

GAO

Testimony

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ANTHRAX VACCINE

Changes to the Manufacturing Process

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Mr. Chairman and Members of the Subcommittee:

We are pleased to be here today to contribute to your hearing on biological warfare defense vaccine programs. This topic is of considerable urgency today in light of the terrorist attacks of September 11 and the exposures to anthrax in recent weeks. Our testimony today is limited to the work we have done in response to your October 2000 request to review the changes to the manufacturing process for the anthrax vaccine that has been produced by the BioPort Corporation and its predecessor entities. As you know, BioPort is the sole facility in the U.S. currently capable of producing anthrax vaccine.

My testimony today will address the changes that occurred in the manufacturing process for anthrax vaccine since 1989, and the status of the approval of those changes by the Food and Drug Administration (FDA). It is, of course, FDA's responsibility to determine that the anthrax vaccine is safe and efficacious, and it is our understanding that FDA officials will be undertaking a review in the near future to determine if vaccine production can be resumed. We appreciate the opportunity to provide information that may be relevant to that determination.

A brief summary of our scope and methodology is provided in appendix I. A list of related GAO products is presented in appendix II.

Background

The original anthrax vaccine was developed by George Wright and others in the 1950s and was first produced on a large scale by the pharmaceutical company Merck Sharp & Dohme (Merck).¹ A clinical study in 1962 evaluated the safety and effectiveness of the Merck vaccine in mill workers.² The results of this study formed the basis for subsequent licensure of the vaccine in 1970. The original license for the production of anthrax vaccine was issued to the Michigan Department of Public Health by the Division of Biologics of the National Institutes of Health.³ In 1995, the facility changed its name to the Michigan Biologic Products Institute.

¹ Merck Sharp and Dohme is currently known as Merck and Co., Inc.

² The most common occurrence of anthrax infection has been in industrial settings like wool mills where workers may be exposed to infected animal products.

³ Prior to the establishment of FDA as the licensing authority for vaccines, the National Institutes of Health was responsible for licensing.

In 1998, the facility was sold, and its name was changed to BioPort Corporation.

Today, FDA, through the Center for Biologics Evaluation and Research (CBER), licenses biological products (that is, biologics) and the facilities in which they are produced. The manufacturer is required to comply with current Good Manufacturing Practices (cGMP) regulations, which regulate personnel, buildings, equipment, production controls, records, and other aspects of the vaccine manufacturing process.⁴

When there is a major change in the manufacturing process—defined as a change determined by FDA to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of a product in relation to safety or effectiveness—the manufacturer must submit evidence to FDA demonstrating that the change does not have any such adverse effects. This requirement is particularly important for vaccines since the quality of biologics cannot be ensured solely from final tests on random samples. Instead, the quality of biologics can be determined only by a combination of strict control of the entire manufacturing process, in-process tests, and end-product tests. When significant process changes are made, the onus is on the manufacturer to ensure that the quality of the product is maintained after such changes are introduced. Depending on the changes made, this may require trial studies (with animals or humans) to evaluate the impact of the new process, followed by comparison of pre- and post-change lots before releasing the post-change lots for use.⁵

As our testimony today reports, in the case of the anthrax vaccine, the Michigan facility did not notify FDA of a number of changes made in the manufacturing process in the early 1990s and no specific studies were undertaken to confirm that vaccine quality was not affected. FDA inspectors did not inspect the Michigan facility's anthrax production room

⁴ cGMP embodies a set of scientifically sound methods, practices, or principles that are implemented and documented during development and production to ensure consistent manufacture of safe, pure, and potent products. Such principles apply to the manufacturing process as well as to the facilities in which products are manufactured. (21 C.F.R., parts 600 through 680.)

⁵ FDA guidance states that, if significant changes to the manufacturing or formulation of a vaccine are made after the original clinical trial, bridging studies may be used to demonstrate that immunogenicity and the occurrence of common adverse events have not been affected adversely by these changes. Anthony, B.F. and A. Sutton, "The Role of the Food and Drug Administration in Vaccine Testing and Licensure," *New Generation Vaccines*, New York, Marcel Dekker, Inc., Ch. 73, p. 1191.

until 1993. According to FDA, access was not granted because its inspectors had not been vaccinated against anthrax. FDA inspectors were able to perform some aspects of inspection—for example, reviewing records—but not equipment and production.⁶

The inspections that FDA ultimately was able to conduct over time found a number of deficiencies, many of which were not corrected in a timely manner. For example, the deficiencies that FDA identified in its February 1998 inspection fell broadly into two categories: (1) those that, although serious, might affect only one or a limited number of batches that were produced when the deficiency was extant and (2) those of a generic nature that could compromise the safety and efficacy of any batch or all batches. Vaccine production was suspended after these findings, and BioPort has been attempting since then to bring the facility and manufacturing process into compliance. We understand from recent testimony by the Secretary of Health and Human Services that BioPort has recently submitted an application for an FDA inspection to approve its facility and manufacturing process.

Changes to the Fermenters and Filters in the 1990s and FDA's Approval of Those Changes

Beginning in 1990, the Michigan state-owned facility (the Michigan facility) that was later sold to BioPort changed both the fermenters and the filters it used in manufacturing the anthrax vaccine.⁷ With regard to fermenters, it replaced the original glass fermenter with two 100-liter stainless steel fermenters in 1990, and installed two similar fermenters in 1993. With regard to filters, the facility changed from ceramic to nylon filters in 1990. After the 1990 change, the facility changed the types of filters two more times, in 1996 and 1997. According to Michigan facility officials, changing the filters reduced processing time for the production of a single lot of anthrax vaccine, while changing and adding additional fermenters increased its production volume. We were informed that both changes were made to increase production before the onset of the Gulf War.

⁶ The purpose of FDA's inspection is to determine that the products are manufactured in compliance with cGMP as described in the license application. Manufacturers who fail to meet product standards or who make unreported or undocumented changes in manufacturing methods may have their license suspended or revoked.

⁷ A fermenter is used to grow the bacteria. A filter is one of the processing stages after the fermentation. The filter removes whole bacteria and other biochemical components.

Under FDA regulations, changes to a vaccine manufacturing process are to be reported to FDA and significant changes may require the manufacturer to submit a license application amendment.⁸ In December 1990, FDA was notified of the replacement of the original glass fermenter with two 100-liter stainless steel fermenters. FDA approved that change in 1993. Although the Michigan facility installed two additional stainless steel fermenters in 1993, it did not notify the FDA about the additional fermenters at that time. Inspection records indicate that FDA was aware of the additional fermenters and encouraged the facility to submit a license amendment application for them in 1993⁹ and again in 1995¹⁰. In January 1999, BioPort submitted a license amendment application with supporting documentation to FDA concerning the two additional fermenters. In May 2001, FDA approved these additional fermenters.

Because we could find no evidence in BioPort or FDA records that the filter changes had been reported to FDA, we contacted FDA officials in December 2000 to discuss the filter changes. They told us that they had not been notified and were not aware of changes to any filters used to produce anthrax vaccine. In February 2001, FDA wrote to BioPort, raising questions about the changes to the filters. In April 2001, BioPort submitted documentation, primarily in-process tests and lot release data, to FDA to demonstrate that the filter changes had not had a significant impact on vaccine quality. FDA reviewed and accepted the data and approved the filter changes in July 2001. Although the lot release data included lots produced immediately before and after the filter changes, the data submitted did not include the type of data that, according to FDA officials, would normally have been required if a license amendment application had been filed contemporaneously with the changes, that is, a direct

⁸ Prior to 1997, FDA regulations required that “important” proposed changes in the vaccine manufacturing process be reported to FDA at least 30 days prior to implementation. Since 1997, FDA regulations have required that “major” changes be reported to FDA at least 30 days prior to implementation and that FDA approve such changes prior to distribution of vaccine made using them.

⁹ The FDA inspection report (May 26, 1993) stated that “any changes to the manufacturing [process] that have the potential to affect the safety, purity, or potency of a biologic must be submitted and approved by CBER prior to implementation.”

¹⁰ In April 1995, Michigan facility officials told FDA that the additional fermenters installed in 1993 were similar, although not identical, to those installed in 1990 and approved in 1993. In response, FDA officials explained that “a different fermenter may cause change in the product, even if the fermenter is similar to the existing fermenter, and would most likely require agency approval.” (FDA/CBER Conversation Record, Apr. 21, 1995.)

biochemical analysis of vaccine samples from before and after the changes. FDA officials told us that such a direct comparison is not possible now, because appropriate pre-1990 vaccine samples no longer exist.

Studies Suggest Possible Changes to the Anthrax Vaccine After the 1990 Manufacturing Changes

Because it is not now possible to definitively resolve the question of whether the anthrax vaccine produced after the filter changes is the same as that produced before the changes (a demonstration that is normally required in a license amendment application), we have reviewed other studies to see if evidence suggests that the question may need to be further examined. We have found two types of such evidence.

First, in an unpublished study performed in 1990, the Department of Defense (DOD) found up to a hundredfold increase in the protective antigen levels in lots produced after the filter change that year.¹¹ (Anthrax toxin is composed of protective antigen, lethal factor, and edema factor. The individual toxin components are not toxic. A protective antigen and lethal factor combination produces lethality, and a combination of protective antigen and edema factor cause swelling.)

In a subsequent article published in 1994, DOD researchers, referencing the earlier study, hypothesized that the filter change altered the composition of the vaccine by increasing the level of protective antigen in the finished product.¹² According to the authors of this article, when DOD questioned the Michigan facility about this increase in 1990, the responsible Michigan facility official attributed it to the change in the filter from ceramic to nylon.

¹¹ J.W. Ezell and T. Abshire, "In Vitro Analysis of Michigan Department of Public Health Human Anthrax Vaccine", U.S. Army Medical Research Institute of Infectious Diseases, Bacteriology Division, Fort Detrick, MD, Oct. 25, 1990. This unpublished study applied a then-new methodology to measure protective antigen that had not been separately validated at the time but is widely used today, and Dr. Ezell told us that the results should be interpreted cautiously as a result. We have had the study reviewed by two experts in anthrax vaccine issues who did not see any evident reasons to question the study methodology. We believe at best, however, it is an indicator that protective antigen levels may have changed after the filter changes. Since it cannot be replicated, it is the only evidence available on this point.

¹² B.E. Ivens and others, "Efficacy of a Standard Human Anthrax Vaccine Against *Bacillus anthracis* Spore Challenge in Guinea Pigs," *Vaccine*, vol. 12 (1994), pp. 872-874.

There are no studies to show what the effect of a significant increase in protective antigen may be on safety or efficacy of the vaccine. However, because the tests that could have demonstrated that the product was not changed in a material way in the context of a timely license amendment application were not done, and cannot now be done, there is potential merit in evaluating the findings of the 1990 DOD study further. We discussed the DOD study further with FDA officials on October 15, 2001, and they told us that they had not evaluated the study because they did not have it. At their request, we have provided the study to them.¹³

Second, we have reported several times in earlier work that, before 1990, anthrax vaccine was used by a small number of at-risk individuals (for example, wool mill workers), and FDA did not have any system to report adverse reactions associated with drugs and vaccines. Safety data, as reported in the product insert, were limited to the information from studies done in the 1960s, long before the fermenter and filter changes discussed here. Published and unpublished data on anthrax vaccine use during the Gulf War and since 1998 show a significantly greater incidence of both local and systemic adverse reactions compared with rates reported in the product insert. For example, the product insert says that the following should be expected: (1) 30 percent of recipients should experience a mild local reaction; (2) 4 percent should experience a moderate local reaction; and (3) 0.2 percent should experience systemic reactions characterized by malaise and lassitude with chills and fever reported in only a few cases. This indicates that some reaction should be experienced by a total of 34.2 percent of recipients. By comparison, in a survey we conducted in calendar year 2000, 85 percent of National Guard and reserve forces in our survey who were given the anthrax vaccine reported some reactions, with local reactions experienced by 76.2 percent of recipients and systemic reactions experienced by 23.8 percent. Chills and fever were reported by between 9 and 11 percent of our surveyed

¹³ Because we had earlier discussed this study with both DOD and BioPort, we had assumed that one or both of them had referred the information to FDA. We had also asked FDA about the study in December 2000 but they did not request a copy from us at that time.

vaccine recipients.¹⁴ These results are consistent with unpublished DOD studies and other published epidemiological work we are aware of.¹⁵

Because there are no data to evaluate the effect of the filter change on the characteristics of the vaccine product, it is difficult to determine whether these greater levels of adverse reactions could be related to changes in the vaccine associated with the filter changes. Ceramic filters (used before 1990) absorb proteins more than nylon ones, and the change to nylon filters in 1990 could theoretically have resulted not only in more protective antigen coming through but also other proteins. The end-product and in-process tests that BioPort submitted to FDA in 2001 in support of the filter changes may lack the capability to evaluate this possibility. Additional biochemical tests would have been required. For example, a filter change could have allowed more edema factor to pass through. The Michigan facility did not routinely test for edema factor in the product. We note that, since 1997, United Kingdom (U.K.) regulations have required the anthrax vaccine produced by the U.K. Center for Applied Microbiology and Research to be tested for both protective antigen and edema factor.¹⁶

Observations

General public health vaccines are produced according to cGMP and are in constant, routine use worldwide. This use permits real-time monitoring of whether the vaccines are performing properly. In contrast, bio-defense vaccines have no such ongoing reality check because of the absence of natural disease and relatively limited use. Thus, only in emergency situations are bio-defense vaccines subjected to the evaluations that public health vaccines undergo all the time. Accordingly, the stringent application of cGMP by FDA in its approval of the resumption of vaccine manufacture at BioPort, as well as subsequent monitoring of the manufacturing process, is vital to ensure that vaccines produced are safe, pure, and of high quality.

¹⁴ The full results of our survey will be reported in the near future.

¹⁵ We reported on the results of several DOD studies in *Anthrax Vaccine: Safety and Efficacy Issues* (GAO/T-NSIAD-00-48, Oct. 12, 1999.) See also Lea Steele, "Prevalence and Patterns of Gulf War Illness in Kansas Veterans: Association of Symptoms with Characteristics of Person, Place, and Time of Military Service." *American Journal of Epidemiology*, Vol. 152, No. 10, 2000, pp. 992-1002.

¹⁶ The Center for Applied Microbiology and Research is the manufacturer of the U.K.'s only licensed anthrax vaccine.

In view of the increasing importance that will be given to the anthrax vaccine in the current environment and whether or not the anthrax vaccine is approved for production in the near future, it is important to ensure that studies continue to evaluate the vaccine's safety and efficacy, particularly with respect to the effect of higher levels of protective antigen and possibly other proteins. If FDA reinstates BioPort's license to manufacture and distribute vaccine, such studies would be strengthened by the implementation, by FDA or DOD, or both of an aggressive active surveillance program to ensure the early identification and analysis of adverse reactions.

Mr. Chairman, this concludes my statement. I will be happy to answer any questions you or Members of this Subcommittee may have.

Contacts and Acknowledgments

For further questions regarding this testimony, please contact Nancy Kingsbury, Ph.D., at (202) 512-2700. Other individuals making key contributions to this testimony include Sushil K. Sharma, Ph.D., DrPH; Jack Melling, Ph.D.; George Bogart; and David Gootnick, M.D.

Appendix I: Scope and Methodology

To conduct our work, we reviewed documents provided to us by FDA, DOD, and the Michigan facility/BioPort Corporation pertaining to the anthrax vaccine. In addition, we reviewed published and unpublished scientific reports on anthrax vaccine and on the safety and efficacy of the vaccine. In addition, we interviewed officials of FDA, DOD, the Michigan facility/BioPort, and experts in anthrax vaccine in U.S. and the U.K.

Appendix II: Related GAO Products

Gulf War Illnesses: Questions About the Presence of Squalene Antibodies in Veterans Can Be Resolved ([GAO/NSIAD-99-5](#), Mar. 29, 1999).

Medical Readiness: Safety and Efficacy of the Anthrax Vaccine ([GAO/T-NSIAD-99-148](#), Apr. 29, 1999).

Contract Management: Observations on DOD's Financial Relationship with the Anthrax Vaccine Manufacturer ([GAO/T-NSIAD-99-214](#), June 30, 1999).

Medical Readiness: Issues Concerning the Anthrax Vaccine ([GAO/T-NSIAD-99-226](#), July 21, 1999).

Anthrax Vaccine: Safety and Efficacy Issues ([GAO/T-NSIAD-00-48](#), Oct. 12, 1999).

Medical Readiness: DOD Faces Challenges in Implementing Its Anthrax Vaccine Immunization Program ([GAO/NSIAD-00-36](#), Oct. 1999).

Medical Readiness: DOD continues to Face Challenges in Implementing Its Anthrax Vaccine Immunization Program ([GAO/T-NSIAD-00-157](#), Apr. 2000).

Gulf War Illnesses: Questions About the Presence of Squalene Antibodies in Veterans Can Be Resolved ([GAO/NSIAD-99-5](#), March 29, 1999).