccines in an emergency. However, FDA rules prohibit the use of expired vaccine.¹⁵ Thus, ASPR's planned use of expired vaccine would violate FDA's current rules and could undermine public confidence because ASPR would be unable to guarantee the potency of the vaccine.

To help ensure the success of future medical countermeasures procurement, we recommend that the Secretary of HHS direct ASPR, NIAID, FDA, and CDC to ensure that the concept of use and all critical requirements for such procurements are clearly articulated at the outset.

¹³All vaccines will eventually expire. However, when there is a large-volume user for stockpile product, not having an effective strategy to ensure stockpile products would be used constitutes waste.

¹⁴Indemnification was originally granted by DOD to the manufacturer in the late 1990s because of the manufacturer's inability to get commercial insurance at a reasonable price.

¹⁵FDA regulations do allow the extension of the expiration date of a vaccine under certain limited circumstances. See 21 C.F.R. 610.53.

To ensure public confidence and comply with FDA's current rules, we recommend that the Secretary of HHS direct ASPR to destroy the expired BioThrax vaccine in the stockpile.

To minimize waste of the BioThrax anthrax vaccine in the stockpile, we recommend that the Secretaries of HHS and DOD develop a single integrated inventory system for the licensed anthrax vaccine, with rotation based on a first-in, first-out principle.

HHS and DOD provided written comments on a draft of this report and generally concurred with our recommendations. In addition, with regard to our recommendation on integrated stockpile, they identified funding and legal challenges to developing an integrated inventory system for BioThrax in the stockpile, which may require legislative action. Although HHS and DOD use different authorities to address BioThrax liability and funding issues, both authorities could apply to either DOD or HHS; consequently, indemnity does not appear to be an insurmountable obstacle for future procurements.

Background

Following the anthrax attacks of 2001, the federal government determined that it would need additional medical countermeasures (for example, pharmaceuticals, vaccines, diagnostics, and other treatments) to respond to an attack involving chemical, biological, radiological, or nuclear (CBRN) agents.

Project BioShield

The Project BioShield Act of 2004 (Public Law 108-276) was designed to encourage private companies to develop civilian medical countermeasures by guaranteeing a market for successfully developed countermeasures.

The Project BioShield Act (1) relaxes some procedures for bioterrorism-related procurement, hiring, and research grant awarding; (2) allows for the emergency use of countermeasures not approved by FDA; and (3) authorizes 10-year funding (available through fiscal year 2013) to encourage the development and production of new countermeasures for CBRN agents. The act also authorizes HHS to procure these countermeasures for the Strategic National Stockpile.

Project BioShield is a procurement program that allows the government to enter into contracts to procure countermeasures while they still are in development, up to 8 years before product licensure is expected. Under this program, the government agrees to buy a certain quantity of

successfully developed countermeasures for the Strategic National Stockpile at a specified price once the countermeasure meets specific requirements. The government pays the agreed-upon amount only after these requirements are met and the product is delivered to the Strategic National Stockpile. If the product does not meet the requirements within the specified time frame, the contract can be terminated without any payment to the contractor. Thus, while Project BioShield reduces the producer's market risk—that is, the possibility that no customer will buy the successfully developed product—it does not reduce the development risk to the producer—that is, the possibility that the countermeasure will fail during development.

In December 2006, the Pandemic and All-Hazards Preparedness Act (Public Law 109-417) modified the Project BioShield Act to allow for milestone-based payments before countermeasure delivery for up to half of the total award. Within HHS, the Biomedical Advanced Research and Development Authority (BARDA) has the authority to directly fund the advanced development of countermeasures that are not eligible for Project BioShield contracts.

Agency Roles in Developing, Procuring, and Stockpiling Medical Countermeasures

DHS's Role

Project BioShield procurement involves actions by the Department of Homeland Security (DHS), HHS (including ASPR, NIAID, FDA, and CDC), and an interagency working group.

The first step in the Project BioShield acquisition process is to determine whether a particular CBRN agent poses a material threat to national security. DHS performs this analysis, which is generally referred to as a population threat assessment (PTA). On the basis of this assessment, the DHS Secretary determines whether that agent poses a material threat to national security. The Project BioShield Act of 2004 requires such a written PTA for procurements using BioShield funds and authorities. This declaration neither addresses the relative risk posed by an agent nor determines the priority for acquisition, which is solely determined by ASPR. Furthermore, the issuance of a PTA does not guarantee that the government will pursue countermeasures against that agent. DHS has issued PTAs for 13 agents, including the biological agents that cause anthrax; multi-drug-resistant anthrax; botulism; glanders; melioidosis; tularemia; typhus; smallpox; plague; and the hemorrhagic fevers Ebola, Marburg, and Junin.

HHS's Role

Various offices within HHS (ASPR, NIAID, FDA, and CDC) fund the development research, procurement, and storage of medical countermeasures, including vaccines, for the Strategic National Stockpile.

ASPR's role: ASPR is responsible for the entire Project BioShield contracting process, including issuing requests for information and requests for proposals, awarding contracts, managing awarded contracts, and determining whether contractors have met the minimum requirements for payment. ASPR maintains a Web site detailing all Project BioShield solicitations and awards.

ASPR has the primary responsibility for engaging with the industry and awarding contracts for large-scale manufacturing of licensable products, including vaccines, for delivery into the Strategic National Stockpile. With authorities recently granted, BARDA will be able to use a variety of funding mechanisms to support the advanced development of medical countermeasures and to award up to 50 percent of the contract as milestone payments before purchased products are delivered.

NIAID's role: NIAID is the lead agency in NIH for early candidate research and development of medical countermeasures for biodefense. NIAID issues grants and awards contracts for research on medical countermeasures exploration and early development, but it has no responsibility for taking research forward into marketable products.

FDA's role: Through its Center for Biologics Evaluation and Research (CBER), FDA licenses many biological products, including vaccines, and the facilities that produce them. Manufacturers are required to comply with current Good Manufacturing Practices regulations, which regulate personnel, buildings, equipment, production controls, records, and other aspects of the vaccine manufacturing process. FDA has also established the Office of Counterterrorism Policy and Planning in the Office of the Commissioner, which issued the draft *Guidance on the Emergency Use Authorization of Medical Products* in June 2005. This EUA guidance describes in general terms the data that should be submitted to FDA, when available, for unapproved products or unapproved uses of approved products that HHS or another entity wishes FDA to consider for use in the event of a declared emergency. The final EUA guidance was issued in July 2007.

CDC's role: Since 1999, CDC has had the major responsibility for managing and deploying the medical countermeasures stored in the Strategic National Stockpile. The Omnibus Consolidated and Emergency

Supplemental Appropriations Act (Public Law 105-277) first provided the stockpile with a fund specially appropriated for purchases. Since then, CDC has maintained this civilian repository of medical countermeasures, such as antibiotics and vaccines.

DOD's Role

DOD is not currently a part of Project BioShield. Beginning in 1998, DOD had a program to vaccinate all military service members with BioThrax. DOD's program prevaccinates personnel for deployment to Iraq, Afghanistan, and the Korean peninsula with BioThrax. For other deployments, this vaccination is voluntary. DOD also has a program to order, stockpile, and use the licensed anthrax vaccine. DOD estimates its needs for BioThrax doses and bases its purchases on that estimate.

Interagency Working Group

Multiple agencies, including HHS and DHS, provide input on priority-setting and requirements activities. For BioShield purchases, the Secretaries of HHS and DHS prepare a joint recommendation, which requires presidential approval before HHS enters into a procurement contract. The Secretary of HHS currently coordinates the interagency process; the National Science and Technology Council previously handled the coordination.

The Nature of Anthrax and the Anthrax Vaccine

The Nature of Anthrax

Anthrax is a rare but serious acute infectious disease that must be treated quickly with antibiotics. Anthrax is caused by the spore-forming bacterium *Bacillus anthracis*. It occurs most commonly in herbivores in agricultural regions that have less effective veterinary and public health programs. Anthrax can infect humans who have been exposed to infected animals or products from infected animals such as hide, hair, or meat. Human anthrax occurs rarely in the United States from these natural causes. However, the anthrax exposures in September and October 2001 through mail intentionally contaminated with anthrax spores resulted in illness in 22 persons and the death of 5.

The Licensed Vaccine for Anthrax

An FDA-licensed anthrax vaccine, BioThrax, has been available since 1970. The vaccine has been recommended for laboratory workers who are involved in the production of cultures of anthrax or who risk repeated exposure to anthrax by, for example, conducting confirmatory or environmental testing for anthrax in the U.S. Laboratory Response Network for Bioterrorism laboratories; persons who may be required to make repeated entries into known *Bacillus anthracis* contaminated areas

after a terrorist attack, such as remediation workers; and persons who work with imported animal hides, furs, or similar materials, if the industry standards and restrictions that help to control the disease are insufficient to prevent exposure to anthrax spores.

Preventive anthrax vaccine is not recommended for civilians who do not have an occupational risk. However, in 1998, DOD began a mandatory program to administer the vaccine to all military personnel for protection against possible exposure to anthrax-based biological weapons. By late 2001, roughly 2 million doses of the vaccine had been administered, most of them to U.S. military personnel. As the vaccination program proceeded, some military personnel raised concerns about the safety and efficacy of the vaccine.¹⁶

The BioShield program stockpiled BioThrax for the Strategic National Stockpile for postexposure use in the event of a large number of U.S. civilians being exposed to anthrax. ASPR officials characterized the acquisition of the licensed vaccine as a “stopgap” measure as they also have been engaged in the development and purchase of a new rPA anthrax vaccine. ASPR had already acquired 10 million doses of BioThrax from Emergent BioSolutions by 2006 and recently purchased an additional 10 million doses.

The Vaccine Development Process

Vaccine research and development leading to FDA approval for use is a long and complex process. It may take 15 years and, according to FDA, cost from \$500 million to \$1.2 billion and require specialized expertise.

Vaccines are complex biological products given to a person or animal to stimulate an immune reaction the body can “remember” if it is exposed to the same pathogen later.¹⁷ In contrast to most drugs, they have no simple chemical characterization. As a result, evaluating them involves measuring their effects on living organisms, and their quality can be guaranteed only through a combination of in-process tests, end-product tests, and strict controls of the entire manufacturing process.

¹⁶GAO, *Anthrax Vaccine: GAO’s Survey of Guard and Reserve Pilots and Aircrew*, GAO-02-445 (Washington, D.C.: Sept. 20, 2002).

¹⁷Biological products are typically derived from living sources, such as humans, animals, bacteria, and viruses.

Vaccines are highly perishable and typically require cold storage to retain potency. Even if they are stored at the recommended temperature, most vaccines have expiration dates beyond which they are considered outdated and should not be used. A great deal of attention is directed to using the vaccine before its expiration date. For example, a recent CDC manual advises users: “Check expiration date on container” and “rotate stock so that the earliest dated material is used first.” After the storage vial has been opened, the vaccine begins to deteriorate quickly in many cases, often necessitating the opened or reconstituted vaccine to be used within minutes to hours or discarded.”¹⁸ Since human challenge studies cannot be conducted for CBRN medical countermeasures, FDA requires animal efficacy data instead.

The FDA process for approving a biologic for use in the United States begins with an investigational new drug (IND) application.¹⁹ A sponsor that has developed a candidate vaccine applies to start the FDA oversight process of formal studies, regulated by CBER within FDA. Phase 1 trials involve safety and immunogenicity studies in a small number of healthy volunteer subjects.²⁰ phase 2 and phase 3 trials gather evidence of the vaccine’s effectiveness in ever larger groups of subjects, providing the documentation of effectiveness and important additional safety data required for licensing. If the data raise safety or effectiveness concerns at any stage of clinical or animal studies, FDA may request additional information or halt ongoing clinical studies.²¹

In vaccine development, clinical trials typically last up to 6 years. After they have been successfully completed, the sponsor applies for FDA’s approval to market the product. FDA’s review of the license application includes review of the manufacturing facility and process. According to FDA, this process is typically completed within 10 months for a standard

¹⁸Centers for Disease Control and Prevention, *Vaccine Management: Recommendations for Storage and Handling of Selected Biologicals*, (Atlanta, Georgia: January 2007).

¹⁹FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population.

²⁰“Immunogenicity” refers to the ability of a vaccine to stimulate a protective immune response.

²¹When FDA decides to halt drug development activity, it issues a “clinical hold,” which begins a series of review activities.

review and 6 months for a priority review. According to industry sources, the challenge in scaling up vaccine production from a research laboratory to a large manufacturing environment while still maintaining quality requires much skill, sophisticated facilities, and a great deal of experience.

Several Factors Contributed to the Failure of ASPR's First Project BioShield Effort for the Production of an rPA Anthrax Vaccine

Three major factors contributed to the failure of the first Project BioShield procurement effort. First, ASPR awarded the first BioShield procurement contract to VaxGen when its product was at a very early stage of development and many critical manufacturing issues had not been addressed. Second, VaxGen took unrealistic risks in accepting the contract terms. Third, key parties did not clearly articulate and understand critical requirements at the outset.

HHS Awarded the Procurement Contract Before Development Had Reached an Appropriate Level of Maturity

ASPR's decision to launch the VaxGen procurement contract for the rPA anthrax vaccine at an early stage of development, combined with the delivery requirement for 25 million doses within 2 years,²² did not take the complexity of vaccine development into consideration and was overly aggressive. Citing the urgency involved, ASPR awarded the procurement contract to VaxGen several years before the planned completion of earlier and uncompleted NIAID development contracts with VaxGen and thus preempted critical development work. (For a time line of events for the first rPA anthrax vaccine development and procurement effort, see appendix I).

In response to the anthrax attacks of 2001, NIAID was assigned responsibility for developing candidate vaccines leading up to licensure, purchase, and storage in the stockpile. NIAID envisioned a strategy of minimizing risk by awarding contracts to multiple companies to help ensure that at least one development effort would be successful. NIAID's strategy was appropriate since failure is not uncommon in vaccine development. Toward this end, NIAID designed a sequence of two contracts—one to follow the other—to advance pilot lots of rPA anthrax vaccine through early characterization work, phase 1 and phase 2 clinical trials, accelerated and real-time (long-term) stability testing, and tasks to evaluate the contractor's ability to manufacture the vaccine in large

²² The contract called for 75 million doses overall, but only 25 million were required within 2 years of award.

quantities according to current Good Manufacturing Practices (cGMP).²³ Additionally, these contracts were cost reimbursable, an appropriate contracting mechanism when uncertainties involved in contract performance do not permit cost to be estimated with sufficient accuracy to use a fixed-price contract. VaxGen was one of the awardees. The other awardee was Avecia, Ltd., of Manchester, United Kingdom. NIAID's development effort with Avecia to prepare a candidate rPA anthrax vaccine for potential purchase for the stockpile is ongoing.

VaxGen's first development contract, awarded in September 2002, had three major requirements: characterize the chemical composition of the pilot lot; conduct phase 1 clinical trials to determine the basic safety profile of the vaccine; and produce a feasibility plan to manufacture, formulate, fill and finish, test, and deliver up to 25 million doses of cGMP vaccine. The initial period of performance for this first contract was 15 months, to be completed in September 2003. However, NIAID twice extended the period of performance to accommodate problems, including stability testing. The final completion date of the contract was December 2006.

The second development contract was awarded to VaxGen in September 2003 to continue development of its vaccine. This contract covered 36 months and was scheduled to end in October 2006. Three of the major requirements were to (1) manufacture, formulate, fill, finish, release, and deliver 3 million to 5 million doses of vaccine from at least three different lots that met cGMP requirements; (2) develop, implement, and execute accelerated and real-time stability testing programs to ensure the safety, sterility, potency, and integrity of the vaccine; and (3) conduct phase 2 clinical trials.

This second development contract covered especially critical steps in the development cycle. For example, only during the phase 2 trials is the vaccine given to a large enough number of human subjects to further project its safety. Under the contract, phase 2 clinical trials, which were to determine the optimum dose and dosing regimen, were expected to take 2 years to complete.²⁴ This second contract also covered accelerated and

²³ Pharmaceutical and biotech firms follow the cGMP to ensure that the products produced meet specific requirements for identity, strength, quality, and purity. FDA regulates these industries to ensure cGMPs are being followed.

²⁴ Industry experts told us that even this time scale is very optimistic.

real-time stability testing programs to ensure the safety, sterility, potency, and integrity of the vaccine. Vaccines, especially those intended to be stockpiled, need to exhibit the necessary stability to ensure they will remain safe and potent for the required storage period.

In early 2004, VaxGen's product entered particularly critical stages of development and scale-up production. According to industry officials we talked to, the challenge in scaling up vaccine production from a research pilot lot to a large manufacturing environment while still maintaining quality is not trivial. It requires a great deal of skill, sophisticated facilities, and experience. The officials also stated that work on the vaccine at this point would have been expected to take multiple years to complete, during which time the contractor would work back and forth with FDA in evaluating, testing, and then reworking both its product and manufacturing capability against criteria for eventual licensure.

However, on November 4, 2004, a little more than a year after NIAID awarded VaxGen its second development contract, ASPR awarded the procurement contract to VaxGen for 75 million doses of its rPA anthrax vaccine. At that time, VaxGen was still at least a year away from completing the Phase 2 clinical trials under the second NIAID development contract. Moreover, VaxGen was still finishing up work on the original stability testing required under the first development contract.

ASPR officials at the time of the award had no objective criteria, such as Technology Readiness Levels (TRL), to assess product maturity.²⁵ They were, however, optimistic the procurement contract would be successful. One official described its chances of success at 80 percent to 90 percent. However, a key official at VaxGen told us at the same time that VaxGen estimated the chances of success at 10 percent to 15 percent. ASPR now estimates that prior to award, the rPA vaccine was at a TRL rating of 8. According to industry experts, a candidate vaccine product at such a level

²⁵TRLs have been used by federal agencies (DOD, the National Aeronautics and Space Administration, and others) to assess the maturity of evolving technologies prior to incorporating that technology into a system or subsystem. The primary purpose of using TRLs is to help management in making decisions concerning the development and transitioning of technology.

is generally expected to be 5-8 years away from completion and to have only a 30 percent chance of development into a successful vaccine.²⁶

When we asked ASPR officials why they awarded the procurement contract when they did, they pointed to a sense of urgency at that time and the difficulties in deciding when to launch procurement contracts. However, November 2004 was 3 years after the anthrax attacks in 2001, and while the sense of urgency was still important, it could have been tempered with realistic expectations. According to industry experts, preempting the development contract 2 years before completing work—almost half its scheduled milestones—was questionable, especially for vaccine development work, which is known to be susceptible to technical issues even in late stages of development. NIAID officials also told us that, in their opinions, it was too early for a BioShield purchase. At a minimum, the time extensions for NIAID’s first development contract with VaxGen to accommodate stability testing should have indicated to ASPR that development on its candidate vaccine was far from complete.

After ASPR awarded VaxGen the procurement contract, NIAID canceled several milestones under its development contract with VaxGen to free up funds for earlier milestones that VaxGen was having trouble meeting. However, this undermined VaxGen’s ability to refine product development up to the level needed to ensure delivery within the 2-year time frame required under the procurement contract.

VaxGen Took an Unrealistic Risk in Accepting the Procurement Contract, Knowing Its Own Technical and Financial Limitations

VaxGen officials told us that they understood their chances for success were limited and that the contract terms posed significant risks. These risks arose from aggressive time lines, VaxGen’s limitations with regard to in-house technical expertise in stability and vaccine formulation—a condition exacerbated by the attrition of key staff from the company as the contract progressed—and its limited options for securing additional funding should the need arise.

Industry experts told us that a 2-year time line to deliver 75 million filled and finished doses of a vaccine from a starting point just after phase 1 trials is a near-impossible task for any company. VaxGen officials told us that at the time of the procurement award they knew the probability of

²⁶In December 2006, at the time the contract was terminated, according to ASPR officials, the TRL level was still at 8.

success was very low, but they were counting on ASPR's willingness to be flexible with the contract time line and work with them to achieve success. In fact, in May 2006, ASPR did extend the contract deadlines to initiate delivery to the stockpile an additional 2 years. However, on November 3, 2006, FDA imposed a clinical hold on VaxGen's forthcoming phase 2 trial after determining that data submitted by VaxGen were insufficient to ensure that the product would be stable enough to resume clinical testing.²⁷ By that time, ASPR had lost faith in VaxGen's technical ability to solve its stability problems in any reasonable time frame. When VaxGen failed to meet a critical performance milestone of initiating the next clinical trial, ASPR terminated the contract.

According to VaxGen's officials, throughout the two development contracts and the Project BioShield procurement contract, VaxGen's staff peaked at only 120, and the company was consistently unable to marshal sufficient technical expertise. While it is not known how a larger pharmaceutical company might have fared under similar time constraints, we believe more established pharmaceutical companies have staff and resources better able to handle the inevitable problems that arise in vaccine development and licensure efforts. For example, according to industry experts, a large firm might be able to leverage an entire internal department to reformulate a vaccine or pursue solutions to a stability issue, while a smaller biotechnology company like VaxGen would likely be unable to use more than a few full-time scientists. In such situations, the smaller company might have to contract out for the necessary support, provided it can be found within a suitable time frame.

External expertise that might have helped VaxGen better understand its stability issue was never applied. At one point during the development contracts, NIAID—realizing VaxGen had a stability problem with its product—convened a panel of technical experts in Washington, D.C.

²⁷A clinical hold is the mechanism that FDA uses to stop a study when it finds that the study should not proceed because of an identified deficiency. When the deficiency is identified in FDA's initial review of the IND application, FDA contacts the sponsor within 30 days of submission of the IND. FDA may also impose a clinical hold on an ongoing study based on its review of newly submitted protocols and amendments, safety reports, or other information. When a clinical hold is issued, a sponsor must address the issue before the hold is removed. FDA has issued a regulation that identifies the deficiencies that provide the basis for a clinical hold. A clinical hold may be imposed, as in this case, because a plan or a protocol for the investigation is clearly deficient in design to meet its stated objectives. All clinical holds are reviewed by FDA management to ensure consistency and quality in FDA's clinical hold decisions.

NIAID officials told us that at the time of the panel meeting, they offered to fund technical experts to work with the company, but VaxGen opted not to accept the offer. Conversely, VaxGen officials reported to us that at the time NIAID convened the panel of experts, NIAID declined to fund the work recommended by the expert panel.

The lack of available technical expertise was exacerbated when key staff at the company began leaving. A senior VaxGen official described the attrition problem as “massive.” Of special significance, VaxGen’s Senior Vice President for Research and Development and Chief Scientific Officer left during critical phase 2 trials. An official at VaxGen described this person’s role as key in both development of the assays and reformulation of the vaccine.²⁸

Finally, VaxGen accepted the procurement contract terms even though the financial constraints imposed by the BioShield Act limited its options for securing any additional funding needed. In accordance with this act, payment was conditional on delivery of a product to the stockpile, and little provision could be made, contractually, to support any unanticipated or additional development needed—for example, to work through issues of stability or reformulation.²⁹ Both problems are frequently encountered throughout the developmental life of a vaccine. This meant that the contractor would pay for any development work needed on the vaccine. VaxGen, as a small biotechnology company, had limited internal financial resources and was dependent on being able to attract investor capital for any major influx of funds.

In such a firm, fixed-price contractual arrangement, the contractor assumes most of the risk because the price is not subject to any adjustment based on the contractor’s cost experience. Thus, even if the contractor costs go up, the delivery price does not. We believe these contracts are appropriate in situations where there are no performance uncertainties or the uncertainties can be identified and reasonable estimates of their cost impact can be made, but this was not the situation in the VaxGen procurement contract. VaxGen had to be willing to accept

²⁸An assay is a laboratory test or procedure carried out in order to measure the amount of a substance present in a product and/or to measure its activity.

²⁹Under Project BioShield, advance payments of up to 10 percent of the contract value could be made if the HHS Secretary deemed it necessary for the success of the program. ASPR officials told us that VaxGen did request such a payment, but ASPR did not grant it.

the firm, fixed-price contract and assume the risks involved. VaxGen did so even though it understood that development on its rPA vaccine was far from complete when the procurement contract was awarded and that the contract posed significant inherent risks.

Key Parties Did Not Clearly Articulate and Understand Critical Requirements

Important requirements regarding the data and testing required for the rPA anthrax vaccine to be eligible for use in an emergency were not known at the outset of the procurement contract. They were defined in 2005 when FDA introduced new general guidance on EUA. In addition, ASPR's anticipated use of the rPA anthrax vaccine was not articulated to all parties clearly enough and evolved over time. Finally, purchase of BioThrax raised the requirement for use of the VaxGen rPA vaccine. All of these factors created confusion over the acceptance criteria for VaxGen's product and significantly diminished VaxGen's ability to meet contract time lines.

Guidance on Emergency Use Authorization Appeared Midcontract and Created Confusion

Criteria for product acceptance need to be clearly articulated and understood by all parties before committing to a major procurement. Terms of art that leave critical requirements unclear are problematic in contract language. After VaxGen received its procurement contract, draft guidance was issued that addressed the eventual use of any unlicensed product in the stockpile. This created confusion over the criteria against which VaxGen's product would be evaluated, strained relations between the company and the government, and caused a considerable amount of turmoil within the company as it scrambled for additional resources to cover unplanned testing.

In June 2005, FDA issued draft EUA guidance, which described for the first time the general criteria that FDA would use to determine the suitability of a product for use in an emergency.³⁰ This was 7 months after the award of the procurement contract to VaxGen and 14 months after the due date for bids on that contract.

Since the request for proposal for the procurement contract was issued and the award itself was made before the EUA guidance was issued,

³⁰FDA is ultimately responsible for determining if available products (unapproved products or approved products for unapproved usage) in the stockpile can be used in an emergency. The data FDA needs to determine whether a product can be used in an emergency are critical to manufacturers to adequately plan and estimate the time and resources required for generating the data.

neither could take the EUA requirements into consideration. The procurement contract wording stated that in an emergency, the rPA anthrax vaccine was to be “administered under a ‘Contingency Use’ Investigational New Drug (IND) protocol” and that vaccine acceptance into the stockpile is dependent on the accumulation and submission of the appropriate data to support the “use of the product (under IND) in a postexposure situation.” FDA officials told us they do not use the phrase “contingency use” under IND protocols.

When we asked ASPR officials about the requirements for use defined in the contract, they said that the contract specifications were consistent with the statute and the needs of the stockpile. They said their contract used “a term of art” for BioShield products. That is, the contractor had to deliver a “usable product” under FDA guidelines. The product could be delivered to the stockpile only if sufficient data were available to support emergency use. ASPR officials told us that FDA would define “sufficient data” and the testing hurdles a product needed to overcome to be considered a “usable product.”

While VaxGen and FDA had monthly communication, according to FDA, data requirements for emergency use were not discussed until December 2005, when VaxGen asked FDA what data would be needed for emergency use. In January 2006, FDA informed VaxGen, under its recently issued draft EUA guidance, of the data FDA would require from VaxGen for its product to be eligible for consideration for use in an emergency. The draft guidance described in general FDA’s current thinking concerning what FDA considered sufficient data and the testing needed for a product to be considered for authorization in certain emergencies.

Because the EUA guidance is intended to create a more feasible protocol for using an unapproved product in a mass emergency than the term “contingency use under an IND protocol” that ASPR used in the procurement contract, it may require more stringent data for safety and efficacy. Under an IND protocol, written, informed consent must be received before administering the vaccine to any person, and reporting requirements identical to those in a human clinical trial are required.³¹ The EUA guidance—as directed by the BioShield law—eased both informed consent and reporting requirements. This makes sense in terms of the logistics of administering vaccine to millions of people in the large-scale,

³¹It also requires an approval from the Institutional Review Board.

postexposure scenarios envisioned. Because EUA guidance defines a less stringent requirement for the government to use the product, it correspondingly may require more testing and clinical trial work than was anticipated under contingency use.

Several of the agencies and companies involved in BioShield-related work have told us the EUA guidance appears to require a product to be further along the development path to licensure than the previous contingency use protocols would indicate. VaxGen officials told us that if the draft EUA guidance was the measure of success, then VaxGen estimated significant additional resources would be needed to complete testing to accommodate the expectations under this new guidance. NIAID told us that the EUA guidance described a product considerably further along the path to licensure (85 percent to 90 percent) than it had assumed for a Project BioShield medical countermeasure (30 percent) when it initially awarded the development contracts.

The Concept of Use for the rPA Vaccine Was Not Clearly Articulated to All Parties

FDA considers a vaccine's concept of use important information to gauge the data and testing needed to ensure the product's safety and efficacy. Under the EUA statute, FDA must determine on the basis of the specific facts presented whether it is necessary and appropriate to authorize use of a specific product in an emergency. According to FDA, data and testing requirements to support a product's use in an emergency context may vary depending on many factors, including the number of people to whom the product is expected to be administered. The current use of an unlicensed product involves the assessment of potential risks and benefits from use of an unapproved drug in a very small number of people who are in a potentially life-threatening situation. In such situations, because of the very significant potential for benefit, safety and efficacy data needed to make the risk benefit assessment might be lower than in an emergency situation where an unlicensed vaccine might be offered to millions of healthy people. This distinction is critical for any manufacturer of a product intended for use in such scenarios—it defines the level of data and testing required. Product development plans and schedules rest on these requirements.

In late 2005, as VaxGen was preparing for the second phase 2 trial and well into its period of performance under the procurement contract, its officials participated in meetings, primarily with FDA but also with ASPR and NIAID representatives, to receive FDA comments on its product development plans and responses to specific requests for regulatory advice. VaxGen needed to have a clear understanding of FDA's data and testing requirements for the rPA vaccine for the upcoming phase 2 trial to

be able to plan for and implement the necessary clinical and nonclinical work to generate that data. Without it, VaxGen did not have adequate means to determine how far along it was toward meeting FDA's requirements.

However, in these meetings, it became clear that FDA and the other parties had different expectations for the next phase 2 trial. FDA officials concluded from the discussion that VaxGen, ASPR, and CDC anticipated the next phase 2 trial to produce meaningful safety and efficacy data to support use of the vaccine in a contingency protocol under IND. However, FDA officials stated that this was a new idea to the agency.³² From FDA's perspective, the purpose of phase 2 trials was to place the product and sponsor (VaxGen) in the best position possible to design and conduct a pivotal phase 3 trial in support of licensure.³³ The lack of a definition of concept of use caused FDA to delay replying to VaxGen until it could confer with ASPR and CDC to clarify this issue. Thus, we conclude that neither VaxGen nor FDA understood the rPA anthrax vaccine concept of use until this meeting.

Purchase of BioThrax for the Stockpile Raised Requirements for Use of rPA Vaccine

The introduction of BioThrax into the stockpile undermined the criticality of getting an rPA vaccine into the stockpile and, at least in VaxGen's opinion, forced FDA to hold it to a higher standard that the company had neither the plans nor the resources to achieve. ASPR purchased 10 million doses of BioThrax in 2005 and 2006 as a stopgap measure for post-exposure situations. After discussions between VaxGen and FDA, VaxGen concluded that this raised the bar for its rPA vaccine. Although BioThrax is currently licensed for use in pre-exposure, and not postexposure, scenarios, the draft EUA guidance states that FDA will evaluate each EUA candidate's safety and efficacy profile. The EUA guidance states that FDA will "authorize" an unapproved or unlicensed product—such as the rPA anthrax vaccine candidate—only if "there is no adequate, approved and available alternative."³⁴ According to the minutes of the meeting between FDA and VaxGen, in January 2006, FDA reported that the unlicensed rPA anthrax vaccine would be used in an emergency after the stockpiled BioThrax, that is, "when all of the currently licensed [BioThrax] had been

³²See FDA's minutes of the December 2005 meeting with VaxGen.

³³In commenting on the draft report, FDA indicated that the purpose of the phase 2 trial is to collect additional safety and, when possible, efficacy data, as well as to determine the dose, route, and schedule for administration.

³⁴This is a requirement of the BioShield law.

deployed.” This diminished the likelihood of a scenario where the rPA vaccine might be expected to be used out of the stockpile.

ASPR Lacks an Effective Strategy to Minimize Waste in the Strategic National Stockpile and Plans to Use Expired Anthrax Vaccine

We identified two issues related to using the BioThrax in the Strategic National Stockpile. First, ASPR lacks an effective strategy to minimize waste. As a consequence, based on current inventory, over \$100 million is likely to be wasted annually, beginning in 2008. Three lots of BioThrax vaccine in the stockpile have already expired,³⁵ resulting in losses of over \$12 million. According to the data provided by CDC, 28 lots of BioThrax vaccine will expire in calendar year 2008. ASPR paid approximately \$123 million for these lots. For calendar year 2009, 25 additional lots—valued at about \$106 million—will reach their expiration dates. ASPR could minimize the potential waste of these lots by developing a single inventory system with DOD—which uses large quantities of the BioThrax vaccine—with rotation based on a first-in, first-out principle.³⁶

Because DOD is a high-volume user of the BioThrax vaccine, ASPR could arrange for DOD to draw vaccine from lots long before their expiration dates. These lots could then be replenished with fresh vaccine from the manufacturer. DOD, ASPR, industry experts, and Emergent BioSolutions (the manufacturer of BioThrax) agree that rotation on a first-in, first-out basis would minimize waste.

DOD and ASPR officials told us that they discussed a rotation option in 2004 but identified several obstacles. In July 2007, DOD officials believed they might not be able to transfer funds to ASPR if DOD purchases BioThrax from ASPR. However, in response to our draft report, DOD informed us that funding is not an issue. However, ASPR continues to believe that transfer of funds would be a problem. DOD stated smallpox vaccine (Dryvax) procurement from HHS is executed under such an arrangement. Further, DOD and ASPR officials told us that they use different authorities to indemnify the manufacturer against any losses or problems that may arise from use of the vaccine. According to DOD, this area may require legislative action to ensure that vaccine purchased by ASPR can be used in the DOD immunization program. Finally, since DOD

³⁵These lots contained 167,990, 168,130, and 183,990 doses of vaccine respectively.

³⁶In 1999, CDC created a stockpile of licensed medical products. CDC officials told us that CDC had a strategy to rotate products in that stockpile on a first-in, first-out principle with other high-volume users, such as the Department of Veterans Affairs.

vaccinates its troops at various locations around the world, there may be logistical distribution issues. A DOD official acknowledged that these issues could be resolved.

Second, ASPR plans to use expired vaccine from the stockpile, which violates FDA's current rules.³⁷ Data provided by CDC indicated that two lots of BioThrax vaccine expired in December 2006 and one in January 2007. CDC officials stated that their policy is to dispose of expired lots since they cannot be used and continuing storage results in administrative costs. FDA rules prohibit the use of expired vaccine.

Nevertheless, according to CDC officials, ASPR told CDC not to dispose of the three lots of expired BioThrax vaccine. ASPR officials told us that ASPR's decision was based on the possible need to use these lots in an emergency. ASPR's planned use of expired vaccine would violate FDA's current rules and could undermine public confidence because ASPR would be unable to guarantee the potency of the vaccine.

Conclusions

The termination of the first major procurement contract for rPA anthrax vaccine raised important questions regarding the approach taken to develop a new anthrax vaccine and a robust and sustainable biodefense medical countermeasure industry by bringing pharmaceutical and biotechnology firms to form a partnership with the government. With the termination of the contract, the government does not have a new, improved anthrax vaccine for the public, and the rest of the biotech industry is now questioning whether the government can clearly define its requirements for future procurement contracts.

Since HHS components have not completed a formal lessons-learned exercise after terminating VaxGen's development and procurement contracts, these components may repeat the same mistakes in the future in the absence of a corrective plan. Articulating concepts of use and all critical requirements clearly at the outset for all future medical countermeasures would help the HHS components involved in the anthrax procurement process to avoid past mistakes. If this is not done, the government risks the future interest and participation of the biotechnology industry.

³⁷See footnote 15.

Given that the amount of money appropriated to procure medical countermeasures for the stockpile is limited, it is imperative that ASPR develop effective strategies to minimize waste. Since vaccines are perishable commodities that should not be used after their expiration dates, finding other users for the stockpile products before they expire would minimize waste. Because DOD requires a large amount of the BioThrax vaccine on an annual basis, it could use a significant portion of BioThrax in the stockpile before it expires.

Recommendations for Executive Action

To avoid repeating the mistakes that led to the failure of the first rPA procurement effort, we recommend that the Secretary of HHS direct ASPR, NIAID, FDA, and CDC to ensure that the concept of use and all critical requirements are clearly articulated at the outset for any future medical countermeasure procurement.

To ensure public confidence and comply with FDA's current rules, we recommend that the Secretary of HHS direct ASPR to destroy the expired BioThrax vaccine in the stockpile.

To minimize waste of the BioThrax vaccine in the stockpile, we recommend that the Secretaries of HHS and DOD develop a single integrated inventory system for the licensed anthrax vaccine, with rotation based on a first-in, first-out principle.

Agency Comments and Our Evaluation

We provided a draft of this report to the Department of Health and Human Services and the Department of Defense for review and comment. HHS and DOD provided written comments on our draft, which are reprinted in appendixes II and III, respectively. Both agencies also provided technical comments, which we have addressed in the report text as appropriate.

HHS and DOD generally concurred with our recommendations. However, with regard to our recommendation on an integrated stockpile, they identified funding and legal challenges to developing an integrated inventory system for BioThrax in the stockpile, which may require legislative action. Although HHS and DOD use different authorities to address BioThrax liability and funding issues, both authorities could apply to either DOD or HHS; consequently, indemnity does not appear to be an insurmountable obstacle for future procurements.

HHS also disagreed with a number of our specific findings. We have addressed these areas of disagreement in detailed comments in appendix II.

We are sending copies of this report the Secretary of the Department of Defense and the Secretary of the Department of Health and Human Services. We are also sending a copy of this report to other interested congressional members and committees. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report or would like additional information, please contact me at (202) 512-6412 or rhodesk@gao.gov, or Sushil K. Sharma, Ph.D., Dr.PH, at (202) 512-3460 or sharmas@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report.

GAO staff who made major contributions to this report included Noah Bleicher, William Carrigg, Barbara Chapman, Crystal Jones, Jeff McDermott, and Linda Sellevaag.

A handwritten signature in black ink, appearing to read 'Keith Rhodes', written in a cursive style.

Keith Rhodes, Chief Technologist
Center for Technology and Engineering
Applied Research and Methods

Appendix I: Time Line of Events in the First rPA Anthrax Vaccine Development and Procurement Effort

Year	Month	Event
2001	Oct.–Nov.	Letters contaminated with anthrax spores sent through U.S. Postal Service, resulting in death of five persons.
2002	April	National Institute of Allergy and Infectious Diseases (NIAID) issues first rPA anthrax vaccine request for proposal (RFP).
	Sept.	NIAID awards rPA contracts to Avecia and VaxGen for first RFP.
2003	May	NIAID issues second rPA anthrax vaccine RFP.
	Aug.	Health and Human Services (HHS) issues request for information (RFI) for large-scale manufacturing capabilities for next generation anthrax vaccines.
	Oct.	NIAID awards Avecia and VaxGen contracts for second rPA RFP.
2004	Mar.	HHS issues Strategic National Stockpile rPA anthrax vaccine RFP.
	July	President George W. Bush signs Project BioShield into law.
	Nov.	HHS awards Strategic National Stockpile contract to VaxGen for rPA anthrax vaccine procurement.
2005	May	HHS awards Emergent Strategic National Stockpile contract for 5 million doses of BioThrax Vaccine.
	June	Food and Drug Administration (FDA) issues draft <i>Guidance for Emergency Use Authorization of Medical Products</i> .
2006	June	NIAID issues RFP for third-generation anthrax vaccine.
	Sept.	HHS issues broad RFI regarding Technology Readiness Levels for medical countermeasures.
		HHS issues draft <i>Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) Strategy</i> .
	Nov.	FDA issues clinical hold notice on Vaxgen’s trial.
		HHS issues “cure” notice on VaxGen.
Dec.	HHS terminates contract with VaxGen for rPA anthrax vaccine.	
2007	Feb.	NIAID cancels RFP for third-generation anthrax vaccine.
	Mar.	HHS issues PHEMCE Strategy.
	Apr.	HHS issues PHEMCE Implementation Plan.
	Apr.	Biomedical Advanced Research and Development Authority (BARDA) releases presolicitation notice for BioThrax.
	May	BARDA releases sources sought notice for rPA vaccine.

Source: GAO.

Appendix II: Comments from the Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

OCT 4 2007

Mr. Keith Rhodes
Director/Chief Technologist
Center for Technology and Engineering
U.S. Government Accountability Office
Washington, DC 20548

Dear Mr. Rhodes:

Enclosed are the Department's comments on the U.S. Government Accountability Office's (GAO) draft report entitled, "Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing Stockpile of Licensed Vaccine" (GAO-08-88).

The Department has provided several technical comments directly to your staff.

The Department appreciates the opportunity to review and comment on this draft before its publication.

Sincerely,

Rebecca Hemard
for Vincent J. Ventimiglia
Assistant Secretary for Legislation

GENERAL COMMENTS FROM THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT: "PROJECT BIOSHIELD: ACTIONS NEEDED TO AVOID REPEATED PAST PROBLEMS WITH PROCURING NEW ANTHRAX VACCINE AND MANAGING STOCKPILE OF LICENSED VACCINE" (GAO-08-88)

The U.S. Department of Health and Human Services (HHS) is grateful for the opportunity to comment on the draft report from the U.S. Government Accountability Office (GAO) entitled *Project BioShield: Actions Needed to Avoid Repeated Past Problems with Procuring New Anthrax Vaccine and Managing Stockpile of Licensed Vaccine*.

Overview

Anthrax remains a top priority for the ongoing public health emergency preparedness efforts at HHS, and the Department is committed to developing and acquiring a robust portfolio of medical countermeasures against this threat. This prioritization is reflected in the discussion of anthrax medical countermeasures in the *HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Implementation Plan for Chemical, Biological, Radiological, and Nuclear (CBRN) Threats (HHS PHEMCE Implementation Plan)*, providing a road map for future medical countermeasure development and acquisition activities throughout HHS.

The Department continues to pursue a comprehensive strategy for the development and acquisition of products to respond to the threat of anthrax. Antibiotics represent the first line of defense to protect the nation following an anthrax attack. We currently have over 40 million courses of antibiotics in the Strategic National Stockpile (SNS). Anthrax vaccines are also an essential element of our national preparedness. Vaccines may be given as post-exposure prophylaxis in combination with antibiotics to potentially provide longer-term protection; this combination may also allow for a reduction in the duration of the antibiotic regimen. HHS has awarded contracts for the acquisition of nearly 30 million doses of anthrax vaccine since 2005, including the recent contract award of 18.75 million doses of Anthrax Vaccine Adsorbed (AVA, BioThrax™). In addition, antitoxins are necessary to treat individuals with advanced stages of infection, and may contribute to a more successful therapeutic outcome. HHS has awarded contracts to two manufacturers to deliver antitoxins sufficient for treating 30,000 people. These vaccine and antitoxin contracts were awarded under the authorities of the Project BioShield Act of 2004.

Maintaining a diversified medical countermeasure program requires a number of concurrent initiatives to improve near-term preparedness while also supporting the development of next-generation products. For example, while procuring currently available anthrax vaccine, HHS is using authorities made available under the Pandemic and All-Hazards Preparedness Act of 2006 to invest over \$40 million in the continued development of an rPA anthrax vaccine. This investment complements the rPA vaccine program that has been ongoing at the National Institute of Allergy and Infectious Diseases (NIAID) since 2002. In addition, the Office of the Biomedical Advanced Research and Development Authority (BARDA) and NIAID released a Broad Agency Announcement in September 2007 that is designed to support multiple third generation anthrax vaccine candidates.

This GAO report does not accurately and completely reflect the anthrax vaccine programs at the Department of Health and Human Services. Evaluations regarding past procurement activities

See comment 1.

GENERAL COMMENTS FROM THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT: "PROJECT BIOSHIELD: ACTIONS NEEDED TO AVOID REPEATED PAST PROBLEMS WITH PROCURING NEW ANTHRAX VACCINE AND MANAGING STOCKPILE OF LICENSED VACCINE" (GAO-08-88)

See comment 2.

must be considered in the context of the sense of urgency felt in the aftermath of the 2001 anthrax attacks, and the authorities available to HHS at the time. We are also concerned that the draft report fails to recognize the many important strides made in the transparency and effectiveness of medical countermeasure initiatives at HHS. The process of developing the *HHS PHEMCE Strategy* and the *HHS PHEMCE Implementation Plan*, published in the spring of 2007, brought together experts from across the federal government to come to a consensus on priorities for medical countermeasure development and acquisition. This process was also informed by substantial input solicited at the 2006 BioShield Stakeholders Workshop, and in response to the publication of the draft *HHS PHEMCE Strategy* in September 2006. In addition, the public release of these documents provided a clear signal of the path forward to our external stakeholders. We continue to improve transparency and foster strong relationships with product developers through the Enterprise Stakeholder Workshops, BARDA Industry Day, and MedicalCountermeasures.gov, and through continued dialogue with the public through other meetings and forums. Feedback about these initiatives from our stakeholders has been universally positive and encouraging.

Below, we have repeated each of the draft recommendations, and responded to each.

Responses to GAO Recommendations

Recommendation: To avoid repeating the mistakes that led to the failure of the first rPA procurement effort, we recommend that the Secretary of HHS direct ASPR, NIAID, FDA, and CDC to ensure that the concept of use and all critical requirements are clearly articulated at the outset for any future medical countermeasure procurement.

Response: HHS agrees with the importance of clearly establishing and articulating the concept of use and critical requirements for each medical countermeasure. For this reason, many of the Requests for Proposal (RFP) issued through BioShield are preceded by a Request for Information (RFI) or draft RFP, to ensure that the final RFP is informed by the best scientific and industry expertise possible. In furtherance of this goal, HHS has published the *HHS PHEMCE Implementation Plan*, which provides guidance concerning the priorities and requirements for future medical countermeasures.

See comment 3.

With respect to the rPA procurement process, the concept of use and critical requirements for anthrax vaccine have not changed, and are clearly articulated in many public documents from HHS, including the *HHS PHEMCE Implementation Plan*. Anthrax vaccine is to be used in combination with antibiotics as post-exposure prophylaxis. However, more specific requirements for the formulation, dosage, and studies necessary to achieve regulatory approval must be made on the basis of each individual product, through the process of direct communication with FDA that is undertaken by every medical product developer. Given that the Project BioShield legislation provides for a time period of eight years during which products must achieve licensure and that the process of product development can be fraught with unexpected complications and delays, it is nearly impossible to know the exact regulatory specifications for a product at the beginning of this process. Nonetheless, HHS has encouraged,

See comment 4.

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and now requires potential bidders to demonstrate early engagement with FDA and understanding of regulatory requirements based upon those discussions.

Recommendation: To ensure public confidence and comply with FDA's current rules, we recommend that the Secretary of HHS direct ASPR to destroy the expired BioThrax vaccine in the stockpile.

See comment 5.

Response: HHS agrees with GAO that expired vaccines cannot be used. The Department has never planned to use any expired products in an emergency, and we strongly disagree with the claim that the Department "planned to use three lots of expired BioThrax vaccine in the stockpile in the event of an emergency". HHS fully understands the regulations surrounding the use of expired medical products, and has no such plans to administer expired doses of BioThrax. The expired vaccine in question is being quarantined until a decision on disposition is made. HHS continues to develop comprehensive life cycle plans for all medical countermeasures in the SNS.

Recommendation: To minimize waste of the BioThrax vaccine in the stockpile, we recommend that the Secretaries of HHS and DOD develop a single integrated inventory system for the licensed anthrax vaccine with rotation based on a first-in, first-out principle.

See comment 6.

Response: HHS agrees with the importance of an inventory management strategy to minimize attrition of BioThrax vaccine doses in the SNS resulting from expiration of the product. The Department is engaged in a broad effort to develop comprehensive life cycle management plans for all medical countermeasures in the SNS. To this end, HHS and the Department of Defense (DOD) are currently exploring a number of inventory management strategies that would include potential exchange of BioThrax between the HHS and DOD stockpiles. However, there are important liability issues and funding differences between DOD and HHS contracts that currently preclude this exchange. These issues are currently the focus of work by both Departments. The efficient transfer of short-dated vaccine from HHS to DOD could save the US Government up to \$25 million per year. The report inaccurately claims that the amount of money lost is "over \$100 million per year".

See comment 7.

The very nature of these products dictates that they have a fixed dating period. If not used during an event, all medical countermeasures will eventually expire and will need to be properly discarded. HHS continues to work diligently as an effective steward of its investments, and seeks to limit unnecessary spending as much as possible, but it is inaccurate to suggest that all expired product represents wasted or lost investments.

See comment 8.

HHS Response to GAO Findings

In addition to our response to specific GAO recommendations above, we would like to correct several particular misconceptions and inaccuracies contained in the draft report.

GENERAL COMMENTS FROM THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT: "PROJECT BIOSHIELD: ACTIONS NEEDED TO AVOID REPEATED PAST PROBLEMS WITH PROCURING NEW ANTHRAX VACCINE AND MANAGING STOCKPILE OF LICENSED VACCINE" (GAO-08-88)

See comment 9.

First, HHS strongly disagrees with the assertion that VaxGen's candidate rPA vaccine was not sufficiently advanced to warrant a Project BioShield contract award. The Project BioShield Act of 2004 is intended to allow medical countermeasure contracts to be awarded that support both product development and acquisition activities. The VaxGen contract award was wholly consistent with the terms of the legislation, and this was validated through findings of an investigation by the HHS Office of the Inspector General. However, we recognize that commitments to acquiring products at early stages of development adds risk and uncertainty to the program. This risk was deemed to be appropriate given the urgency of the requirement. Additionally, HHS was continuing to support another rPA vaccine candidate through research and development contracts at NIAID. Fortunately, through modifications to the Project BioShield Act instituted in the Pandemic and All-Hazards Preparedness Act of 2006, BARDA now has the ability to include milestone payments in these contracts that will provide financial support for manufacturers as important product development activities are completed. BARDA is working to incorporate these payments into its future Project BioShield procurements, but this mechanism was not available to be used for the VaxGen rPA contract.

See comment 10.

The report also claims that the evaluation of VaxGen's rPA vaccine candidate was a subjective one. HHS maintains stringent processes to evaluate objective criteria and make the most appropriate contract awards. The determination of capabilities of the four different manufacturers who responded to the Request for Proposals (RFP) was based on a rigorous technical evaluation process. In addition, a Request for Information (RFI) for rPA vaccines was released in 2003, and those results were used to inform the requirements of the RFP in 2004. The responses to the RFI indicated that the anticipated timeline for rPA development and acquisition was achievable. The respondent to any solicitation is required to provide a full and honest assessment of their technical and financial capabilities. At the time of contract award, VaxGen provided the government with comprehensive project plans and timelines that projected a successful vaccine development and manufacturing process.

See comment 11.

It is also important to note that, contrary to that stated in the draft report, the VaxGen Project BioShield award did not pre-empt other support for product development that was being provided to VaxGen through its NIAID contract. Simultaneously, HHS continued to support development programs by other anthrax vaccine manufacturers with grants administered by NIAID.

See comment 12.

Next, it is inaccurate to state that "the purchase of BioThrax for the stockpile as a stopgap measure raised the bar for the VaxGen vaccine." The minimum amount of data and information needed to consider VaxGen's rPA vaccine potentially "usable" under either a "Contingency Use" IND or, subsequently, an EUA, did not change because there was a stockpile of BioThrax. Although the necessary data and information to support the use of the rPA vaccine in an emergency did not change, the likelihood of using the rPA in an emergency was reduced given ASPR's decision to first use the licensed BioThrax. Furthermore, using this logic, HHS could never buy existing medical countermeasures while next-generation products were in

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development. Maintaining a robust product pipeline requires concurrent efforts to improve near-term preparedness by acquiring available products while also supporting the development of improved next-generation products. More specifically, we do not see any particular characteristics of the BioThrax products that would adversely impact the expectations for an rPA vaccine.

See comment 13.

The draft report claims that HHS changed the requirements for the VaxGen rPA vaccine. However, the requirement for the acquisition of 25 million courses of anthrax vaccine was established following medical consequence modeling and input from public health experts. Since the Project BioShield legislation provides for up to eight years of development prior to achieving licensure, it is very difficult to predict when a contract is awarded exactly what the required studies and specific characteristics of each product will be. To resolve this problem, HHS is very clear that any companies interested in responding to a solicitation will be in frequent contact with the Food and Drug Administration (FDA) to keep the FDA up-to-date with their progress and to maintain a clear understanding of the studies that will be required for their product to achieve licensure. It is now a requirement of Project BioShield contracts that companies communicate with FDA early and often to ensure the success of each acquisition program.

In the field of medical product development, it is the responsibility of all manufacturers to be responsive to and communicative with FDA, and to incorporate regulatory feedback into their product development plans. Over the course of the VaxGen rPA contract, HHS was similarly responsive to the evolution of the candidate product. VaxGen experienced a failure in its Phase 2 clinical trial in 2004 that produced results that could not be interpreted. As a result of this and other product development delays, HHS instituted a contract modification that extended VaxGen's delivery schedule for an additional three years. It is not clear that VaxGen made equivalent efforts to remain aware of FDA guidance. There are no regulated or mandated timelines for development of a new product. The interactions of FDA's Center for Biologics Evaluation and Research (CBER) with VaxGen were typical of those with any sponsor during the IND stages of development of any product, especially during early stages, prior to VaxGen getting the BioShield contract. Post-contract award, November 2004, VaxGen, CBER and other HHS agencies had frequent meetings and extensive technical discussions to aid in development of this important product. VaxGen did not request information regarding the specific data and information needed by CBER to potentially allow use under a "Contingency Use" IND, as specified in the RFP, until December 2005, so they could more appropriately account for development costs, predict manufacturing and delivery timelines and have a clear understanding of the criteria which would make their product considered "usable (term used by HHS)" and thus appropriate for acquisition and stockpiling. CBER provided this information in January 2006.

See comment 14.

One of the central claims of this report is that product requirements were not known to VaxGen at the outset of the procurement contract. As with any medical product development program, it is the responsibility of the manufacturer to engage effectively with FDA. It is also unclear what GAO is trying to convey by the following two sentences: "This confused FDA officials and

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caused them to balk at replying to VaxGen until it could meet with ASPR and CDC to clarify this issue. As a result, VaxGen was placed in a position where it had to respond to different requirements." The meeting referenced occurred in December 2005. It is also CBER's impression that VaxGen wanted the next Phase II trial to support use of the vaccine in a "contingency use" protocol under IND. However, the purpose of Phase II trials, in order to position the product for the pivotal Phase III trial in support of licensure, is to collect additional safety, and when possible efficacy data, as well as to determine the dose, route and schedule for administration. Since VaxGen had not previously requested information regarding the specific data and information needed by CBER to potentially allow use under a "Contingency Use" IND, as specified in the RFP, it appears that VaxGen may not have clearly understood that the data needed to support this use should be gathered using final drug product administered by the dose, route and schedule determined to be most immunogenic and safe in the Phase II trials. Since CBER was asked the question regarding use during an emergency during this meeting, CBER needed time to respond and provided the information in January 2006.

See comment 15.

The report also makes inaccurate statements regarding Emergency Use Authorization guidance from FDA. The draft guidance "Emergency Use Authorization of Medical Products" which was issued in June 2005, and published as final guidance in July 2007, was drafted directly from and intended to provide information regarding the Agency's current thinking concerning one way to meet the statutory requirements defined in Section 564 of the Federal Food, Drug, and Cosmetic Act, as it was amended by the Project BioShield Act of 2004. Section 564 is self-executing and does not require implementing regulations or guidance. As stated in the guidance "The document is intended to inform industry, government agencies, and FDA staff of the Agency's general recommendations and procedures for issuance of EUAs." It goes on to clarify that the amount of data and information needed will be determined on a case-by-case basis and that this document summarizes the types of data that FDA would recommend submitting. The EUA guidance also discusses the conditions that must be met to authorize use of a product under an EUA, as well as other conditions of authorization that may be imposed. In discussing these issues, the guidance clarifies that the exact type and amount of data may vary depending on the nature of the declared emergency and the product under consideration.

See comment 16.

HHS is dedicated to building a comprehensive stockpile of medical countermeasures that would be available in the case of a public health emergency. The very nature of these products dictates that they have a fixed dating period. If not used during an event, all medical countermeasures will eventually expire and will need to be properly discarded. However, all expired product does not represent wasted or lost investments, and it is disingenuous to suggest as much. HHS continues to serve as a responsible and effective steward of its investments as it works to achieve our mission to prevent, prepare for, and respond to the adverse health effects of public health emergencies.

The following are GAO's comments on the Department of Health and Human Services' letter dated October 4, 2007.

GAO Comments

1. Our draft report acknowledged the Office of the Assistant Secretary for Preparedness and Response's (ASPR) sense of urgency to develop an rPA anthrax vaccine following the 2001 attack. However, our report also stated that by November 2004, ASPR had had sufficient time and opportunity to thoroughly evaluate contractual risks and issues without being overly influenced by the sense of urgency. By November 2004, it was clear that significant manufacturing issues needed to be overcome and that a 2-year time scale to produce 25 million doses was accordingly unrealistic.
2. We agree that ASPR has taken several steps to develop and communicate its strategy and plans to acquire medical countermeasures to potential manufacturers. In addition, HHS has conducted several workshops to stimulate discussion with potential manufacturers. However, these steps were taken just before or after VaxGen's procurement contract was terminated. While we reviewed the HHS Public Health Emergency Medical Countermeasures Enterprise Strategy and Implementation Plan for Chemical, Biological, Radiological, and Nuclear Threats, we did not find these documents to be relevant to our evaluation of ASPR's performance with regard to VaxGen's procurement contract.
3. ASPR's definition of the concept of use refers, as expressed in its comments, to the anthrax vaccine in combination with antibiotics as post-exposure prophylaxis. However, our report discusses the potential use of the unlicensed rPa vaccine in the stockpile when the licensed anthrax vaccine was already available. We cite the Food and Drug Administration's position that it would give preference to the licensed vaccine over the unlicensed vaccine.

With regard to critical requirements, HHS acknowledged that critical requirements would change for different products. Therefore, HHS should have known the consequences of changing requirements for a fixed-price contract with a 2-year time limit.

4. We agree with HHS that it is not always possible to know the exact regulatory specifications for a product at the beginning of the procurement process. However, ASPR failed to recognize that changing requirements under a fixed-price procurement contract could significantly affect the finances and the 2-year delivery time line it established.

5. The acting director of ASPR told us that the principal deputy of ASPR had decided not to destroy the expired lots in case they were needed for use in an emergency. However, using the expired vaccine would violate the FDA rule. In response to the draft of this report, HHS now states that it is quarantining the expired lots until a decision can be made regarding disposal. We do not understand HHS's rationale for continuing to hold the vaccine in quarantine for nearly a year and the justification for the administrative expenses involved.

6. Although HHS and the Department of Defense (DOD) use different authorities to address BioThrax liability and funding issues, both authorities could apply to vaccines purchased by either DOD or HHS; consequently, indemnity does not appear to be an insurmountable obstacle for future procurements. As indicated in our report, DOD and HHS should continue to explore the legal implications of different indemnity authorities and present a legislative proposal to Congress if they determine that a statutory change is required to establish a joint inventory.

7. Since, as ASPR acknowledges, it does not have a strategy to minimize waste, we calculated the potential \$100 million annual wastage based on expiration dates of the current vaccine inventory. ASPR stated that the annual saving would only be up to \$25 million per year but did not provide any basis for this estimate. However, according to DOD, in contract year 2006, it purchased BioThrax valued at about \$55 million, a savings of more than double ASPR's estimate.

A strategy to minimize waste in the stockpile should include not only integration of inventory based on a first-in, first-out principle but also reexamination of requirements derived from consequence modeling with regard to the size of the inventory. Such a strategy would result in savings closer to \$100 million.

8. We did not mean to suggest that all expired products represent waste or lost investment. We clarified our definition of waste in the report. When there is a large-volume user for the stockpile product, not having an effective strategy to ensure that stockpile product would be used constitutes waste. However, since DOD is a large user of BioThrax, unnecessary waste will result from ASPR not making an effort to ensure that to the extent possible, DOD uses the vaccine in the stockpile.

9. We did not question the legality of the contract award to VaxGen but rather the rationale underlying the contract's requirement for 25 million doses in 2 years.

10. ASPR officials told us that they did not have tools to assess product maturity at the time of the contract award, and that they were guided by a sense of urgency. On the basis of these statements, we concluded that their assessment was subjective.

11. We disagree that the VaxGen Project BioShield award did not preempt other support for product development that was being provided to VaxGen through its National Institute of Allergy and Infectious Diseases contract. According to our analysis of the contract document and discussions with NIAID officials, funding under the development contract largely ceased once the procurement contract was awarded.

12. We clarified the report text to attribute to VaxGen officials the statement that the purchase of BioThrax for the stockpile as a stopgap measure raised the bar for the VaxGen vaccine.

13. Our draft report did not say that HHS changed the requirements for the VaxGen rPA vaccine. However, we have clarified the text to state that purchase of BioThrax for the stockpile raised the requirement for the use of rPA anthrax vaccine.

14 We clarified the report text to indicate that neither FDA nor VaxGen understood the concept of use prior to January 2006.

15. We clarified the report text to indicate that ASPR officials told us that FDA would define "sufficient data" and the testing hurdles a product needed to overcome to be considered a "usable product."

16. See our response to comment 8.

Appendix III: Comments from the Department of Defense

Note: GAO comments supplementing those in the report text appear at the end of this appendix.



NUCLEAR AND CHEMICAL
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PROGRAMS

ASSISTANT TO THE SECRETARY OF DEFENSE
3050 DEFENSE PENTAGON
WASHINGTON, DC 20301-3050

OCT 3 2007

Mr. Keith Rhodes
Director/Chief Technologist, Center for Technology and Engineering
U.S. Government Accountability Office
441 G Street, N.W.
Washington, DC 20548

Dear Mr. Rhodes:

This is the Department of Defense (DoD) response to the GAO draft report 08-88, "PROJECT BIOSHIELD: Actions Needed to Avoid Repeated Past Problems with Procuring New Anthrax Vaccine and Managing Stockpile of Licensed Vaccine," dated September 20, 2007, (GAO Code 460590).

The Department partially concurs with the GAO recommendation. Our position on this recommendation is explained in the enclosure.

My point of contact for this matter is Dr. Robert Borowski, who can be reached at (703) 416-4682 or at Robert.Borowski@anser.org.

A handwritten signature in black ink, appearing to read "D. Jarrett".

David G. Jarrett, COL, MC, USA
Deputy and Medical Director
OSA(CBD&CDP)

Enclosure

GAO Draft Report Dated SEPTEMBER 20, 2007
GAO-08-88 (GAO CODE 460590)

**“PROJECT BIOSHIELD: ACTIONS NEEDED TO AVOID
REPEATED PAST PROBLEMS WITH PROCURING NEW
ANTHRAX VACCINE AND MANAGING STOCKPILE OF
LICENSED VACCINE”**

**DEPARTMENT OF DEFENSE COMMENTS
TO THE GAO RECOMMENDATION**

RECOMMENDATION: The GAO recommends that in order to minimize waste of the BioThrax® vaccine in the stockpile, HHS and DoD develop a single integrated inventory system for the licensed anthrax vaccine with rotation based on a first-in, first-out principle. (p. 25/GAO Draft Report)

DOD RESPONSE: The DoD partially concurs with the GAO recommendation.

- While the recommendations in the draft GAO report have merit, it should be underscored that there are operational, logistical, and legal challenges to implementation that may require potential legislative action to overcome.
 - Logistical challenge: The HHS stockpile is far larger than the amount DoD consumes on an annual basis and hence, if a joint stockpile is created, DoD will only be able to use a fraction of the expiring doses. It should also be noted that DoD can not distribute expiring stocks at the last minute and would require some level of lead time to distribute and dispense the soon-to-expire stocks. The DoD will also work with HHS to specifically analyze the potential cost avoidance with the proposal.
 - Legal challenge: DoD and HHS have differing methods of liability protection. DHHS plans to use the Public Readiness and Emergency Preparedness (PREP) Act provisions to limit the liability of manufacturers of medical countermeasures, versus DoD's use of P.L. 85-804 indemnification. DoD has identified this area of differing methods of liability protection as one that will require further discussion between the agencies' legal staffs. This area may require legislative action to ensure that vaccine purchased by DHHS can be used in the DoD immunization program.
- The DoD and HHS have been and will continue to coordinate the actions of this effort in the best interests of the United States Government.

See comment 1.

The following is GAO's comment on the Department of Defense's letter dated October 3, 2007.

GAO Comment

1. Although HHS and DOD use different authorities to address BioThrax liability, both authorities could apply to vaccines purchased by either DOD or HHS; consequently, indemnity does not appear to be an insurmountable obstacle for future procurements. As indicated in our report, DOD and HHS should continue to explore the legal implications of different indemnity authorities and present a legislative proposal to Congress if they determine that a statutory change is required to establish a joint inventory.

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