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ANTHRAX

Federal Agencies Have Taken Some Steps to Validate Sampling Methods and to Develop a Next-Generation Anthrax Vaccine

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

May 9, 2006

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Highlights

Highlights of GAO-06-756T, a testimony before the Chairman, Subcommittee on National Security, Emerging Threats, and International Relations, House Committee on Government Reform, House of Representatives

Why GAO Did This Study

GAO has done many studies over the past 7 years on anthrax vaccine safety and anthrax detection methods. GAO has reported the lack of validated methods for detecting anthrax contamination and has recommended a coordinated approach to improving the overall process for detecting anthrax that included a probability-based sampling strategy.

GAO also reported that the vaccine has not been adequately tested on humans; no studies have been done to determine the optimum number of doses; the long-term safety has not been studied and data on short-term reactions are limited; however, women report higher rates of reactions than do men. Given these problems, GAO recommended the development, of a better, alternative vaccine.

What GAO Recommends

The Secretary of Homeland Security needs to develop a formal strategic plan, including a roadmap, outlining how individual agency efforts would lead to the validation of the overall sampling process.

www.gao.gov/cgi-bin/getrpt?GAO-06-756T.

To view the full product, click on the link above. For more information, contact Keith Rhodes at (202) 512-6412 or rhodesk@gao.gov.

What GAO Found

The threat of bioterrorism has long been recognized in the United States and abroad. The Department of Defense (DOD) considers inhalation anthrax to be the greatest biological warfare threat to U.S. military forces. The U.S. Army Medical Research Institute of Infectious Diseases has been conducting basic and applied research on biological threats since 1969, in order to develop medical countermeasures—prophylactics, vaccines, medical diagnostics—to protect warfighters.

The anthrax incidents in 2001 highlighted major gaps in civilian preparedness to detect and respond to anthrax attacks, leading the federal government to focus on developing new drugs, vaccines, and therapeutics to protect U.S. citizens. As a result, the Department of Health and Human Services (HHS) now has major responsibility to ensure that appropriate medical countermeasures are available for civilians. And the Department of Homeland Security (DHS) assumes major responsibility for coordinating federal responses to national incidents of chemical, biological, radiological, and nuclear release.

Despite the many recommendations GAO has made over the past few years regarding problems related to the anthrax vaccine's safety and effectiveness and the reliability of anthrax detection, deficiencies remain. While agencies have taken steps in the right direction, the government still lacks a strategic plan outlining how individual agency efforts would lead to the validation of the overall sampling process, including methods, and the development of a probability-based sampling strategy that accounts for the complexity of indoor environments.

In November 2004, HHS awarded a contract for $877.5 million to procure 75 million doses of a new anthrax vaccine–the first contract awarded under Project Bioshield for medical countermeasures procurement. The terms of the award state that the urgency of the current threat requires an accelerated pace of vaccine development, testing, approval, and procurement. While developing vaccine is known to be difficult and highly likely to encounter testing and production issues in the best of circumstances, the contract's milestones leave little room for slippage from established delivery dates.

The biotechnology sector is watching to see if government and industry can make this partnership work. Understanding the unique issues in this early phase of the biodefense strategy is important. Problems with this initial Project Bioshield contract could affect the biotechnology industry's response to future government overtures to develop and procure medical countermeasures against the many other biothreat agents still to be addressed.

Mr. Chairman and Members of the Subcommittee:

We are pleased to be here today to discuss the status of our recommendations on two bodies of work that we did at your request: licensed anthrax vaccine and anthrax detection methods.[1] As you know, the threat of bioterrorism had been recognized for a considerable time in the United States, as well as internationally. The Department of Defense (DOD) has considered inhalation anthrax in an aerosolized form to be the greatest biological warfare threat to U.S. military forces for quite some time. The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) has been conducting basic and applied research on biological threats since its inception in 1969, in order to develop medical countermeasures—for example, prophylactics, vaccines, and medical diagnostics—to protect the warfighter.

The anthrax incidents in September and October 2001 highlighted major gaps in our civilian preparedness to detect and respond. It also led the federal government to focus attention on the importance of developing new drugs, vaccines, and therapeutics to protect U.S. citizens.

Consequently, the Department of Health and Human Services (HHS) has the major responsibility to ensure that appropriate medical countermeasures are available for the civilian population, while the Department of Homeland Security (DHS) has assumed the major

[1]For our work on anthrax detection methods, see GAO, *Anthrax Detection: Agencies Need to Validate Sampling Activities in Order to Increase Confidence in Negative Results*, GAO-05-251 (Washington, D.C.: Mar. 31, 2005), and GAO, *U.S. Postal Service: Issues Associated with Anthrax Testing at the Wallingford Facility*, GAO-03-787T (Washington D.C.: May 19, 2003). For our work on anthrax vaccine, see *Gulf War Illnesses: Questions about the Presence of Squalene Antibodies in Veterans Can Be Resolved*, GAO/NSIAD-99-5 (Washington, D.C.: Mar. 29, 1999); *Medical Readiness: Safety and Efficacy of the Anthrax Vaccine*, GAO/T-NSIAD-99-148 (Washington, D.C.: Apr. 29, 1999); *Contract Management: Observations on DOD's Financial Relationship with the Anthrax Vaccine Manufacturer*, GAO/T-NSIAD-99-214 (Washington, D.C.: June 30, 1999); *Medical Readiness: Issues Concerning the Anthrax Vaccine*, GAO/T-NSIAD-99-226 (Washington, D.C.: July 21, 1999); *Anthrax Vaccine: Safety and Efficacy Issues*, GAO/T-NSIAD-00-48 (Washington, D.C.: Oct. 12, 1999); *Medical Readiness: DOD Faces Challenges in Implementing Its Anthrax Vaccine Immunization Program*, GAO/NSIAD-00-36 (Washington, D.C.: Oct. 22, 1999); *Medical Readiness: DOD Continues to Face Challenges in Implementing Its Anthrax Vaccine Immunization Program*, GAO/T-NSIAD-00-157 (Washington, D.C.: Apr. 13, 2000); *State Department: Serious Problems in the Anthrax Vaccine Immunization Program*, GAO-01-21, (Washington, D.C.: Dec. 13, 2000); *Anthrax Vaccine: Changes to the Manufacturing Process*, GAO-02-181T (Washington, D.C.: Oct. 23, 2001); *Anthrax Vaccine: GAO's Survey of Guard and Reserve Pilots and Aircrew*, GAO-02-445 (Washington, D.C.: Sept. 20, 2002).

responsibility for coordinating federal responses to national incidents of chemical, biological, radiological, and nuclear material release.

The President's 2006 federal budget includes $1.8 billion allocated to the National Institutes of Health (NIH) to fund biodefense research and development activities, which includes the development of new and improved medical countermeasures. Additionally, under Project Bioshield, a discretionary reserve fund of $5.6 billion has been allocated to procure medical countermeasures for the Strategic National Stockpile (SNS) through fiscal year 2013.[2]

To respond to your request, we interviewed officials from federal agencies—HHS, including the Food and Drug Administration (FDA); the Centers for Disease Control and Prevention (CDC); the National Institute of Allergy and Infectious Disease (NIAID); DHS, and DOD. In addition, we reviewed documents provided by these agencies as well as those provided by the United States Postal Services (USPS). We visited and interviewed the officials of the company that is developing the new anthrax vaccine. Finally, we reviewed scientific literature on this issue. We conducted our review from March 2006 to April 2006 in accordance with generally accepted government auditing standards.

In today's testimony, I will specifically report on (1) the problems we identified with the anthrax detection methods and the licensed anthrax vaccine, (2) recommendations we made, (3) the extent to which federal agencies have taken corrective actions, and (4) what remains to be done.

Results in Brief

With regard to anthrax detection methods, federal agencies responsible for responding to the 2001 anthrax incidents adopted a targeted sampling strategy that they based on their best judgment at the time. When the level of contamination is extremely high and dispersed in a facility, the method of sampling (for example, using wipes versus swabs) may not be critical, if the purpose is to find some contaminant. However, at lower levels, away of interpreting negative results is needed, and this requirement emphasizes the importance of the validation of the methods and the need for statistically based sampling strategies.

[2]The SNS is a national repository of medical countermeasures, such as antibiotics and vaccines. 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.

Therefore, it is necessary to invest in empirical studies so as to develop a probability-based sampling strategy that will account for the complex geometry and surface types of many facilities. Using a probability-based sampling strategy, together with validated methods for detecting contamination, would provide a known level of confidence with which to interpret any negative results and would thus enable agencies to be more definitive in determining necessary actions.

The lack of validated methods for assessing contamination in postal facilities in 2001 impeded the agencies in responding to the incidents. The significance of the lack of validated methods was exemplified in the case of one postal facility where negative preliminary results were obtained by field-based methods of analysis, with limitations that appear to have been not well understood by some agencies.

Given the lack of validated methods for detecting anthrax contamination in facilities, we recommended that the Secretary of Homeland Security develop a coordinated approach to (1) improve the overall process for detecting anthrax and (2) increase confidence in negative test results generated by that process. This approach would include working with agencies to ensure that appropriate validation studies of the overall process of sampling activities, including the methods, are conducted. Specifically, we recommended that the Secretary

1. take a lead role in promoting and coordinating the activities of the various agencies that have the technical expertise related to environmental testing;

2. ensure that a definition of validation is developed and agreed on;

3. guarantee that the overall process of sampling activities, including methods, is validated so that performance characteristics, including limitations, are clearly understood and results can be correctly interpreted;

4. see that appropriate investments are made in empirical studies to develop probability-based sampling strategies that take into account the complexities of indoor environments;

5. ensure that appropriate, prioritized investments are made for all biothreat agents; and

6. ensure that agency policies, procedures, and guidelines reflect the results of such efforts.

When we issued our report, CDC, DHS, and USPS agreed with our conclusion—that methods for detecting anthrax contamination in facilities were not validated—and with the thrust of our recommendations—calling for a coordinated, systematic effort to validate the methods to be used for such testing, but they (1) disagreed with or expressed concern about our conclusions or the recommendation dealing with targeted versus probability sampling, (2) emphasized that validated testing methods for anthrax were not available in 2001 and that federal and state organizations did the best they could under the circumstances, and (3) identified factors or issues that need to be considered in validating testing methods.

In addition, uncertainty over which agency would take the lead role in improving the overall process for detecting anthrax, and how studies were to be funded, continued after the release of our report. DHS stated that while it has overall responsibility for coordinating the federal response during future biological attacks, the Environmental Protection Agency (EPA) had the "primary responsibility for establishing the strategies, guidelines, and plans for the recovery from a biological attack" while HHS had the lead role for any related public health response and guidelines. DHS also stated that it coordinated regularly with EPA's National Homeland Research Center to exchange information on research needs and to discuss priorities and gaps for a wide range of security-related research areas. DHS stated that it would coordinate with EPA to ensure that appropriate investments were made to explore improved sampling. Consequently, it was unclear how DHS could ensure that appropriate prioritized investments were made for all biothreat agents, with respect to agencies other than EPA, and how such priorities and gaps would be addressed.

Although in the past there had been confusion as to which federal agency would take the lead, as well as the responsibility for ensuring that our recommendations are addressed, DHS is now accepting responsibility. On May 3, 2006, DHS told us that DHS recognizes that it is the principal agency responsible for coordinating the federal response and would be responsible for ensuring that sampling methods, including the process, are validated. DHS also would work toward developing a probability-based sampling strategy.

While actions taken by DHS are steps in the right direction, DHS needs to develop a formal strategic plan that includes a "roadmap" outlining how individual agency efforts would lead to (1) validation of the overall process of sampling activities, including the methods, and (2) development

of a probability-based sampling strategy that takes into account the complexity of indoor environments.

With regard to the licensed anthrax vaccine, we identified a number of problems, including, among others, greater understanding of

1. the need for a six-shot regimen and annual booster shots;

2. the long-term and short-term safety of the vaccine, including gender differences; and

3. the vaccine's efficacy.

In addition, we provided information on the disadvantages of the licensed anthrax vaccine and the status of federal efforts to develop an improved vaccine. Given these problems, and taking into account promising early DOD research into an alternative, recombinant protective antigen (rPA) vaccine for anthrax, we recommended the development of a second-generation vaccine, based on this technology.

In September 2002 and September 2003, NIAID awarded contracts to develop a new rPA vaccine against inhalation anthrax. These contracts to develop and test candidate rPA vaccines included the requirement to evaluate safety, efficacy, and a potential provider's manufacturing capability to achieve eventual licensing from FDA.

The objectives in these two NIAID contracts addressed some of the problems we identified with the licensed vaccine, including requiring a recombinant vaccine to address issues of purity, potency, and manufacturing consistency; the need for fewer doses for the civilian population; and the capability for postexposure use. However, studies on gender differences and long-term safety were not explicitly required.

In November 2004, in the first contract under Project Bioshield, HHS awarded a contract for $877.5 million for the manufacture and delivery of 75 million doses of rPA anthrax vaccine for SNS. In the production contract's RFP, HHS stated that the urgent nature of the current threat required an accelerated pace of development, testing, approval, and procurement of the vaccine. While developing vaccine is known to be difficult and highly likely to encounter testing and production issues, even in the best of circumstances, early development work to ensure safety of the vaccine and a solid large-scale manufacturing capability had not been completed before awarding the full procurement contract. Additionally,

the contract milestones leave little to no provision for slippage and, being a fixed-price contract, if there is an unexpected slip in schedule, the financial burden will be fully on the contractor. While the government should not pay out money to a contractor unless and until it has met the terms of its contract, contractors that do not have the resources to assume such risk will not be able to meet the contract requirements, thus limiting the pool of companies that are capable of meeting the nation's needs.

While the government should be a tough negotiator when contracting for major procurements, it is important to understand the unique issues at stake in this early phase of implementing the U.S. biodefense strategy. Failure of this initial Project Bioshield contract 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.

Background

The History and Nature of Anthrax and the Anthrax Vaccine

Anthrax is an acute infectious disease caused by the spore-forming bacterium Bacillus anthracis. It can infect humans but occurs most commonly in warm-blooded animals (herbivores) in the agricultural regions of the countries that have less standardized and less effective public health programs. Human anthrax occurs only rarely in the United States from natural causes. However, the anthrax attacks in October 2001 through contaminated mail resulted in the death of five persons.

Human infection normally results from an occupational exposure to infected animals or animal products. For example, workers may be exposed to dead animals or to products such as wool, hides, leather, or hair products (especially goat hair). Since there have been no reports, even now, of the disease spreading from person to person, anthrax is most likely not spread in humans directly.

Anthrax infection can occur in three forms: (1) cutaneous, usually through a cut or an abrasion; (2) gastrointestinal, by ingesting contaminated meat; and (3) inhalation, by breathing anthrax spores into the lungs. Symptoms depend on how the disease is contracted but usually appear within 7 days. The disease can be treated with antibiotics: tetracycline and doxycycline are preferred, but penicillin, erythromycin, chloramphenicol, or ciprofloxacin can also be used. To be effective, treatment should be started early.

The original anthrax vaccine in the United States was developed by George Wright and others in the 1950s and was first produced on a large scale by the pharmaceutical manufacturer Merck Sharp & Dohme.[3] A 1962 clinical study that evaluated the safety and effectiveness of the Merck vaccine in mill workers formed the basis for the subsequent licensing of a modified vaccine in 1970.[4] The Division of Biologics of the National Institutes of Health issued the original license for anthrax vaccine to the Michigan Department of Public Health.[5] In 1995, the facility changed its name to Michigan Biologic Products Institute. In 1998, the facility was sold, and its name was changed to BioPort Corporation.

Anthrax Vaccine and the Federal Role

As the lead agency for public health and medical response to manmade or natural disasters, HHS has the responsibility for developing, licensing, procuring, and storing medical countermeasures, which includes vaccines, for SNS. In 2002, HHS established the Office for Public Health Emergency Preparedness (OPHEP) with responsibility for implementing HHS's strategy for protecting civilians from bioterrorism and other public health emergencies. OPHEP coordinates transitions between NIH medical countermeasures development, FDA approval and licensing, and CDC storage and maintenance within SNS.

Within NIH, NIAID is the lead agency for early candidate research and development for medical countermeasures for biodefense. NIAID issues grants and contracts for research on medical countermeasures exploration and early development but has no responsibility in taking research forward into marketable products. Within OPHEP, the Office of Research and Development Coordination (ORDC) has the primary responsibility for contracting with industry for the large-scale manufacturing of licensable products, including vaccines, for delivery into SNS. Distinct from development contracts, ORDC production contracts typically require the submission of a formal request for FDA product licensing, license supplements, long-term maintenance of the stockpiled products, and a long-term manufacturing base to continue replenishing the stockpile as product expires.

[3]Merck Sharp & Dhome is a subsidiary of Merck & Co., Inc.

[4]Anthrax infection has occurred most commonly in settings like wool mills, where workers may be exposed to infected animal products.

[5]Before FDA was established as the licensing authority for vaccines, NIH performed that function.

Through the Center for Biologics Evaluation and Research (CBER), FDA licenses biological products, which include vaccines, and the facilities they are produced in. 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.[6]

The Characteristics and Development of Vaccines

Vaccines have three distinguishing features that contrast with those of chemical drugs. First, either they have no clearly chemically defined composition or simple chemical analysis is insufficient for their effective characterization. Second, they are properly evaluated, qualitatively or quantitatively, usually by measuring their effects in the living organism. Third, quality can be guaranteed not from final tests on random samples but only from a combination of in-process tests, end-product tests, and strict controls of the entire manufacturing process.

The quality of a vaccine is closely linked to its manufacturing process, which must be rigorously controlled to ensure that batches of vaccines produced at different times are reproducible and consistent in quality. In general, quality is achieved by applying the current good manufacturing practice. This process is not static but involves manufacturers and regulators in continuing assessment and upgrades as scientific progress, technical development, and experience help identify deficiencies and make improvements possible. Such principles also apply to the manufacturing facilities and equipment. Accordingly, vaccine production is very highly regulated to ensure that the products are consistent in quality and safe and effective for the purposes for which regulatory approval was granted.

The development of a vaccine is similar to the development of drugs and other immunizing agents. A sponsor who has developed a candidate vaccine and wishes to begin clinical trials with human subjects must submit an investigational new drug (IND) application to FDA.[7] This starts

[6]The regulations embody a set of scientifically sound methods, practices, or principles that are implemented and documented during development and production to ensure the consistent manufacture of safe, pure, and potent products. Such principles apply to the manufacturing process as well as to the facilities products are manufactured in. (21 C.F.R., parts 600 through 680.)

[7]An IND application is a request for authorization from FDA to administer an investigational drug or biological product to humans.

an official oversight process of formal studies, regulated by CBER within FDA, typically composed of three phases of clinical trials involving an increasing number of human subjects.[8] Phase 1 trials are safety and immunogenicity studies performed in 20 to 100 healthy, volunteer subjects. Phase 2 studies, which may involve hundreds of subjects, take an in-depth look at the effectiveness of the drug and may include analysis of dose ranges and dose regimens. Finally, Phase 3 trials typically involve thousands of individuals and provide the documentation of effectiveness and important additional safety data required for licensing. At any stage of the clinical or animal studies, if the data raise significant concerns about either safety or effectiveness, FDA may request additional information or studies or may halt ongoing clinical studies. Clinical trials typically last 6 years.

After successful completion of all three phases, the sponsor submits a biologics license application for FDA's review and approval. The proposed manufacturing facility is inspected during this stage, and production of the vaccine as it is in progress is examined in detail. This FDA review process can take several years, depending on the product.

To ensure continuing safety, FDA oversees the manufacturing process for as long as the manufacturer holds a license for the product. 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.

Anthrax Detection in Postal Facilities and the Federal Role

The federal agencies involved in the response in the postal facilities had differing responsibilities. CDC and state and local health departments primarily provided public health advice and assistance to USPS. CDC has had primary responsibility for national surveillance of specific diseases, including anthrax; it has also conducted epidemiologic investigations to determine, among other things, the source of the disease. The Federal Bureau of Investigation (FBI) has been responsible for criminal

[8]In May 2002, FDA published *Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible* (21 C.F.R. 601, Subpart H, as well as 21 C.F.R. 314, Subpart I for New Drugs). This rule, known as the "Animal Rule," permits the substitution of animal studies for human trials where human efficacy studies are not ethical and field trials are not feasible, provided a scientifically valid animal model for the disease exists. This rule does not obviate the need for safety data, which must still be established.

investigations involving interstate commerce and the mail and crimes committed on federal property. EPA has been the nation's lead agency for responding to a release of hazardous substances into the environment.

Responding to health emergencies, including bioterrorist attacks, is generally a local responsibility, but localities could and did request CDC's assistance in fall 2001. CDC performed the tests needed to confirm cases of anthrax and analyzed the substances in the two contaminated letters recovered in New York City. The Agency for Toxic Substances and Disease Registry and the National Institute for Occupational Safety and Health within CDC helped USPS conduct environmental tests of some of its facilities and advised USPS on its facilities' decontamination.

USAMRIID has conducted basic and applied research in the diagnosis, treatment, and prevention of hazardous infectious diseases for the military. It analyzed some environmental samples from postal facilities. It also performed detailed analyses, for the FBI, of anthrax spores in the letters addressed to Senators Tom Daschle and Patrick Leahy. The Occupational Safety and Health Administration, responsible for employee health and safety issues, provided technical assistance and guidance to USPS on the decontamination of postal facilities.

The response to the incident in the American Media Incorporated building in Florida in September 2001 led to the identification of mail as the potential source of contamination; eventually, it led to the sampling of the postal facilities. The agencies began sampling on October 12, 2001, in Florida and stopped on April 21, 2002, when the Wallingford, Connecticut, facility was sampled for the last time.

On October 8, 2001, the President created the Office of Homeland Security to develop and coordinate a comprehensive national strategy for dealing with domestic terrorist threats or attacks. The office, which had limited involvement in the 2001 response, was superseded by the Homeland Security Act of 2002, which transferred many of its functions to DHS. DHS, which became operational in 2003, was created by combining many previously separate agencies. It is assigned the lead role in coordinating the efforts of federal agencies that respond to acts of terrorism in the United States.

Agency Sampling Detection Methods Were Not Validated

As you know, the agencies that sampled postal facilities in 2001—USPS, CDC, and EPA—did not use validated sample collection and analysis methods to perform their tests. According to these agencies, validated methods were not available at that time. They conducted several interdependent activities, including sample strategy development, followed by sample collection, transportation, and analysis of the samples to detect anthrax. Neither these activities nor the overall process had been validated for anthrax testing.

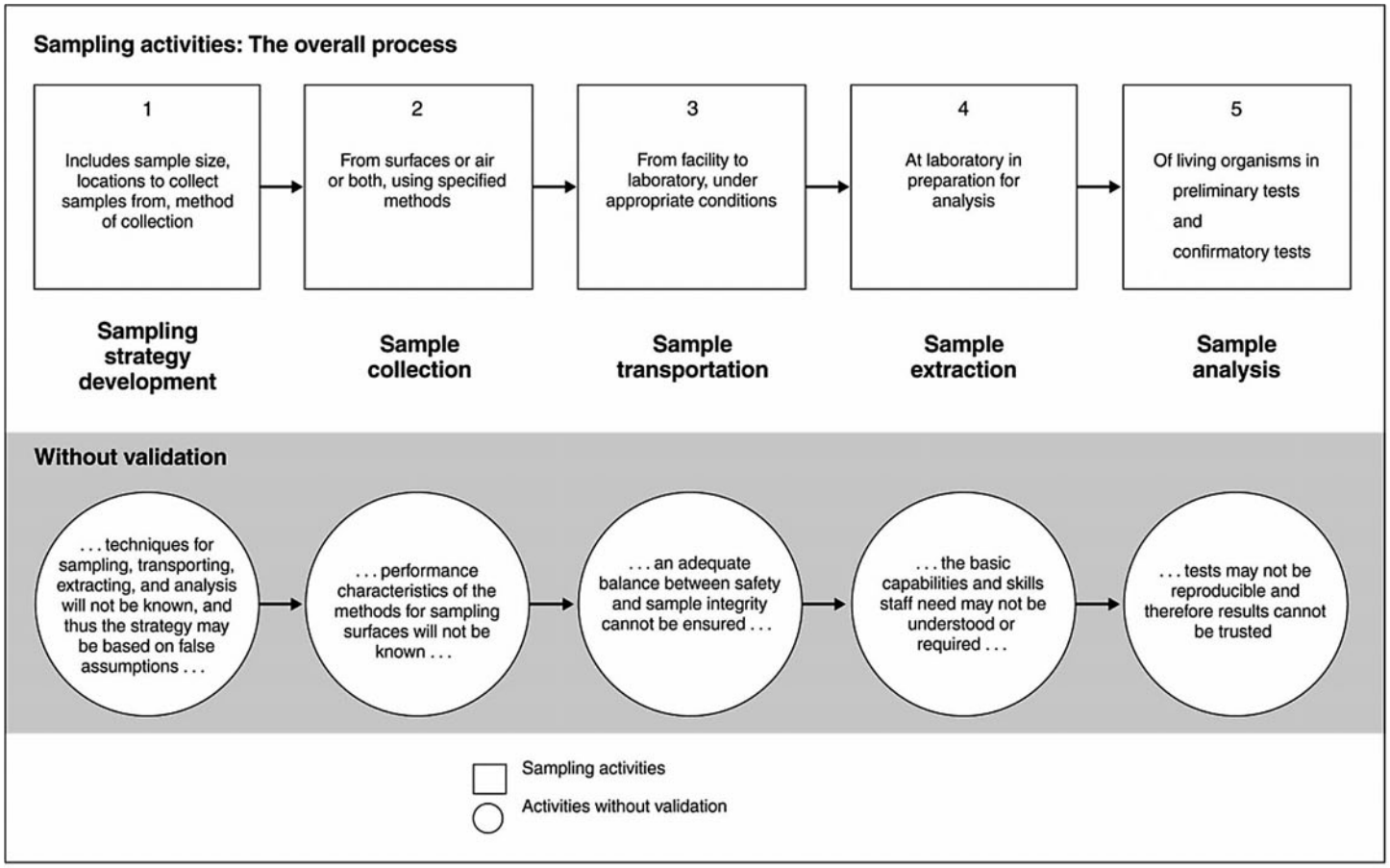
Validation is a formal, empirical process in which an authority determines and certifies the performance characteristics of a given method. Therefore, investments are also needed to validate these methods, as well as the overall anthrax detection process. Validating the overall process is important because operational and health-related decisions are made on the basis of testing results that the process generates.

CDC and USPS officials said that they used targeted sampling; that is, they collected samples from specific areas considered—based on agencies' technical judgments—more likely to be contaminated. Such judgments can be effective in some situations, for example, in determining the source of contamination in a disease outbreak investigation, provided results are positive. However, if the results are negative, the basic question—Is this building contaminated?—cannot be answered with statistical confidence.

When the level of contamination is extremely high and dispersed in a facility, the method of sampling (for example, wipes versus swabs) may not be as critical if the purpose is to find some contaminant. However, at lower levels, a way of interpreting negative results is needed, and this requirement emphasizes the importance of the validation of the methods and the need for statistically based sampling strategies. This emphasizes the need for methods that have been validated and sampling strategies that are likely to find contamination at low levels. Probability-based sampling does allow conclusions at specific levels of confidence about testing results.

Using a probability-based sampling strategy, together with validated methods for detecting contamination, would provide a known level of confidence with which to interpret any negative results. This would allow agencies to be more definitive in determining necessary actions. Figure 1 shows how lack of validation could affect individual activities—which include the sampling strategy—as well as the results generated by the overall process.

Figure 1: Lack of Validation Can Affect Individual Activities and the Overall Process



Source: GAO analysis of CDC, EPA, and USPS data.

The lack of validated methods for assessing contamination in postal facilities impeded the agencies in responding to the incidents. The significance of the lack of validated methods was exemplified in the case of the one postal facility, where negative preliminary results were obtained by field-based methods of analysis, with limitations that appear to have been not well understood by some agencies. Negative results do not necessarily mean a facility is free from contamination. As we reported, results can be negative if (1) samples were not collected from places where anthrax was present, (2) the detection limit of the method was greater than the actual contamination level, (3) not enough samples were recovered from the sample material, (5) analysis of the sample extract did not detect spores, or (6) anthrax was not present in the facility.

Given the lack of validated methods for detecting anthrax contamination in facilities, we recommended that the Secretary of Homeland Security develop a coordinated approach to (1) improve the overall process for detecting anthrax and (2) increase confidence in negative test results generated by that process. This approach would include working with agencies to ensure that appropriate validation studies of the overall process of sampling activities, including the methods, are conducted. Specifically, we recommended that the Secretary

1. take a lead role in promoting and coordinating the activities of the various agencies that have the technical expertise related to environmental testing;

2. ensure that a definition of validation is developed and agreed on;

3. guarantee that the overall process of sampling activities, including methods, is validated so that performance characteristics, including limitations, are clearly understood and results can be correctly interpreted;

4. see that appropriate investments are made in empirical studies to develop probability-based sampling strategies that take into account the complexities of indoor environments.

When we issued our report, CDC, DHS, and USPS agreed with our conclusion—that methods for detecting anthrax contamination in facilities were not validated—and with the thrust of our recommendations—calling for a coordinated, systematic effort to validate the methods to be used for such testing, but they (1) disagreed with or expressed concern about our conclusions or the recommendation dealing with targeted versus probability sampling, (2) emphasized that validated testing methods for anthrax were not available in 2001 and that federal and state organizations did the best they could under the circumstances, and (3) identified factors or issues that need to be considered in validating testing methods.

Also, at that time, uncertainty over which agency would take the lead role in improving the overall process for detecting anthrax, and how studies were to be funded, continued after our report was released. DHS stated that while it has overall responsibility for coordinating the federal response during future biological attacks, EPA had the "primary responsibility for establishing the strategies, guidelines, and plans for the recovery from a biological attack" while HHS had the lead role for any related public health response and guidelines. DHS also stated that it

coordinated regularly with EPA's National Homeland Research Center to exchange information on research needs and to discuss priorities and gaps for a wide range of security-related research areas. DHS stated that it would coordinate with EPA to ensure that appropriate investments were made to explore improved sampling. Consequently, it was unclear how DHS could ensure that appropriate prioritized investments were made for all biothreat agents, with respect to agencies other than EPA, and how such priorities and gaps would be addressed.

DHS Has Taken Some Actions to Implement Our Recommendations on the Validation of Sampling Methods and Strategies

Concerning our recommendation about probability-based sampling strategies, DHS said that it first wanted to develop sampling requirements and then evaluate both targeted and probability-based sampling against those requirements. While CDC and USPS stated that they agreed with the importance of using validated testing methods, they raised various concerns about our discussion of targeted versus probability-based sampling.

DHS formally responded to our recommendations on September 19, 2005, stating that it agreed with them and was taking several actions to address them. These actions included working with agencies through interagency memorandums of understanding, interagency committees, working groups, and collaborations, with various federal agencies such as HHS and EPA. In particular, a memorandum of understanding for coordinating and monitoring biological threat agents among DHS, DOD, HHS, USPS, and the Department of Justice was signed on May 9, 2005. Another involved several agencies—DOD, EPA, HHS, Justice, and the Department of Agriculture, to name a few—and was to establish an integrated consortium of laboratory networks. Also, in fiscal year 2005, DHS said it was to standardize and validate the method by which hazardous materials technicians (for example, first responders) collect, transport, and store suspicious powder samples.

In preparation for this testimony, we asked USPS, CDC, DHS, and EPA for comments regarding actions they have taken to implement our recommendations. EPA did not provide us comments. Comments from USPS, CDC, and DHS are summarized below.

USPS, on April 24, 2006, reported to us that it has been assisting DHS to implement our recommendations. DHS has asked USPS to become part of a subject matter expert team as a result of the real-world experience gained during the 2001 anthrax attacks and the subsequent response,

clean-up, and remediation efforts at a number of mail processing facilities and post offices. (For more on USPS's actions, see app. I.)

CDC, on May 5, 2006, told us it is taking steps we believe are in the right direction. CDC officials told us that CDC has not changed its position on using targeted sampling as its primary strategy for initial response sampling but is exploring probability-based sampling to augment this approach. CDC officials told us that CDC has also developed a program to expand its microbiology objectives; the program's focus areas include plans for evaluating priority biothreat agents, including anthrax, in a variety of media. Further, CDC told us it has completed or has ongoing studies on the recovery of Bacillus anthracis spores from various types of surfaces. (More on CDC's actions is in app. II.)

On May 3, 2006, DHS stated that it

"concurs with the GAO that use of stratified and probabilistic sampling strategies, together with validated methods for detecting contamination, would provide a known level of confidence with which to interpret any negative results and would thus enable agencies to be more definitive in determining necessary actions."

DHS reported to us several actions it had taken toward implementing the recommendations. (For more on DHS's actions, see app. III.)

While we believe that DHS's individual actions are in the right direction, DHS needs to develop a formal strategic plan that includes a "roadmap" outlining how individual agencies' efforts would lead to (1) the validation of the overall process of sampling activities, including methods, and (2) the development of a probability-based sampling strategy that takes into account the complexities of indoor environments. Such a plan would assist DHS in monitoring progress and measuring agency performance toward improving the detection of anthrax and other prioritized threat agents.

The Licensed Anthrax Vaccine Had Several Limitations

Starting in 1999, we identified a number of problems with the licensed anthrax vaccine. These included, among others, (1) the need for a six-shot regimen and annual booster shots; (2) questions about the long-term and short-term safety of the vaccine, including how safety is affected by gender differences; and (3) uncertainty about the vaccine's efficacy. In addition, we provided information on the disadvantages of the licensed vaccine and the status of federal efforts to develop an improved anthrax vaccine.

The dosing regimen, or protocol, for the licensed anthrax vaccine calls for a series of six shots over 18 months. An initial series of three shots is given at 2-week intervals, followed by a series of three shots at 6-month intervals. Annual boosters are required thereafter. The required six-dose schedule and annual boosters complicate the logistics and increase the cost of vaccination. At the time of our earlier reports, no studies had been done on the optimum dosing regimen. Recently, however, CDC has begun conducting studies to determine the feasibility of a three-dose schedule. FDA would have to review and approve any change in product labeling.[9]

The long-term safety of the licensed vaccine has not been studied. Data on the prevalence and duration of short-term reactions to the vaccine are limited but suggest that women experience a higher rate of adverse reactions, both local and systemic, than men do.

Before the vaccine was licensed, a study on the efficacy of the original vaccine concluded that it provided protection to humans against cutaneous anthrax. In the 1980s, DOD began testing the efficacy of the licensed vaccine on animals, focusing on its protection against inhalation anthrax. DOD's studies, while showing some positive results, may not be extrapolated to humans until serologic correlates of immunity in an animal model that can be applied to humans are established.

According to researchers and the Institute of Medicine of the National Academy of Sciences, the licensed anthrax vaccine has several additional disadvantages.[10] The amount of protective antigen in the vaccine varies from lot to lot, because the manufacturing process cannot precisely quantify the antigen.[11] Also, there is some evidence that the current anthrax vaccine may have diminished efficacy against certain virulent strains of anthrax.

The licensed vaccine has been given primarily to military personnel. DOD, however, has a unique set of requirements, as it has a narrow, relatively

[9]CDC is conducting a wide range of anthrax vaccine research activities, including ensuring the vaccine's safety while minimizing the number of doses.

[10]P. S. Brachman and A. Friedlander, "Anthrax," in *Vaccines*, eds. S. A. Plotkin and E. A. Mortimer Jr. (Philadelphia: W. B. Saunders Company, 1994), p. 737, and Institute of Medicine, *Chemical and Biological Terrorism: Research and Development to Improve Civilian Medical Response* (Washington, D.C.: National Academy Press, 1999), p. 135.

[11]Institute of Medicine, *Chemical and Biological Terrorism*, p. 135.

young, healthy, and homogenous, target population. This reduces many problems, although not all, as in the case of reactogenicity by gender. DOD requirements also assume a continuous threat for which they require preexposure immunization. Civilian populations, in contrast, are much more diverse than military populations, and immunization of civilians would likely be difficult to justify, based on the available bio-threat assessments.

HHS Has Taken Steps to Fund the Development of a Second-Generation Anthrax Vaccine

In the late 1980s, DOD research identified a second-generation recombinant protective antigen (rPA) anthrax vaccine, created with a process that is fully defined, quantified, and controlled in terms of protective antigen; that can be developed; and that requires fewer doses.[12] DOD research also showed that an rPA anthrax vaccine could be created with modern techniques to produce highly purified protective antigen. This process not only would remove unwanted bacterial proteins but would also enable precise amounts of the purified protective antigen to be incorporated into the vaccine. A further potential benefit was that compared to the current vaccine, the protective antigen could be produced in a nonspore-forming organism. As a result, according to DOD officials, manufacturers could use their buildings and equipment to produce the anthrax vaccine as well as other vaccines.

In 1995, the USAMRIID developed a pilot lot of a new rPA vaccine against anthrax. It has been tested successfully in experiments using animals but has not been tested on humans. USAMRIID officials stated that this testing would take about 3 years; FDA approval of the manufacturing could take years longer. In 1999, DOD considered further development of this vaccine an unfunded requirement. In response to the perceived threat of bioterrorism, HHS's NIAID formed a working group to develop and test a second-generation anthrax vaccine and, accordingly, funded several active research grants.

[12]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.

In September 2002 and September 2003, NIAID awarded contracts to develop a new rPA vaccine effective against inhalation anthrax.[13] The contracts were for developing and testing candidate vaccines, with a requirement for evaluating safety, efficacy, and a potential provider's capability for manufacturing the vaccine and achieving FDA licensing. The contracts—for $13.6 million in 2002 and $80.3 million in 2003—were awarded to VaxGen Inc., a California-based biopharmaceutical company.[14]

The 2002 RFP called for developing, manufacturing, characterizing, and evaluating pilot lots of an rPA anthrax vaccine developed under conditions necessary to support the product's use as an investigational new drug. The 2003 RFP built on the 2002 work and was to further develop a vaccine candidate suitable for commercial-scale manufacturing that demonstrated safety and immunogenicity in clinical and animal studies.

The stated objectives in these two RFPs addressed some of the problems we identified with the licensed vaccine, including our recommendation. First, they required the development of a recombinant vaccine. As noted, DOD research showed that modern recombinant techniques could produce a vaccine that would contain highly purified and precise amounts of protective antigen, thereby reducing lot-to-lot variation, whose disadvantage was noted with the licensed anthrax vaccine.

Second, as we reported, the six-dose, 18-month immunization regimen, followed by annual booster shots, was problematic. In the 2002 RFP, NIAID required that the rPA candidate vaccines be administered in not more than three doses.

We also reported that the long-term safety of the licensed vaccine had not been studied and that data on short-term reactions, although limited, suggested that women experience a higher rate of adverse reactions, both local and systemic, than men do. NIAID requirements in the two development RFPs included Phase I and Phase II clinical trials to evaluate short-term safety, but neither RFP included analysis of gender differences. In discussions with company officials, however, VaxGen has stated that it

[13]The RFP for the 2002 contract was NIH-NIAID-DMID-02-26; for the 2003 contract, NIH-NIAID-DMID-03-29.

[14]For the 2002 RFP, two awards totaling $22.5 million were given—$13.6 million to VaxGen and $8.9 million to Avecia Ltd. of Manchester, England.

included both male and female subjects in its clinical trials and is examining this issue.

An issue that remains outstanding, however, is that long-term safety studies have not been conducted or required before making awards for full procurement.

We also found that because terrorist events would be likely to occur with little or no warning, postexposure immunization capability would be beneficial. A stated objective in the 2002 RFP was to investigate candidate vaccines that would provide protection when administered both before exposure and in a postexposure immunization regimen, when combined with antibiotics.

NIAID has taken steps to anticipate downstream, large-scale manufacturing issues by requiring a feasibility plan for the manufacture and delivery of 25 million doses in the 2002 contract and, in the 2003 contract, the actual delivery of 3 million to 5 million doses of rPA anthrax vaccine from at least three consistency lots, following good manufacturing practices. The 2003 RFP also included objectives to develop and validate product release and characterization criteria to support eventual submission to FDA for licensing.

HHS's Procurement Strategy Is Very Aggressive

In November 2004, in the first contract under Project Bioshield, ORDC awarded VaxGen a contract for $877.5 million for the manufacture and delivery of 75 million doses of rPA anthrax vaccine in prefilled syringes for SNS. Among other things, the contract requires VaxGen to obtain FDA licensure for both preexposure use and postexposure use with antibiotics, and the initiation and completion of special population clinical trials, including pediatric and geriatric populations.

In the RFP for the contract, ORDC stated that the urgent nature of the current threat required an accelerated pace of development, testing, approval, and procurement of the vaccine and anticipated that it would have to be administered under a "contingency use"

IND protocol, held by CDC, if needed, prior to licensure by FDA. However, the RFP also specified that all vaccine manufactured and acquired under the contract must meet the regulatory deliverables as required for licensure.

The normal schedule for taking a vaccine from preclinical studies to licensure varies, depending on what is known about both the specific nature of the infectious disease and the planned application of the vaccine in terms of when and on whom the vaccine is to be used. These factors can prolong the development of a vaccine as long as 15 years (for civilian use) or as short as 8 years (for military use). Because of the U.S. government's stated need for a vaccine that can counter a domestic biothreat against civilian populations, HHS has undertaken an aggressive procurement of a vaccine on a very short schedule.

The NIAID development and test contracts, whose purpose was presumably to aid in making the best procurement award decision, are not yet completed and, in fact, overlap to a great degree with the procurement contract. At the time the full procurement contract was awarded in November 2004, the initial 2002 development contract to study the basic safety and immunogenicity of candidate vaccines was still ongoing, and the 2003 contract was only part way through Phase II clinical trials. In fact, today, neither the 2002 nor the 2003 contract—intended to ensure a candidate vaccine with appropriate characteristics and a provider's manufacturing capability sufficient for licensing and successful delivery—has yet been completed, only 6 months before first delivery of 25 million doses of SNS-ready product is required. HHS officials acknowledge that the procurement contract's milestones are very aggressive and agree that the contract contains little to no provision for slippage. Additionally, the procurement contract is fixed-price and specifies that no payment will be made before delivery. The financial burden is fully on the contractor should additional costs arise because of an unexpected slip in schedule.

In conclusion, a contract schedule with no margin for error, especially for vaccine development, which is known to be risky, is not conducive to building confidence that a vaccine will be available for use within the arbitrarily defined time period. While the government should not pay out money to a contractor unless and until it has met the terms of its contract, contractors that do not have the resources to assume such risk will not be able to meet the contract requirements, thus limiting the pool of companies that are capable of meeting the nation's needs.

While the government should be a tough negotiator when contracting for major procurements, 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.

Mr. Chairman, this concludes my prepared remarks. I would be happy to respond to any questions that you or other members of the subcommittee may have at this time.

Contacts and Acknowledgments

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Abbreviations

AVA	anthrax vaccine adsorbed
AVRP	Anthrax Vaccine Research Program
AVST	Anthrax Vaccine Safety Team
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
DHS	Department of Homeland Security
DOD	Department of Defense
EPA	Environmental Protection Agency
FBI	Federal Bureau of Investigation
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IND	investigational new drug
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OPHEP	Office for Public Health Emergency Preparedness
ORDC	Office of Research and Development Coordination
rPA	recombinant protective antigen
SDST	Subcommittee of Decontamination Standards Technology
SNS	Strategic National Stockpile
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USPS	United States Postal Service

Appendix I: United States Postal Service Initiatives

U.S. Postal Service (USPS) officials reported to us these activities in responding to our recommendations:

On the recommendation addressed to the Department of Homeland Security (DHS) to develop appropriate validation studies of various activities in detecting anthrax:

- USPS has been helping DHS implement that recommendation. It has been working with its federal partners to further examine existing biological coordination and protocol efforts, within the National Capital Region.
- USPS is also working with state and local public health departments by participating in several biological working groups chartered to help clarify and reduce variance in procedures and protocols and, per GAO's recommendations, to develop validation procedures to help ensure that biothreat test results are reliable and can be clearly understood and correctly interpreted.
- DHS has asked USPS to become part of a subject matter expert team as a result of the real-world experience USPS gained in the 2001 anthrax attacks, its response, and its cleanup and remediation efforts at a number of mail processing facilities and post offices.
- USPS was asked to help develop and implement the guidance as part of the National Capital Region BioWatch Advisory Council.

Appendix II: Centers for Disease Control and Prevention Initiatives

Centers for Disease Control and Prevention (CDC) officials reported information on their work on anthrax detection and anthrax vaccine. With respect to anthrax detection, CDC said it is developing a probabilistic sampling approach. This project will augment the targeted sampling approach that it uses for initial response sampling. CDC officials told us that CDC is "exploring the need for probability sampling in those instances when statistical inferences are necessary."

CDC has also developed a program that will expand its environmental microbiology objectives. This program has several focus areas. One is identifying priority agents, through sampling strategy development, sample collection, sample transportation, and sample analysis. Another is risk reduction activities, such as determining the risk of infection and evaluating techniques and procedures for reducing risk, including improving decontamination methods.

Further, CDC has completed studies and has studies in progress on the recovery of Bacillus anthracis spores from various types of surfaces using different collection methods, including macrofoam swabs, wipes, and HEPA vacuum. It also plans to study the survival rates of other biothreat agents on nonporous surfaces and to evaluate HEPA-vacuum samples for microbial analysis.

The National Immunization Program and the National Center for Infectious Diseases components of the proposed National Center for Immunization and Respiratory Diseases appreciated the opportunity to share information about the status of CDC's Anthrax Vaccine Research Program.

In 1999, CDC received funding to conduct studies of the safety and efficacy of the U.S. licensed anthrax vaccine—anthrax vaccine adsorbed (AVA). CDC's Anthrax Vaccine Research Program (AVRP) consists of a human clinical vaccine trial with quantitative primary serological endpoints, corroborative antibody functional analyses, and an immunological correlates of protection study in rhesus macaques.

The focus of AVRP is a large-scale, multicenter, Phase III human clinical trial with 1,564 participants. The study's objective is to optimize the use of AVA, the only licensed anthrax vaccine in the United States.[1] The study

[1]AVA, or BioThrax, is licensed to BioPort Corporation, Lansing, Michigan.

evaluates the potential for changing the route of administration, reducing the number of primary series vaccinations for the licensed vaccine, and improving the profile of side effects. A successful conclusion to the study will double the availability of AVA, increase vaccine acceptance and uptake because of a reduction in side effects, and provide animal study data demonstrating long-term protection against inhalation anthrax afforded by a priming series of three intramuscular injections.

Analysis of the human clinical trial serological and reactogenicity data at an intermediate stage in the study showed that it is possible to drop the dose at week two, change the route of administration to intramuscular, and reduce side effects without making an impact on antibody responses to a priming series of three injections. The interim report was submitted to the Food and Drug Administration (FDA) in February 2005, and subsequently the vaccine manufacturer filed a supplement to its biologics license application to add this new regimen.

The AVRP's remaining research goals are to confirm that two additional doses can be dropped from the priming series at 12 months and 18 months, thus moving to a three- injection intramuscular regimen; to adopt biennial rather than annual boosters; and to establish in nonhuman primate models the onset and duration of the protection of the three-dose intramuscular regimen (the "correlates of protection" study).

CDC's Anthrax Vaccine Safety Team (AVST) is conducting a wide range of anthrax vaccine safety research activities critical to accomplishing the objectives in CDC's 1999 congressional mandate. These activities' goals are to (1) address important anthrax vaccine safety questions, (2) build an infrastructure to ensure the anthrax vaccine's safety, (3) build a system to address concerns regarding vaccine safety and aid in resolving potential liability questions, and (4) optimize the vaccination schedule and the vaccine's administration to ensure its efficacy while minimizing the number of doses required, reducing the occurrence of adverse events, and maximizing the availability of the only licensed anthrax vaccine in the United States.

In collaboration with the Army Medical Surveillance Activity of the Department of Defense (DOD) and FDA, CDC established the Vaccine Analytic Unit in 2003 on the Walter Reed Army Medical Center Campus. It uses data from the Defense Medical Surveillance System to assess whether specific longer-term adverse events are associated with AVA and other biodefense vaccines; this system is a unique source of active surveillance data containing medical, vaccination, and deployment histories for U.S.

military personnel. The Vaccine Analytic Unit's research agenda for investigating potential AVA adverse events and an AVA study on optic neuritis are in press, and a multiple near-concurrent immunization study has been completed. Funded studies include evaluations of AVA and Stevens Johnson Syndrome/Toxic Epidermal Necrolysis, connective tissues diseases, diabetes mellitus, Guillain–Barré Syndrome, and atrial fibrillation

Studies to assess the possible effects of AVA on health-related quality of life and the role of hormones as the basis for adverse AVA events occurring more frequently in women are ongoing in participants of CDC's AVRP, begun in 2002 for administering AVA to workers occupationally at high risk for exposure to Bacillus anthracis. Also, AVST has ongoing collaborative research studies with CDC's Immunization Safety Office, FDA, and DOD to enhance AVA adverse event surveillance and improve AVA acceptability.

Appendix III: Department of Homeland Security Initiatives

Department of Homeland Security (DHS) officials reported the following activities to us in addressing our recommendations:

DHS has taken a lead role in promoting and coordinating the activities of various agencies that have technical expertise related to environmental testing. DHS

- led the formulation of a memorandum of understanding among DHS, DOD, the Department of Health and Human Services (HHS), and USPS on coordinated monitoring of biological threat agents and is leading the execution of the memorandum;
- is leading an effort to establish an Integrated Consortium on Laboratory Networks;
- has established a Federal Postal and Shipping Integrated Project Team;
- is co-chairing the Subcommittee of Decontamination Standards Technology (SDST);
- is co-sponsoring the Second (and First) National Conference on Environmental Sampling for Bio-Threat Agents.

DHS has adopted the International Quality Management Standard definition of validation.

DHS has developed a process to standardize and validate methods; it

- has validated a method for sampling suspicious powders and
- is developing a method for the validation of public health actionable assays.

DHS has invested in both targeted and probabilistic sampling strategies and in methodologies that are appropriate for monitoring facilities and that apply to wide-area and facility restoration. Its research and development efforts include

- performance characterization of three sampling methods on varied surfaces;
- developing the Building Restoration Operations Optimization Model;

- sponsoring the Visual Sample Module;
- developing Annotated Characterization and Clearance Sampling Plan Templates for preplanning the response to a biological facility attack;
- developing BioWatch Preparedness and Response Guidance, which includes Part III: BioWatch Environmental Sampling;
- developing native air sample collection strategies and protocols associated with transportation facilities.

DHS has prioritized investments for high-risk biological agents through internal and interagency coordination, to include

- SDST research and development investment strategy;
- agency-to-agency discussions on leveraging research and development opportunities;
- internal strategic planning and requirements generation.

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