

IDA

INSTITUTE FOR DEFENSE ANALYSES

**Resuming Production of the Anthrax
Vaccine as Quickly as Possible:
Analysis of Alternative
Business Arrangements**

Volume 1: Main Report

Thomas P. Frazier, Project Leader
Maria Borga
John W. Bailey
Alec W. Salerno
John J. Cloos
Julia Klare Burr

With the assistance of
Richard A. Rettig of RAND

October 2000

Approved for public release;
distribution unlimited.

IDA Paper P-3553

Log: H 00-002051

20010404 085

This work was conducted under contract DASW01 98 C 0067, Task AO-7-1929, for the Office of the Director, Acquisition Resources and Analysis. The publication of this IDA document does not indicate endorsement by the Department of Defense, nor should the contents be construed as reflecting the official position of that Agency.

© 2000, 2001 Institute for Defense Analyses, 1801 N. Beauregard Street, Alexandria, Virginia 22311-1772 • (703) 845-2000.

This material may be reproduced by or for the U.S. Government pursuant to the copyright license under the clause at DFARS 252.227-7013 (NOV 95).

INSTITUTE FOR DEFENSE ANALYSES

IDA Paper P-3553

**Resuming Production of the Anthrax
Vaccine as Quickly as Possible:
Analysis of Alternative
Business Arrangements**

Volume 1: Main Report

Thomas P. Frazier, Project Leader
Maria Borga
John W. Bailey
Alec W. Salerno
John J. Cloos
Julia Klare Burr

With the assistance of
Richard A. Rettig of RAND

PREFACE

The Institute for Defense Analyses (IDA) prepared this paper for the Office of the Director, Acquisition Resources and Analysis, under a task titled "An Assessment of the Anthrax Vaccine Production Facility." The two-volume paper fulfills the task objective of identifying and evaluating the advantages and disadvantages of converting an anthrax vaccine-production facility in Lansing, Michigan, (now privately owned and operated by BioPort Corporation) to a government-owned, contractor-operated facility. This volume contains the main report. Volume 2 contains proprietary BioPort information, some of which we used to estimate costs.

Jeffrey H. Grotte, Stanley A. Horowitz, and Thomas A. Musson of IDA were the technical reviewers for this paper. The study team also benefited from the comments of Jerome Bracken, J. Richard Nelson, and Ross Anthony.

CONTENTS

Executive Summary	S-1
A. Introduction.....	1
B. Background.....	2
1. Lansing Facility, 1970 to 1998	3
2. BioPort Corporation Purchase	5
C. Current Status	7
1. BioPort's Supplement Application	7
2. Schedule.....	8
3. Expected Time for BioPort To Gain FDA Approval.....	9
4. History Suggests BioPort Will Not Gain Approval in 2001.....	10
5. DoD's Strategy	12
D. Government-Owned, Contractor Operated (GOCO) Facilities	13
1. Trend Is Away from GOCO Model	13
2. Two GOCO Scenarios	14
E. Converting the Lansing Facility to a GOCO	15
1. Purchasing BioPort	16
2. Transfer of License Is Not Assured	18
3. If Not BioPort, Who?.....	20
F. Hiring a Contractor to Operate the GOCO	21
1. Schedule and Cost Estimates for the Current Strategy	22
2. Schedule and Cost Estimates for a New Contractor	22
3. Schedule and Cost Estimates for Re-hiring BioPort.....	25
G. Summary of Findings.....	27
Sources.....	A-1
Abbreviations.....	B-1

FIGURES

1. Timeline of Relevant Events.....	3
2. BioPort’s BLA Supplement Timeline.....	9
3. Most Optimistic Schedule with the Current Strategy	22
4. Most Likely Schedule with the Current Strategy	22
5. Most Optimistic Schedule with a New Contractor	23
6. Most Likely Schedule with a New Contractor.....	23
7. Most Optimistic Schedule with the Same Contractor.....	25
8. Most Likely Schedule with the Same Contractor	26

TABLES

1. Comparison of Advantages and Disadvantages.....	28
2. Schedule and Cost Comparisons.....	29

EXECUTIVE SUMMARY

The Department of Defense (DoD) and members of the congressional defense committees are concerned about the nation's ability to supply sufficient anthrax vaccine adsorbed (AVA) to meet the current schedule for inoculating all 2,400,000 members of the United States armed forces (active duty and Reserve components). BioPort Corporation is the nation's only licensed producer of AVA. A series of technical problems has delayed U.S. Food and Drug Administration (FDA) approval for BioPort to sell AVA to the DoD. BioPort is preparing for a new FDA review, and the DoD is providing both financial relief and technical assistance to augment BioPort's efforts. Under this strategy, the earliest BioPort could resume AVA delivery is June 2001. A more realistic expectation is delivery in the first half of 2002.

In response to a query from the Chairman of the Senate Committee on Armed Services, the DoD tasked the Institute for Defense Analyses (IDA) and the RAND Corporation to conduct a month-long study of the advantages and disadvantages (in terms of earlier resumption of AVA delivery) of converting the privately owned BioPort Corporation to a government-owned, contractor-operated (GOCO) operation. We investigated two scenarios. In the first scenario, the DoD purchases BioPort's Lansing, Michigan, AVA-production facility and selects a new company (i.e., not BioPort) to run it. In the second scenario, the DoD purchases the Lansing facility and selects BioPort to run the facility.

Our findings indicate that neither option will result in vaccine being delivered faster than under the current strategy. Under the first GOCO option, the earliest AVA delivery would be in 2003, although the most probable date for new deliveries would be in late 2004. Under the second option, the earliest delivery would be August 2001. That is 2 months later than the current strategy, although delays could extend this considerably. The most probable date for new deliveries under this option would be in late 2002. This option closely resembles the current situation but with the additional disadvantages of costing more and making the government responsible for a biohazard facility that will become obsolete in a few years. Since the federal government probably cannot own the AVA license, the only remaining advantage of a GOCO conversion is a small increase in government control over the operation of the facility. However, in return for that control, the government would incur additional costs, delays, and liabilities.

Table S-1 summarizes the study team’s estimates of the earliest and most likely dates that the vaccine could be delivered under the current strategy and each GOCO option. The table also lists the advantages and disadvantages of each option.

Table S-1. Summary of Findings

Option	Date of AVA availability		Advantages (+) and Disadvantages (-)
	Most Optimistic Schedule	Most Likely Schedule	
Current Strategy	June 2001	April 2002	<ul style="list-style-type: none"> + BioPort has the technical ability to win FDA approval to produce, test, and distribute AVA - DoD does not have total control
GOCO—New Contractor	March 2003	November 2004	<ul style="list-style-type: none"> + DoD gains additional control - DoD still does not have total control because it would not hold the license - Not likely to attract big name pharmaceutical firm to operate the facility - Agreeing to a price could be difficult - In a few years, DoD would own an obsolete, hazardous plant - Retention of key personnel becomes a concern - DoD assumes many risks and liabilities from being responsible for production and distribution of biologics products - Estimated cost is \$95M to \$130M greater than the current strategy
GOCO—BioPort	August 2001	October 2002	<ul style="list-style-type: none"> + DoD gains additional control - DoD still does not have total control because it would not hold the license - Outcome is almost identical to the current strategy - Agreeing to a price could be difficult - A few years later, DoD would own an obsolete, hazardous plant - Departure of key personnel could endanger license - DoD assumes many risks and liabilities from being responsible for production and distribution of biologics products - Estimated cost is \$42M to \$56M greater than the current strategy

A. INTRODUCTION

On 18 May 1998, the Secretary of Defense approved implementation of the Anthrax Vaccination Program for the total force.¹ This decision came after a 2-year review based on the recommendation of the Chairman of the Joint Chiefs of Staff. The plan is to inoculate the entire force with a six-shot series of the anthrax vaccination in a phased immunization program between now and 2005. A new inoculation requires four shots in the first year and two in the second. Maintenance of anthrax immunity requires a one-shot booster each year thereafter. All shots, initial and booster, are the same strength. Approximately 5 million doses of the vaccine will be needed each year for the next 6 years.² Once the total force is inoculated, about 3.4 million doses per year will be required to administer booster shots and protect new personnel.³

At the time the Secretary approved the program, the Michigan Biologic Products Institute (MBPI), the nation's sole producer of anthrax vaccine (more accurately called anthrax vaccine adsorbed or AVA), was modernizing and expanding its facilities in Lansing, Michigan, to meet the anticipated surge in demand for the vaccine. Unfortunately, MBPI and the current owner of the facilities, the BioPort Corporation, experienced a series of technical problems that led to delays in Food and Drug Administration (FDA) approval to sell AVA to the DoD.

The delays have become so serious that the Chairman of the Senate Committee on Armed Services asked the DoD to consider alternative business arrangements to ensure that the approved vaccine can be administered to the total force in a timely manner. In the meantime, the Deputy Secretary of Defense has ordered a temporary slowdown in the anthrax immunization program until additional FDA-approved vaccine becomes available.⁴

¹ Secretary of Defense Memorandum, *Implementation of the Anthrax Vaccination Program for the Total Force*, 18 May 1998. The Department of Defense (DoD) estimates that enough vaccine to inoculate about 3 million personnel will be required to implement the order: about 1.4 million personnel in the active-duty military; about 1 million personnel in the Reserves, National Guard, and Coast Guard; plus the commander's reserve, essential civilian personnel, and certain allied forces in Canada and the United Kingdom.

² We refer to the amount of vaccine required for each shot as a *dose*.

³ An annual booster for each previously protected individual (about 3.0 million) is required, plus four shots in the first year and two shots in the second year to protect each new individual. The Joint Program Office for Biological Defense thus estimates an annual steady-state requirement of 3.4 million doses.

⁴ Deputy Secretary of Defense Memorandum, *Temporary Slowing and Future Resumption of Anthrax Vaccine Immunization Program (AVIP)*, 17 July 2000.

The DoD tasked the Institute for Defense Analyses (IDA) and the RAND Corporation to examine these alternative business arrangements. Specifically, the study team was to identify and evaluate the advantages and disadvantages of converting the privately owned BioPort AVA-production facility in Lansing, Michigan, to a government-owned, contractor-operated (GOCO) facility. The study team was instructed to evaluate these advantages and disadvantages in the context of the DoD's overarching goal of resuming vaccine production as quickly as possible. The study began on 18 July 2000.

During the course of the study, the study team interviewed and obtained data from individuals within the DoD, the FDA, the pharmaceutical industry, and the BioPort Corporation. Their names and affiliations are listed in the Sources section at the back of the paper.

B. BACKGROUND

A confluence of events contributed to the present delays in getting AVA to U.S. troops. An abbreviated version of the story follows.

The Michigan Department of Public Health founded the Lansing biologics laboratory in 1926. AVA production was first licensed there in 1970. As early as 1993, the FDA mandated several improvements to the laboratory as part of its continuing approval for AVA production. Some of these improvements required renovations to the facility. In 1995, the state of Michigan created MBPI as a public corporation for the express purpose of selling it into the private sector.⁵ In 1996, the FDA found that the problems still had not been adequately addressed, and in 1997 it began the process to halt AVA production at the facility. In 1998, the Secretary of Defense decided to inoculate the total force with the vaccine. Later that year, the state of Michigan sold MBPI and its AVA-production facility to the BioPort Corporation. In response to the DoD's need for AVA, BioPort and the DoD began a vigorous program to bring the facility into compliance and to resume vaccine production.

In the meantime, the FDA had raised the standards on all biologics laboratories as a result of some deadly contamination problems that had occurred elsewhere in the country. When the time came to inspect the facility renovation, the FDA imposed the

⁵ Before it was sold to BioPort, MBPI was one of the last state-owned biologics facilities in the country.

new standards on BioPort. It asked for process and validation upgrades even though it had originally stated that only the facilities would be inspected. BioPort was able to rectify some of the minor problems found with the facility. However, BioPort will not be able to satisfy the rest of the FDA concerns, including long-run facilities issues, until at least mid-2001 or, more likely, early 2002.

1. Lansing Facility, 1970 to 1998

To better understand the current situation, it is helpful to review the relevant events at the Lansing AVA-production facility over the past 30 years (see Figure 1).

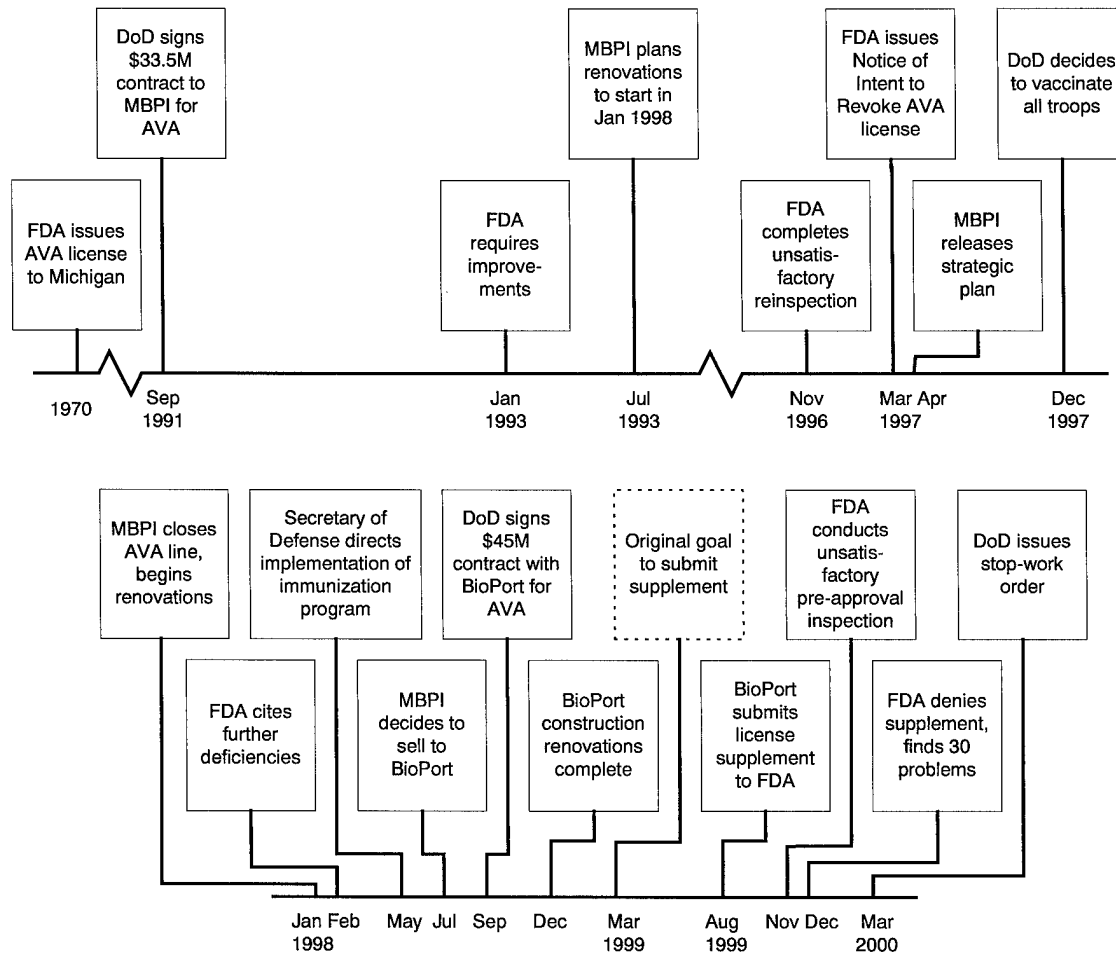


Figure 1. Timeline of Relevant Events

The first substantial DoD contract for AVA was signed in September 1991⁶ with the Michigan Department of Public Health, which was the sole holder of an FDA license to produce AVA. The contract included terms to remodel the existing facility as well as to test, package, and store AVA through July 1999. After subsequent modifications, the value of that contract totaled \$33.5 million.

In January 1993, the FDA inspected the Lansing facility and required several improvements as part of its continuing approval for AVA production.⁷ Facility improvements as well as the planned renovations to the facility were approved by the state of Michigan in July 1993, although the work was not scheduled to begin until January 1998. In 1995, the facility became known as MBPI after the state of Michigan formed this corporation as a precursor to divesting it. In November 1996, the FDA made another routine inspection of the facility and determined that insufficient progress had been made. In March 1997, the FDA issued a Notice of Intent to Revoke pertaining to the MBPI AVA license.

At that same point in time, the DoD determined the MBPI facility was inadequate to meet future needs, prompting plans for further renovations. In April 1997, MBPI responded with a Strategic Plan for Compliance that described how it intended to implement quality systems and Current Good Manufacturing Practice improvements to achieve compliance with the FDA.

In January 1997, a month after the DoD decided to vaccinate all the armed forces and Reserves against anthrax, MBPI closed its AVA-production line to begin a \$3.7-million renovation. In February 1998, the FDA issued an inspection report that listed deficiencies not related to the planned production line renovations.

⁶ The 1991 contract, number DAMD 17-91-C1139, is a firm-fixed-price contract with two cost reimbursement items. We confined our study to contracts still open as of June 1999. This coincides with the contracts reviewed in the detailed financial audits performed by the Defense Contract Audit Agency.

⁷ The FDA conducts more or less annual inspections of licensed biologics facilities. Issues arising from these inspections may be minor or major. Any issues must be addressed and corrected; however, serious or persistent issues can lead to further action such as a Notice of Intent to Revoke or the revocation of a license.

2. BioPort Corporation Purchase

In July 1998, the state of Michigan decided to sell MBPI, which had been losing money and was seeking a buyer, to BioPort for \$25 million.⁸ Payment was in the form of cash (\$3.25 million), secured notes (\$12.1 million), and product donations (\$4.6 million in rabies vaccine and immune globulin) and royalties (\$5 million over 5 years) to the state of Michigan. At the time of the sale, the state of Michigan had calculated the value of MBPI to be no more than \$10.5 million.⁹ Twenty firms from nine countries had investigated purchasing the facility after Michigan announced it was seeking a buyer for MBPI.

Ownership of BioPort is shared among the former managers of MBPI and several investors. Seven former MBPI managers, led by former director Robert Myers and former deputy director Robert Van Ravenswaay, own the majority of the newly formed Michigan Biologics Products, Inc. (not to be confused with the original entity, Michigan Biologics Products Institute). The new MBPI holds a 32 percent stake in BioPort. Intervac L.L.C., a Maryland pharmaceutical investment firm holds another 58 percent interest in BioPort. Neogen Corporation, a Lansing-based food safety research and development company, holds the remaining 10 percent interest in BioPort.¹⁰ Retired Admiral William Crowe Jr., Fuad El-Hibri (president of BioPort), and El-Hibri's wife and father share ownership of Intervac.¹¹

BioPort offered all MBPI employees salary increases and stock options, and many decided to continue to work at the facility, including the key individuals essential to retaining FDA approval to produce the vaccine. The FDA therefore approved the transfer of MBPI's AVA-production license #1260 to BioPort. The sale was completed on 5 September 1998. Also in September, another DoD contract was awarded for \$45 million to produce, test, package, and store AVA through November 2000.¹²

⁸ Office of the Inspector General, Department of Defense, "Contracting for Anthrax Vaccine," Report No. D-2000-105, 22 March 2000.

⁹ "State OK's Sale of Vaccine Lab," *The Detroit News*, [Online], 1998. Available: <http://detnews.com/1998/metro/9807/07090021.html>, accessed 16 August 2000.

¹⁰ Ibid.

¹¹ Fuad El-Hibri, President and Chief Executive Officer, BioPort Corporation, Testimony before the Subcommittee on National Security, Veterans Affairs, and International Relations of the House Committee on Government Reform, 30 June 1999.

¹² The 1998 contract, number DAMD 17-98-C8052, is a firm-fixed-price contract.

In December 1998, the construction phase of the planned renovations to the laboratory were completed. Equipment calibration and preparation for AVA production occurred through March 1999, and by April 1999, AVA production had resumed at risk. The production of AVA allowed BioPort to collect contract progress payments even though the product could not be released until the FDA approved the new facilities. In August 1999, BioPort submitted a Biologics License Application (BLA) supplement to the FDA. The FDA requires a supplement to be filed whenever there are changes to the product, production process, equipment, facilities, or responsible personnel that have a “substantial potential” to have an adverse effect on the identity, strength, quality, purity, or potency of a vaccine.¹³ This submission was somewhat later than BioPort had originally planned; BioPort had hoped to be operational within a year of the purchase (by September 1999) and a supplement approval takes 6 months for the FDA to review.¹⁴ BioPort would have had to submit the supplement in March 1999, instead of in August, in order to deliver AVA by September 1999. A 4-month delay in the renovation process contributed to this slippage, according to officials at BioPort.

In November 1999, while reviewing the BioPort BLA supplement, the FDA conducted an on-site pre-approval inspection (PAI) of the renovated Lansing facility. The following month, BioPort was notified that the PAI had identified 30 problems. The formal notice of the results of the review came in the FDA’s response letter of 31 December 1999. This response cited 18 comments and questions that needed to be resolved before BioPort would be allowed to resume AVA distribution or testing of stockpiled AVA. That meant BioPort had to make a further BLA supplement submission, which would be followed by another PAI and formal response by the FDA. In

¹³ The relevant regulations are promulgated under Section 351 of the U.S. Public Health Service Act (42 USC 262), as amended by the Food and Drug Administration Modernization Act of 1997, and are found in Title 21 of *Code of Federal Regulations* (21 CFR 601.12). For changes under this category, an applicant is required to submit a supplement to the approved license application that includes a detailed description of the proposed change; the products involved; the manufacturing sites or areas affected; a description of the methods used and studies performed to evaluate the effect of the change on the product’s identity, strength, quality, purity, and potency as they may relate to its safety or effectiveness; the data derived from those studies; relevant validation protocols and data; and a reference list of relevant standard operating procedures.

¹⁴ According to Fuad El-Hibri, the goal was to be operational by September 1999. (Fuad El-Hibri, President and Chief Executive Officer, BioPort Corporation, Testimony before the Subcommittee on National Security, Veterans Affairs, and International Relations of the House Committee on Government Reform, 30 June 1999.)

March 2000, the DoD decided to issue a stop-work order on the 1998 AVA-production contract.¹⁵

Because of the supplement resubmission and ensuing FDA review, BioPort is not expected to receive FDA approval until May 2001 at the earliest. The more likely time frame for approval is early 2002. The estimated approval time is explored in more detail in the following section.

C. CURRENT STATUS

1. BioPort's Supplement Application

BioPort is planning to resubmit the final portion of its BLA supplement to the FDA on 22 January 2001. The FDA has indicated that it will expedite the review of BioPort's application and respond within 4 months. This timetable implies the *earliest* BioPort could receive approval to manufacture the vaccine is late May 2001. BioPort's problems in preparing the supplement and its plans to solve those problems are detailed below.

The FDA raised concerns in four areas of BioPort's BLA supplement: potency test, process validation, steam-in-place, and filling and packaging. In response to the FDA's concerns, BioPort created a Special AVA Initiative Program made up of approximately 40 people dedicated to solving the problems highlighted by the FDA. Having identified over 2,500 specific tasks that must be successfully completed to have the necessary conditions for FDA approval, BioPort has offered its employees monetary incentives tied to successful completion of these tasks. Progress on solutions is described below.

- **Potency test:** By far the most serious of the four problem areas, the potency test involves verifying that the vials of AVA have sufficient and consistent potency. The testing is conducted by BioPort and observed by an independent firm. Potency testing involves measuring the time to death of guinea pigs that have been immunized with different dilutions of vaccine and then exposed to virulent anthrax. The test is described in the FDA-approved product license. Before 1998, all lots of AVA released by the FDA had passed the same potency test. So far, the results of these tests are not consistent enough to establish a reliable measure of

¹⁵ Contract DAMD 17-98-C8052.

potency for the vaccine. BioPort's current estimate is that it will submit successful potency test results to the FDA by 19 December 2000.

- **Process validation:** Problems involve 35 protocols that must be submitted to the FDA. Twenty-six of these have already been completed. The remaining 9 will be submitted by 22 January 2001. The most serious of the final 9 protocols is the one associated with the potency test. (Since the problematic results from the potency testing could be due to either the design or the conduct of the test, both must be addressed.)
- **Steam-in-place:** Steam-in-place is a sterilization process. BioPort has hired a contractor to help implement a series of tasks to satisfy the FDA. BioPort plans to submit the sterilization process and test results to the FDA by 22 January 2001.
- **Filling and packaging:** Although the FDA did not find critical problems with this aspect of BioPort's operations, BioPort has implemented a plan to improve its filling and packaging facilities and estimates the 5-month effort will be completed in February 2001. At the same time, BioPort is pursuing the option of subcontracting the filling and packaging operations.¹⁶

2. Schedule

Figure 2 shows BioPort's latest timeline for submitting its BLA supplement. BioPort plans to break its BLA supplement submission into four components and to submit them to the FDA on three separate dates, as shown in the figure. The FDA has agreed to review BioPort's submission in an incremental fashion by taking 4 months to review each component. That means the FDA would conclude its review 4 months after the last component is received, accelerating the normal, statutorily imposed 6-month review process by 2 months.¹⁷ This implies the *earliest* BioPort could receive approval to manufacture the vaccine is late May 2001.¹⁸

¹⁶ Although the filling and packaging issues the FDA raised are not expected to cause a delay in the approval of the supplement, they may pose a serious long-term problem for BioPort. One industry expert told us that BioPort's filling and packaging facility is below industry standards.

¹⁷ Mark Elengold, Deputy Director, Operations, Center for Biologics Evaluation and Research (CBER), interview with the authors, 26 July 2000.

¹⁸ In a 30 August 2000 interview with Bascom Anthony, industry consultant and former FDA division director, we learned the statutory review time for an application response does not have to be contiguous. Although the FDA is statutorily bound to respond to a BLA supplement in 6 months, if it has a question about an application, it can issue a request for information. The review is then suspended until the applicant delivers a response. Because of these interruptions, the calendar time of a review is often longer than the official elapsed time. Our minimum time calculations assume no such interruptions; they should be construed simply as lower bounds and not as realistic estimates.

Task	Start Date	End Date	2000				2001						
			Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Relative Potency	8/8/00	12/19/00	██████████										
FDA Evaluation	12/20/00	4/10/01					██████████						
Contract F&P	8/8/00	1/15/01	██████████										
FDA Evaluation	1/16/01	5/16/01					██████████						
Process Validation	8/8/00	1/22/01	██████████										
FDA Evaluation	1/23/01	5/23/01					██████████						
Steam-in-place Modifications	8/8/00	1/22/01	██████████										
FDA Evaluation	1/23/01	5/23/01					██████████						

Source: Fax from the Joint Program Office for Biological Defense, 7 August 2000.

Figure 2. BioPort's BLA Supplement Timeline

It is important to note that BioPort officials told the study team that these estimates are optimistic and do not contain any margin for errors or failures. Later in this report, we discuss other data from independent sources that highlight how optimistic these schedules may be. We also present statistics from recent FDA submissions that suggest BioPort's chances of winning approval by May 2001 may be *less than* 50 percent.

3. Expected Time for BioPort To Gain FDA Approval

The FDA is reluctant to provide specific answers to hypothetical questions. FDA officials did tell us that BioPort had the technical capability to win FDA approval to produce and test AVA, but they could not guarantee a date by which approval would be granted. We consulted with industry experts and used FDA-approval statistics reported in the *U.S. Regulatory Reporter*¹⁹ to estimate the total calendar time before BioPort gains approval.²⁰

The *U.S. Regulatory Reporter* used BLA submissions and approval data from FY 1998 and FY 1999 to generalize about the time required to gain FDA approval. The overall average time required between a BLA submission and final BLA approval was 1.7 years. Because review of many applications is delayed due to questions that must be answered or deficiencies that must be corrected, the elapsed calendar time is longer than the statutory review time imposed on the FDA. The total time includes the time for a company to respond to questions or to resubmit an application in the case of an initial

¹⁹ *U.S. Regulatory Reporter*, Parexel International Corp., Waltham, Massachusetts, April 2000, pp. 7-8.

²⁰ Arthur Elliott, consultant, interview with the authors, 31 August 2000.

denial of approval. If an application is resubmitted after a failure to gain approval, as is the case with BioPort's 1999 supplement application, a new review cycle starts at the time of the resubmission.

Independently, we learned from the FDA that the review of a supplement application such as BioPort's would take 6 months. However, because of the expedited status of BioPort's supplement, the FDA offered to compress the review to 4 months by beginning the review as soon as BioPort completes any of its components. As Figure 2 shows, BioPort plans to submit its last increment to the FDA on 22 January 2001. A successful 4-month review with no interruptions for questions means that the earliest date for approval would be in late May 2001. To compare the BioPort experience so far with the industry average of 1.7 years, we must start counting from August 1999, the time of BioPort's first submission. Using the industry average, we would expect approval in April 2001. However, that date is unrealistic given the current status of BioPort's application, and indeed, history suggests something different.

4. History Suggests BioPort Will Not Gain Approval in 2001

The previously mentioned *U.S. Regulatory Reporter* article stated that only 31 percent of the applications that had failed for other than minor reasons on their first attempt at approval were approved during the second review. Since BioPort falls into the category of having major issues, it is reasonable to assume it will probably fail to gain approval by the end of the second review cycle (late May 2001). Therefore, a third review will likely be required.

We do not have statistics on the likelihood of gaining approval after a third submission. Industry experts told us the process of correcting deficiencies becomes easier since only the failed areas of the BLA must be resubmitted and reviewed. However, even if we add only one additional application and review cycle beginning in June 2001, including 6 months to prepare the resubmission (instead of the 13 months BioPort plans to spend preparing its second submission) and an additional 4-month FDA review, the approval date stretches to April 2002. Although some biologics approvals end up taking many years beyond their estimated schedules, an expected date that is 10 months beyond the most optimistic schedule is consistent with the estimates we obtained from industry officials and independent consultants (see Sources). Nevertheless, the most likely schedules we estimated should not be construed as the maximum possible time required for approval. We learned of several cases of biologics approvals that took many years

longer than planned or are still pending, not because of any fault of the applicants but because of the difficulty of the science required.

We spoke to industry consultants to gain perspective on the apparently longer-than-average time it is taking for BioPort to obtain approval for its BLA supplement. The consultant most familiar with the review of biologics cited three reasons why BioPort's situation would be expected to take longer than average.²¹

1. The main reason stems from the deadliness of bacillus anthracis (the bacteria that causes an anthrax infection). Because of the high cost of an error, in terms of either an ineffective vaccine or an unintentionally active vaccine (that could cause an infection), the FDA must be particularly thorough in every aspect of the submission.²² For this reason, we were told to assume that a BLA supplement in this situation would be at least as difficult to prepare and have approved as a new BLA. We therefore used new BLA statistics as baselines for comparison with BioPort's supplement application.
2. The second reason involves the history of the MBPI facility and the number of citations of deficiency previously issued by the FDA.²³ In reviewing any subsequent applications from a facility with a recent history of deficiencies, the FDA can be expected to be particularly thorough.
3. Related to the second reason is that the FDA has instituted a special team for the review of biologics since the previous approval for MBPI to produce AVA. Team Biologics, assembled only in the last few years, has a reputation for being extremely demanding and conservative in its inspections and reviews.²⁴

The same consultant's opinion about the expected time required to obtain approval for a supplement to an anthrax biologics license under the current conditions was consistent with the experience at BioPort. Whereas a routine application might take 4 to 6 months to prepare and 6 more months to review, the special circumstances surrounding the BioPort application

²¹ Ibid.

²² The strain of anthrax used to develop the vaccine is a mutation that is not dangerous to humans, so there is theoretically no such risk. FDA procedure requires that precautions still be taken, however. Also, guinea pigs are exposed to deadly anthrax to test the potency of each production lot of vaccine.

²³ These citations are known as "483s" because the FDA uses form number 483 to notify a company of deficiencies.

²⁴ Although it is not the same team that is approving BioPort's supplement application, Team Biologics will conduct a routine inspection within a year of supplement approval. Observers have pointed out that the appearance of Team Biologics, which was formed in late 1997 to address fatalities caused in the mid-1990s by contaminated blood albumen from an approved laboratory, has had the effect of increased standards in all of the FDA's biologics operations.

could easily mean a 2- or 3-year effort, according to this expert. Several sources, however, provided assurances that the process does converge and that BioPort clearly has the expertise and equipment to eventually gain approval.

5. DoD's Strategy

The current strategy consists of BioPort continuing to prepare a new BLA supplement to the FDA and the DoD providing both financial relief and technical assistance to augment that effort. The DoD has taken the following actions in hopes of helping BioPort gain FDA approval in mid-2001:²⁵

- granted extraordinary contract relief;²⁶
- hired The Quantic Group of Livingston, New Jersey, a consulting company that assists pharmaceutical companies to achieve satisfactory compliance with FDA requirements;
- hired Mitretek Systems of McLean, Virginia, to do supplemental vaccine lot testing; and
- placed additional government representatives at the Lansing facility.

The DoD is considering a plan that includes the construction of a new, government-owned, contractor-operated vaccine facility.²⁷ However, the new facility would not likely come on line until FY 2008 at the earliest.²⁸ While this new facility does not factor into

²⁵ In addition to these actions, the DoD has pursued some "hedging" actions such as requesting information on potential second manufacturing sources. More on the second sources is presented in Section E.3.

²⁶ In June 1999, BioPort formally requested extraordinary contract relief to fund operating expenses, ease cash flow shortages, and repay loans to the state of Michigan. The Defense Contract Audit Agency conducted several audits of BioPort and forwarded its results and recommendations to the DoD. BioPort was granted extraordinary contract relief, in accordance with Federal Acquisition Regulations and under Public Law 85-804, in the net amount of \$24.1 million via amendments to contract DAMD 17-98-C8052.

²⁷ This "Biological Defense Vaccine Production Facility" would produce not only anthrax vaccine but also several other vaccines to counter known or expected biological warfare threats. The facility under consideration would cost approximately \$420 million in FY 2002-07.

²⁸ The bacillus anthracis is a spore-forming organism and, under current practice, the vaccine must be manufactured in a dedicated facility. Building a new single-purpose anthrax vaccine production facility at a new site approved by the FDA would take at least 5 to 7 years and cost between \$70 million and \$100 million. (Fuad El-Hibri, president of BioPort, Testimony before the Subcommittee on National Security, Veterans Affairs, and International Relations of the House Committee on Government Reform, 30 June 1999.) Milan Blake of North American Vaccine, Inc., independently estimated the facility cost of a new biologics laboratory would be around \$50 million but added that the cost of the building and equipment alone is not the only investment required to start up a new facility. (Milan Blake, Senior Director, Molecular Biology and Protein Chemistry, North American Vaccine, Inc., Columbia, Maryland, interview with the authors, 21 August 2000.)

solving the near-term problem of resuming anthrax vaccine production as quickly as possible, it has some long-term implications that are discussed later in this report.

D. GOVERNMENT-OWNED, CONTRACTOR OPERATED (GOCO) FACILITIES

GOCO facilities are industrial facilities and equipment owned by the government and operated by a commercial activity under a government contract. The GOCO arrangement had its origins in World War II and continues today. For example, the U.S. Army has several ammunition plants operating as GOCO facilities and the Department of Energy uses GOCO arrangements for several of its laboratories.

As a general policy, the DoD tries to minimize government ownership of facilities and relies on private industry to provide and operate the facilities. However, in cases where private investment is inadequate or unavailable, where a viable commercial market for the product or service does not exist, where liability issues may pose difficulties for the private sector, and where there is a need to ensure product or service availability to meet essential peacetime, surge, and mobilization requirements, the government may choose to own the necessary facilities. Also, our research has not produced any examples of the case under study here, converting a contractor-owned, contractor-operated (COCO) facility to a GOCO.

1. Trend Is Away from GOCO Model

The rules governing the establishment and operation of GOCO facilities are fragmented and scattered among the Federal Acquisition Regulations, DoD Directives, and Service policy letters.²⁹ There is no single defining regulation or directive that enumerates the level of government involvement in GOCO operations or the exact contractual relationship between the government and the contractor. One can appreciate the need for ambiguity in such guidelines; the government requires a wide assortment of goods and services from a large number of private firms, and ambiguity allows the government flexibility to tailor arrangements to the specific product or supplying industry.

As a result of this ambiguity, we found that management involvement and oversight by the government varies by both agency and business circumstances. If we think of this

²⁹ The references to GOCO facilities are predominately found in Title 48 of the *Code of Federal Regulations*, Parts 27, 31, and 45, and in DoD Directive 4275.5, "Acquisition and Management of Industrial Resources," October 6, 1980.

variation as a continuum of GOCO arrangements, we find at one end of the continuum “virtual GOGOs” (government-owned, government-operated facilities), which are characterized by a high degree of government involvement in day-to-day activities. Examples of GOCO facilities with the greatest amount of government control include the Department of Energy laboratories and, until recently, the Army’s GOCO ammunition plants. The Army is now aggressively divesting itself of these GOCO facilities and is reducing its role in the operation of the remaining ones. For example, in 1997, the Army owned 24 GOCO ammunition plants. The Army plans to reduce that number to 11 within the next few years.

At the other end of the continuum, we find “virtual lease” arrangements, which are characterized by a low degree of government involvement in day-to-day activities. In this case, the contractor makes almost all the decisions concerning manufacturing processes, resource allocations, safety, and maintenance. The government’s role is one of making sure that the contractor is being a good steward of the facilities. The Air Force’s Industrial Plants are examples of this type of arrangement. As with the Army, the Air Force is divesting itself of the real property and related equipment at its GOCO facilities by selling eight of its twelve Air Force Industrial Plants.

What motivates the DoD strategy to transition ownership from the government to the private sector? There appear to be two primary motivations:

1. *Enhance efficiency of operations.* The commercial sector is perceived to be more efficient than government organizations in shedding unneeded workers, facilities, and equipment.
2. *Reduce government involvement, investment, and other potential costs and liabilities associated with a plant.* Examples of these liabilities include environmental remediation costs.

For these and other reasons, the trend is clearly away from the GOCO model and towards commercial ownership and operation.

2. Two GOCO Scenarios

We investigated two scenarios for converting the privately owned BioPort AVA production facility to a government-owned, contractor-operated facility. The timetables for the two scenarios were different enough to be studied and discussed separately. The two scenarios are as follows:

1. The DoD purchases the Lansing facility from the BioPort Corporation and selects a new contractor (i.e., not BioPort) to operate the facility through either a sole-source arrangement or an expedited competition.

2. The DoD purchases the Lansing facility from the BioPort Corporation and selects BioPort to run the facility.

While the second scenario seems questionable given that the outcome would closely resemble the current situation, it is possible that in competing the award to operate the facility, the BioPort Corporation (or an equivalent successor company employing the same key individuals) could win the contract. Also, employing BioPort in a GOCO arrangement would still enable the government to exercise the added control it desires relative to the current situation.³⁰ Because the license transfer could be quicker in this situation, we studied this potential outcome as a separate scenario. The next section discusses the process of converting BioPort's Lansing facility to government ownership. The section following that (Section F) explores the schedule, costs, and risks associated with installing a contractor to operate the facility.

E. CONVERTING THE LANSING FACILITY TO A GOCO

As noted in the preceding discussion, we found no example of a COCO having been converted to a GOCO. In the absence of relevant examples from which we could draw analogies, we conjectured about the necessary actions required to establish a GOCO at the Lansing facility. We drew upon an unpublished 1998 internal IDA document that studied the advantages and disadvantages of the GOCO arrangement as they pertain to DoD test and evaluation facilities such as weapons test ranges.³¹ We also searched for relevant government regulations and guidance on the topic.³² Further, we noted that Congress must approve federal purchases of major facilities, a process that can take from one to several years to complete. We assumed this process would occur in parallel with

³⁰ According to the program office, having the authority to proceed in a manner deemed most beneficial to the DoD would be the main advantage to owning the facility. (Winifrede Fanelli, Acting Director, Joint Program Office for Biological Defense, interview with the authors, 25 July 2000.)

³¹ "Background Paper, Government Owned, Contractor Operated (GOCO) Facilities," Institute for Defense Analyses, Draft, 3 February 1998.

³² An example discussion on the use of GOCO facilities appears in the Veterans Affairs regulations on acquisition planning, 807.304-70, which includes the following language: "Generally, a COCO operation, if it will provide adequate services and is contractually feasible, is the preferred contract option. COCO contracts eliminate the Government's risks and costs inherent in capital ownership. However, such benefits of COCO performance must be weighed against the potential benefits of GOCO performance, such as ease of quality assurance evaluation, effective use of existing facilities, and ease of converting to government performance [GOGO] if the need arises." Of these example benefits for a GOCO arrangement, only the issue of quality assurance could be argued to be a factor in the BioPort facility.

planning and negotiating for the sale. Given the high priority of the AVA program, we assumed congressional approval would occur before completion of the sale.

1. Purchasing BioPort

The first step to installing a GOCO operation at the Lansing facility would be the sale of the facility to the government. BioPort officials indicated they would entertain offers to buy the facility. What is a fair market value for BioPort's Lansing facility?

To answer that question, we first made the assumption that BioPort will gain FDA approval to manufacture AVA. Without the ability to obtain FDA approval, its value to the DoD is near zero. Although the purchase of BioPort becomes unnecessary once approval is granted, we assumed that BioPort's investors would only agree to a price that reflects the intrinsic value of its unique FDA license, even before production can be resumed.

If we assume BioPort will gain FDA approval, then its fair market value depends in large part on three key variables: fair market value of its assets, value of any outstanding liabilities, and the projected income from future vaccine sales. The relationship of these variables to the fair market value for BioPort can be depicted as an equation:

$$\text{market value} = \text{assets} - \text{liabilities} + \text{current value of the projected income from future sales.}$$

Assets and liabilities can be estimated using BioPort's financial statements. However, the value of any future sales of AVA is much more difficult to ascertain. We discuss the value of each of the three variables in turn, beginning with assets.

BioPort purchased the Lansing facility from the state of Michigan for \$25 million in 1998. At that time, independent appraisals conducted by the state of Michigan estimated the value of the facility to be between \$0 and \$10.5 million. As of the end of 1999, BioPort estimated the net book value (historical cost less depreciation) of its property, plant, and equipment to be \$8.4 million as of the end of 1999.³³

BioPort has incurred liabilities since it purchased the facility in 1998. Part of the extraordinary contract relief the DoD provided to BioPort was in the form of an interest-free advance of \$18.7 million. The relief package also included a reduction in the total

³³ Robert Kramer, Chief Operating Officer, BioPort Corporation, interview with the authors, 26 September 2000.

number of doses to be produced from 7.9 million to 4.6 million and an increase in the price per dose to \$10.64. BioPort used \$12.5 million of the advance to repay loans from the state of Michigan.³⁴ The remainder of the funds went to repay other outstanding debt obligations and to fund operations.

The advance made the DoD the primary lien holder of BioPort's assets. As of February 2000, BioPort had repaid nearly \$7.4 million of the advance payment.³⁵ However, due to continued cash shortages, the DoD refunded those payments to the company to fund operations. For the purpose of this estimate, we assumed that the majority of BioPort's creditors have been paid using funds from the advance payment. Since the DoD refunded all the company's payment, the value of the lien is effectively \$18.7 million, which exceeds BioPort's net book value by about \$10 million.

The last variable is the current value of the projected income from future sales of the vaccine. BioPort is optimistic that it will eventually be able to sell the AVA commercially and to other friendly governments (in both cases only with permission from the DoD). Because BioPort's estimates are based on company proprietary information, we independently estimated the value of BioPort's income from future vaccine sales. Our valuation was based on earnings. We estimated BioPort's potential annual earnings derived from DoD sales to be between \$3 million to \$4 million. Using the mid-point of this range and a multiple of 10 times earnings yields a valuation of \$35 million. We also assumed a small amount of vaccine sales other than to the DoD that net to \$1 million in earnings. Using a multiple of 10 times these non-DoD-derived earnings yields an additional valuation of \$10 million.³⁶ These calculations provide a \$45 million estimate of the current value of the projected income from future sales of the vaccine (\$35 million plus \$10 million). Substituting this number along with the assets and liabilities estimates into our simple valuation equation yields:

$$\$34.7 \text{ million} = \$8.4 \text{ million} - \$18.7 \text{ million} + \$45.0 \text{ million}.$$

³⁴ Office of the Inspector General, Department of Defense, "Contracting for Anthrax Vaccine," Report No. D-2000-105, 22 March 2000, p. i-ii.

³⁵ Robert Kramer, Chief Operating Officer, BioPort Corporation, interview with the authors, 3 August 2000.

³⁶ Although BioPort does have a rabies vaccine business, we assumed no future revenue from it. Production of the rabies vaccine has ceased and all resources are being devoted to the AVA product.

It would seem the DoD, dealing from a position of relative strength, could negotiate a purchase price close to \$35 million.³⁷ However, BioPort has a considerable strategic advantage: it holds the FDA AVA license. And, although the transfer of the license to another company is possible under the right circumstances, it is not clear that the license could be transferred to the government. The next subsection outlines the reasons the license transfer might prove to be difficult.

2. Transfer of License Is Not Assured

The FDA transfer of the AVA license is not assured if the facility is sold to another owner. The FDA does not permit its licenses to be bought or sold; however, the FDA will approve a license transfer (such as it did when BioPort bought MBPI) as long as it is satisfied that the new holder is qualified. A license is tied to a facility, the manufacturing process, and the key personnel involved. A significant change (“material impact” is the term the FDA uses) to one of these three elements requires FDA review and approval. There is no assurance that the FDA will find the personnel, processes, and experience of the new company to be sufficient to allow that company to hold the license.

One apparent advantage to operating the AVA-production facility as a GOCO would be so that the DoD could hold the license, thus enabling it to replace the contractor more easily. However, the FDA expressed reservations about the DoD holding the license. In discussions with the study team, the FDA cited two reasons. First, the FDA is concerned about the group actually producing the vaccine. The FDA wants the license holder to be the responsible party, the party that can be held liable for negligence. Under the GOCO scenario, it is the contractor’s personnel who would be making the vaccine, and must therefore hold the license, and not the government. The second reservation involves concern about the oversight and control of one federal department by another. The FDA is reluctant to oversee another federal department for the very fact that it might be put into the position of citing a federal official for violations. If the license were issued to the DoD, would the Secretary of Defense be the responsible party? While we

³⁷ This estimate was developed for cost-estimating purposes only and is not intended as an appraisal for business valuation purposes. The actual fair market value would only be determined at a specific point in time when a willing buyer (e.g., the government) and a willing seller (BioPort) agree on a mutually acceptable price. In this kind of bilateral monopoly situation (a single purchaser without competition buying from a monopolistic seller), the price is often more a matter of negotiating acumen than of economics.

acknowledged the FDA's concerns, there are examples of one federal agency successfully regulating other agencies (e.g., the Environmental Protection Agency over the DoD).

Considering these circumstances, the most favorable arrangement, from the DoD's perspective, would be to request that the FDA reissue the license to the contractor the DoD selects to operate the facility once the government takes title to the facility.³⁸ A license reissue would involve negotiations between the FDA and the new contractor. The FDA would review the new contractor's strategic plans for production processes, its modifications and upgrades to facilities, and the qualifications of its key personnel.

Clearly, the license transfer process could not begin until the new contractor is selected. Also, as part of the negotiations on the sale of the facility, the DoD and BioPort would have to come to an agreement about facility maintenance and the maintenance of a "warm" production base until the new contractor takes over. These issues are more complicated in the general case than in the 1998 takeover of the MBPI license and facility by BioPort. In that example, there were no material effects on the key personnel, process, or facility. (It was the renovation of the facility that triggered the need for further FDA review and approval.)

We estimated it would take from 4 to 6 months to complete the transfer of the license under the most optimistic conditions. We based this estimate on the transfer from MBPI to BioPort in 1998. In that case, many MBPI employees continued to work at the facility, including the key individuals needed to maintain continuing FDA approval to produce the vaccine. If however, key personnel decided not to join the new contractor, thus requiring a large number of new personnel to be hired, the license reissuance could take significantly longer than 6 months. Indeed, in the worst-case scenario, the assumption of BioPort's operations by another contractor could result in such significant changes that the FDA would require a new license to be obtained.

There is reason to believe the key BioPort employees might not join the new contractor. BioPort is a privately held company with 50 percent of the stock reserved for employees. BioPort uses stock options as a recruiting and retention tool. These economic

³⁸ Under the rules promulgated in the *Code of Federal Regulations* as published in the *Federal Register*, 20 October 1999, the actual series of events would require the FDA first to revoke BioPort's license (21 CFR 601.5, Revocation of License) and then to reissue that license to the new contractor (21 CFR 601.9, Licenses; reissuance).

incentives may not be as lucrative under a new regime. Also, the employees could profit from the sale of the facility to the government and decide to leave the company.

In our view, retention of key BioPort personnel depends on how commercial sales are handled. Based on our discussions with BioPort, we believe a government contract that allows BioPort to keep the profits from commercial sales would be a strong incentive for key personnel to remain with the company.

3. If Not BioPort, Who?

So far in this analysis, we assumed another contractor could be identified and brought under contract to operate the GOCO facility. Because of its experience with modern FDA requirements and inspections, a big-name pharmaceutical company (e.g., Merck & Company, Inc., or Pfizer, Inc.) might have the advantage of being able to obtain and maintain approvals more readily than the smaller BioPort, which is now having its first experience in these matters. However, our discussions with various industry trade groups, biologics manufacturers, and drug companies suggested getting a big-name pharmaceutical company to become involved in AVA research or production would be extremely difficult for several reasons. Among them are:

- The volume of business is too small. The steady-state demand for AVA could be as low as 3.4 million doses per year.³⁹ In comparison, commercially produced vaccines, such as those to protect against influenza or pertussis, are produced at a rate of millions of doses per *month*.
- A military contract to provide vaccine that has a limited commercial market would not be expected to produce the relatively high profit margins that other pharmaceutical products carry.
- Pharmaceutical companies expressed concern that the production of AVA could have the potential to open up all their facilities to international inspection under the 1972 Biological and Toxin Weapons Convention (BTWC).⁴⁰ There is no explicit provision for on-site inspection under BTWC; however, the pharmaceutical firms were concerned that there could be such

³⁹ This is the estimate of the Joint Program Office for Biological Defense. The same source indicated that the steady-state production capacity of the Lansing facility (assuming one 8-hour shift, 5 days a week) would be about 5.4 million doses per year.

⁴⁰ "The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction," signed at London, Moscow, and Washington, DC, 10 April 1972.

inspections in the future.⁴¹ They were fearful that these inspections could make them vulnerable to industrial espionage.

- The potential liability associated with AVA production may affect the cost of company insurance and self-insurance.

We can get a good idea of the number, size, and experience of firms that would most likely respond to the GOCO contract competition from the results of a request the Joint Program Office for Biological Defense issued in *Commerce Business Daily*.⁴² The announcement solicited sources to establish a second source for the manufacture of the AVA. Specifically, the announcement sought: knowledge of good manufacturing practices and FDA regulatory requirements, experience in working with Bio-Safety Level-3 material, and availability of a compliant facility.

Five firms responded to the announcement, two of which were foreign. All five represented themselves as having knowledge of good manufacturing practices and FDA regulatory requirements. Four of the five stated they had experience with handling Bio-Safety Level-3 material, and one of the five (one of the foreign firms) had experience with anthrax vaccine production. All five were relatively small firms, certainly not big-name pharmaceutical companies.

F. HIRING A CONTRACTOR TO OPERATE THE GOCO

Once the government owns the Lansing AVA production facility, a contract would be negotiated with a firm to continue its operation. We investigated two scenarios because of the difference in the estimated delay each would add to the availability of AVA to the DoD. The first scenario involves hiring a contractor other than BioPort to operate the facility. The second scenario involves hiring BioPort to continue to operate the facility. The second scenario closely resembles the current situation, but it could allow the government to exercise more control over the operational decisions being made.

The following subsections contain the schedule and cost estimates for the current strategy and the two contractor scenarios. In all cases, we computed a most optimistic schedule and cost and a most likely schedule and cost. All options are shown to begin on 1 September 2000 and are compared either on the basis of their most optimistic schedules

⁴¹ "A BTWC Protocol: European Union Common Position," 17 May 1999, calls for the establishment of an ad hoc group to develop a verification regime for the BTWC.

⁴² *Commerce Business Daily*, 5 July 2000.

or their most likely schedules. Because we used data proprietary to BioPort to estimate the costs of the various schedules, explanations of how we derived the cost estimates are contained in an appendix that appears in a separate, proprietary volume.

1. Schedule and Cost Estimates for the Current Strategy

We used estimates of the schedules and costs associated with the current strategy as baselines against which other estimates could be compared. Figures 3 and 4 show the baseline schedules for the most optimistic and the most likely outcomes, respectively. The extra time for the most likely schedule allows additional preparation time for the BLA supplement and FDA review, as discussed in Section C.4. We estimated the cost of the schedules to be \$31.5 million (most optimistic) and \$66.5 million (most likely).

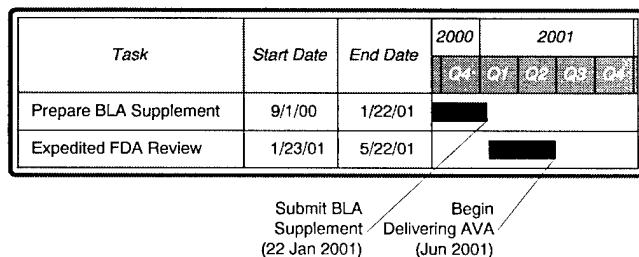


Figure 3. Most Optimistic Schedule with the Current Strategy

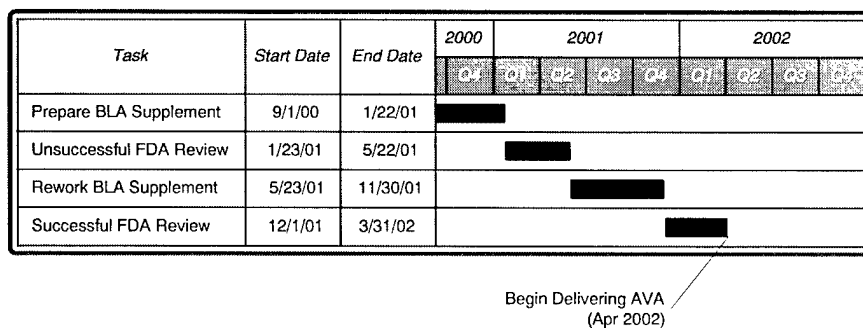


Figure 4. Most Likely Schedule with the Current Strategy

2. Schedule and Cost Estimates for a New Contractor

This subsection presents estimates of the schedule and cost associated with the GOCO option requiring the selection of a new contractor. Figures 5 and 6 depict the most optimistic and most likely schedules for this GOCO option. The same facts and assumptions presented in the previous subsection apply.

Task	Start Date	End Date	2000	2001				2002				2003			
			Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Purchase facility/ select new contractor	9/1/00	6/30/01	██████████												
New contractor start-up	7/1/01	8/31/01					████								
Negotiate with FDA to transfer license	9/1/01	12/31/01					██████								
Prepare BLA supplement	1/1/02	10/31/02					██████████								
Expedited FDA review	11/1/02	2/28/03									████				

Begin Delivering AVA
(Mar 2003)

Figure 5. Most Optimistic Schedule with a New Contractor

Task	Start Date	End Date	2000	2001				2002				2003				2004			
			Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Purchase facility/ negotiate new contract	9/1/00	6/30/01	██████████																
New contractor start-up	7/1/01	8/31/01					████												
Negotiate with FDA to transfer license	9/1/01	2/28/02					██████												
Prepare BLA supplement	3/1/02	2/28/03					██████████												
Typical FDA review (including questions)	3/1/03	10/31/04									██████████								

Begin Delivering AVA
(Nov 2004)

Figure 6. Most Likely Schedule with a New Contractor

For a new contractor to take over the Lansing facility under a GOCO arrangement, the DoD must take the following three steps: (1) negotiate a contract with the BioPort Corporation to purchase the facility; (2) select a contractor to run the facility; (3) negotiate a contract with the new contractor to operate the facility. We made no distinction in our schedule estimate as to whether the contract to purchase the facility would be competed or awarded on a sole-source basis.

We believe these three initial events could be completed in 10 months, assuming a new contractor could be identified and brought under contract in time. We assumed negotiations with BioPort and the new contractor would proceed in parallel. We estimated an additional 2-month start-up time for the new contractor to move into the facility before full operations begin, for a total of 12 months to install a new contractor in the Lansing facility. We did not vary our estimate for this initial period between our most optimistic and most likely schedules, as shown in Figures 5 and 6. The largest risk factor, which could be a considerable one, is the ability to identify a qualified new contractor. A

more pessimistic estimate about the time required to identify a new contractor would lengthen the first line in Figure 6.

The costs for this period include the ramp-down of BioPort's involvement and the transfer of its corporate knowledge to the new contractor, the price of the facility, and the ramp-up period for the new contractor. We assumed BioPort would taper off its efforts over the 10-month period just discussed.

We used a purchase price for the facility of \$35 million and assumed the new contractor will have a ramp-up period of 2 months. We added the ramp-up time because no other contractor has experience with BioPort's technology and the AVA production and testing processes, and the DoD would have to fund this transfer of knowledge.

The FDA approval period following the new contractor start-up is where the most likely schedule differs from the most optimistic one. We assumed the initial step of obtaining the license transfer would require a minimum of 4 months but most likely 6 months. We then assumed that it will take a minimum of 10 months but most likely 12 months to prepare another BLA supplement for the FDA to review. To arrive at these figures, we reduced somewhat the 13 months it is taking BioPort to prepare its submission because of the knowledge BioPort has acquired about the process and FDA expectations. Finally, in the most optimistic schedule, we showed the expedited review time of 4 months for FDA to review the submission and to approve the new contractor for production. In the most likely schedule, we used the industry average for a new BLA submission of 1.7 years. This might seem excessive since only a BLA supplement is required and a significant amount of work has already been done. However, we wanted to avoid repeating the mistake of using best-case assumptions, as has been done to develop previous cost and schedule estimates for this program. We had data that support the 1.7-year assumption, and the present experience at BioPort is consistent with that data.

Under this scenario, the DoD would incur costs over and above the costs under the current strategy. We estimated the cost to achieve FDA approval under the most optimistic schedule using the GOCO option with a new contractor to be \$95 million more than the cost of the most optimistic schedule with the current strategy. We estimated \$35 million of that cost would be to purchase the BioPort facility. The remainder involves paying BioPort to maintain a warm production base, ramping up the new contractor, and paying the new contractor's costs for the estimated 18 months it will take for them to obtain the license transfer and achieve FDA approval to produce the vaccine. The estimated cost to the DoD under the most likely scenario is \$130 million more than the most likely estimate with the current strategy.

3. Schedule and Cost Estimates for Re-hiring BioPort

Under this scenario, the DoD purchases the Lansing facility from the BioPort Corporation and selects BioPort to run the facility.⁴³ We made no distinction in our schedule estimate as to whether the contract would be competed or awarded on a sole-source basis. BioPort and the DoD would need to negotiate a contract to sell the facility as well as a contract to operate the facility. We assumed this series of events could be completed concurrently in 10 months. The same considerations detailed in Section E.1 about reaching a mutually acceptable purchase price between the government and BioPort also hold for this scenario. We also assumed BioPort rather than the DoD would hold the license under this scenario. We see no distinction between this scenario and the scenario with a new contractor as it pertains to the FDA's reticence to issue the license to the DoD.

We assumed this option would cause a minimum of a 2-month delay in preparing the BLA supplement. Thus, we estimated the final segment of the application would be sent to the FDA in late March 2001, instead of late January 2001, as previously represented in the most optimistic schedule. That, in turn, would mean the earliest possible date for approval would slip to late July 2001. Figure 7 illustrates the minimum time for the most optimistic case. We estimated costs would be \$73.5 million, \$42 million more than the most optimistic case with the current strategy.

Task	Start Date	End Date	2000		2001		
			Q4	Q1	Q2	Q3	Q4
Purchase facility/ negotiate new contract	9/1/00	6/29/01	■	■	■	■	■
Prepare BLA supplement	11/1/00	3/30/01	■	■	■	■	■
Expedited FDA review	4/1/01	8/1/01			■	■	■

Begin Delivering AVA
(Aug 2001)

Figure 7. Most Optimistic Schedule with the Same Contractor

⁴³ We did not distinguish between the present BioPort Corporation and a new company that includes the key individuals required, in the FDA's view, to maintain uninterrupted ownership of the AVA production license. The main distinction for purposes of estimation between this option and the previous option is the time saved by not having to transfer the license or corporate knowledge to a new group of individuals.

Because this scenario involves the least deviation from the current status, we added only a small time penalty to estimate the most likely schedule. Figure 8 presents our estimated timeline for this scenario. We estimated costs to total \$122.5 million, \$56 million more than the most likely schedule with the current strategy.

Figure 8 reflects an additional 4-month delay in the preparation of the BLA supplement over the most likely estimate for the current strategy. We added the 4 additional months to allow for the adverse effects the sale would have on personnel turnover and task schedules. We noted earlier that more than 2,500 individual tasks are being tracked as components of the process to obtain FDA approval. The changes in personnel that could result from the company’s uncertain future will mean significant lost time from the loss of corporate knowledge, initiation of new employees, and repetition of tasks.

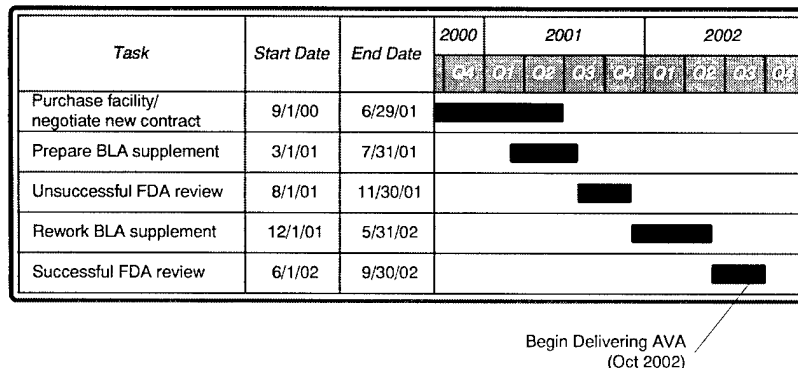


Figure 8. Most Likely Schedule with the Same Contractor

It could be argued that this scenario provides the DoD with complete control of the production of the vaccine for the least additional time and effort. However, BioPort would still be the facility operator and license holder. Having the government as the landlord does little to help solve the major issues involving the vaccine’s potency and the manufacturing process. In fact, the loss of personnel and experience that could occur during the upheaval could adversely affect the situation.

Another hypothesis is that by owning the facility, the DoD would have more leverage over BioPort than it does now. This line of reasoning suggests that the DoD would be in a better position to terminate BioPort and bring another contractor onboard if BioPort falters. However, we question the logic behind this hypothesis. First, the DoD already exercises significant influence with BioPort through its contract oversight, on-site presence, and DoD-paid consultants working in the BioPort organization. The DoD is BioPort’s only customer at this time and for the prospective future. As discussed in the

previous subsection, bringing on a new contractor involves delays. We estimated that switching contractors would delay the process by 12 to 18 months, even if the FDA allowed the license to be transferred again. What the DoD does get is the additional responsibility for any risk, such as environmental or liability issues that attend to the ownership of the facility.

Finally, under both GOCO scenarios, the DoD is making an investment in a facility and process that will most likely be rendered obsolete by the end of the decade. The DoD is considering a multi-faceted, state-of-the-art, vaccine-production facility at a new site for the future. This facility would make several different products. With regard to AVA, the new facility would most likely employ a direct antigen-development process using recombinant technology to produce the vaccine. One expert described this process as the "way of the future" and the method in which the DoD should be investing.⁴⁴ However, according to another expert, it might take another 10 years to fully develop this alternate vaccine, which has been known for over 10 years, into a safe and effective product.⁴⁵

G. SUMMARY OF FINDINGS

The major finding of this study is that neither GOCO arrangement is likely to get the anthrax vaccine to U.S. troops faster than the current COCO strategy. With the current strategy, BioPort would continue to prepare a new BLA supplement and the DoD would provide both financial relief and technical assistance. Under the current strategy, the earliest BioPort could obtain FDA approval is late May 2001. However, data on recent BLA submissions suggest BioPort has only a one-in-three chance of passing the impending FDA review. If a third review is required, the approval date could stretch to April 2002. We consider this the more likely approval date.

Under the GOCO scenario with a new contractor, 2003 would be the earliest the FDA could grant approval. A more likely date would be late 2004. The other option, with BioPort remaining as the operator of the facility, could impose a small time penalty relative to the current strategy. We estimated this penalty to be a minimum of 2 months,

⁴⁴ Milan Blake, Senior Director, Molecular Biology and Protein Chemistry, North American Vaccine, Inc., Columbia, Maryland, interview with the authors, 21 August 2000.

⁴⁵ James Kenimer, consultant, Biologics Consulting Group, interview with the authors, 1 September 2000.

but with high risks associated with it. Because of personnel turnover that might occur, we estimated this option would more likely add 6 months to the current strategy schedule. This option would resemble the current situation with BioPort still conducting day-to-day operations, but the government would have paid a price to own the facility.

While the time delay associated with the GOCO options is the most important factor relative to the DoD’s goal of resuming vaccine production as quickly as possible, it is not the only drawback. Under the GOCO scenarios, the DoD would likely not hold the AVA license but would assume the environmental liabilities associated with the facility. If and when a new government facility to produce vaccine becomes operational, this scenario would further require the government to dispose of an obsolete Bio-Safety Level-3 facility, an expensive and difficult process. These are some of the many reasons that the trend in the DoD is to move away from the GOCO model.

The advantages and disadvantages associated with the current strategy and both GOCO options are shown in Table 1.

Table 1. Comparison of Advantages and Disadvantages

	Option		
	Current Strategy	GOCO (New Contractor)	GOCO (BioPort)
Advantages	BioPort has the technical ability to win FDA approval to produce, test, and distribute AVA	DoD gains some additional control	DoD gains some additional control
Disadvantages	DoD does not have total control	<p>DoD still does not have total control because it would not hold the license</p> <p>DoD is not likely to attract a big name pharmaceutical firm to operate the facility</p> <p>Agreeing to a price could be difficult</p> <p>In a few years, DoD would own an obsolete, hazardous plant</p> <p>Retention of key personnel becomes a concern</p> <p>DoD assumes many risks and liabilities from being responsible for production and distribution of biologics products</p>	<p>DoD still does not have total control because it would not hold the license</p> <p>Outcome is almost identical to the current strategy</p> <p>Agreeing to a price could be difficult</p> <p>In a few years, DoD would own an obsolete, hazardous plant</p> <p>Departure of key personnel could endanger the license</p> <p>DoD assumes many risks and liabilities from being responsible for production and distribution of biologics products</p>

We estimated the cost of achieving FDA approval under the GOCO option with a new contractor to be at least \$95 million and more likely \$130 million more than the current strategy. These are costs to the DoD only and include the cost to purchase the BioPort facility. The remainder involves paying BioPort to maintain a warm production base, ramping up the new contractor, and paying the new contractor's costs for the estimated 1.7 years it will take for it to achieve FDA approval to produce the vaccine. We estimated the cost of achieving FDA approval under the GOCO-BioPort option to be at least \$42 million and more likely \$56 million more than the current strategy.

Table 2 summarizes our estimates of both the earliest and most likely dates the vaccine could become available for the current strategy and both GOCO options. It also lists the additional cost of the GOCO options over the current strategy cost.

Table 2. Schedule and Cost Comparisons

Option	Most Optimistic Schedule		Most Likely Schedule	
	Date of AVA Availability	Additional Cost (millions)	Date of AVA Availability	Additional Cost (millions)
Current Strategy	June 2001	—	April 2002	—
GOCO—New Contractor	March 2003	\$95	November 2004	\$130
GOCO—BioPort	August 2001	\$42	October 2002	\$56

SOURCES

The study team conducted a number of interviews in the course of the research. Listed below are the names and affiliations (and where important, the location) of the people we interviewed.

BioPort Corporation

El-Hibri, Faud, President and Chief Executive Officer
Johnson-Leva, Renita, Vice President, Regulatory Affairs
Kramer, Robert, Chief Operating Officer
Myers, Robert, Chief Scientist
Mocca, Lou, Program Manager
Schiller, Fred, Manager of Engineering

Department of Defense

Fanelli, Winifrede, Acting Director, Joint Program Office for Biological Defense.
Johnson-Winegar, Anna, Deputy Assistant to Secretary of Defense (Chemical-Biological Defense).
Kinney, Van, Office of the Under Secretary of Defense (Acquisition, Technology and Logistics).
Larsen, Douglas, Office of the Secretary of Defense General Counsel.
Lennon, Peter, Office of the Under Secretary of Defense (Acquisition, Technology and Logistics).
McKamey, Verne, Office of the Under Secretary of Defense (Acquisition, Technology and Logistics).
Moses, Lt. Col. Terry, Defense Contract Management Agency, Lansing, Michigan.
Nemetz, Robert, Office of the Under Secretary of Defense (Acquisition, Technology and Logistics).
Pieper, Joseph, Army Procurement Industrial Base Policy.
Randolph, Col. Gaston, Anthrax Vaccine Immunization Program Agency.
Selfridge, Lynn, Contracting Office, Fort Detrick, Maryland.
Wakefield, Larry, Joint Program Office, Lansing, Michigan.
Winchester, Jay, Army Legal Counsel, Fort Detrick, Maryland.

Food and Drug Administration

Elengold, Mark, Deputy Director, Operations, Center for Biologics Evaluation and Research.

Pharmaceutical Industry

Anthony, Bascom, consultant, former Director of the Division of Bacterial Products, Food and Drug Administration.

Blake, Milan, Senior Director, Molecular Biology and Protein Chemistry, North American Vaccine, Inc.

Director, Regulatory Affairs, a mid-size pharmaceutical company (anonymity requested).

Elliott, Arthur, consultant, former chief operating official North American Vaccine, Inc., also formerly with Merck, Inc.

Kenimer, James, consultant, Biologics Consulting Group, Alexandria, Virginia.

Richards, Melissa, Pharmaceutical Research and Manufacturers Association.

ABBREVIATIONS

AVA	anthrax vaccine adsorbed
BLA	Biologics License Application
BTWC	Biological and Toxin Weapons Convention
COCO	contractor-owned, contractor-operated
DoD	Department of Defense
FDA	Food and Drug Administration
GOCO	government-owned, contractor-operated
GOGO	government-owned, government-operated
IDA	Institute for Defense Analyses
MBPI	Michigan Biologic Products Institute
PAI	pre-approval inspection

UNCLASSIFIED

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 2220-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE October 2000	3. REPORT TYPE AND DATES COVERED Final Report, Jul 2000-Oct 2000	
4. TITLE AND SUBTITLE "Resuming Production of the Anthrax Vaccine as Quickly as Possible: Analysis of Alternative Business Arrangements," Volume 1: Main Report			5. FUNDING NUMBERS DASW01 98 C 0067	
6. AUTHOR(S) Thomas P. Frazier, Maria Borga, John W. Bailey, Alec W. Salerno, John J. Cloos, and Julia Klare Burr, with the assistance of Richard A. Rettig of RAND			AO-7-1929	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Institute for Defense Analyses 1801 N. Beauregard Street Alexandria, VA 22311-1772			8. PERFORMING ORGANIZATION REPORT NUMBER IDA Paper P-3553, Vol. 1	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Mr. Peter Lennon OUSD(AT&L)/Acquisition Resources and Analysis Room 3D161, Pentagon Washington, DC 20301			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12A. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited.			12B. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) A series of technical problems has delayed FDA approval for BioPort Corporation to deliver anthrax vaccine adsorbed (AVA) to the DoD. BioPort is preparing for a new FDA review, and the DoD is providing both financial relief and technical assistance to augment BioPort's efforts. Under this strategy, the earliest BioPort could gain FDA approval and resume AVA delivery is late May 2001. A more realistic expectation is delivery in the first half of 2002. IDA and the RAND Corporation studied the advantages and disadvantages of the DoD purchasing BioPort's Lansing, Michigan, AVA-production facility and converting it to a government-owned, contractor-operated (GOCO) operation. In one scenario, the DoD would select a new company to run the facility; in another, the DoD would have BioPort run the facility. We found that neither option would result in vaccine being delivered faster than under the current strategy. Under the first GOCO scenario, the earliest AVA could be delivered would be 2003 (more probably late 2004). Under the second scenario, the earliest delivery date would be August 2001 (more probably late 2002). This report is the first of two volumes.				
14. SUBJECT TERMS Government Owned Contractor Operated (GOCO); BioPort Corporation; Anthrax; Vaccines			15. NUMBER OF PAGES 46	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)

Prescribed by ANSI Std. Z39-18

298-102

UNCLASSIFIED