



October 6th, 2009

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Re: Final Report (DARPA Cooperative Agreement HR0011-07-2-0003)

Ladies and Gentlemen:

On behalf of the University of Pittsburgh Medical Center (UPMC), please find the attached copy of UPMC's final technical report entitled: *Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government: A Summary of Key Findings and Conclusions*. This report has passed the Department of Defense's security review process and is approved for public release; distribution unlimited. Submittal of the final report completes UPMC's work under the above-referenced Cooperative Agreement.

If you have any questions, please contact me at 202-719-1053 or at bairdac@upmc.edu.

Sincerely,

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Report Documentation Page

Form Approved
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| | | | | | |
|--|------------------------------------|-------------------------------------|---|--|---------------------------------|
| 1. REPORT DATE 06 OCT 2009 | | 2. REPORT TYPE N/A | | 3. DATES COVERED | |
| 4. TITLE AND SUBTITLE Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government: A Summary of Key Findings and Conclusions | | | | 5a. CONTRACT NUMBER | |
| | | | | 5b. GRANT NUMBER | |
| | | | | 5c. PROGRAM ELEMENT NUMBER | |
| 6. AUTHOR(S) | | | | 5d. PROJECT NUMBER | |
| | | | | 5e. TASK NUMBER | |
| | | | | 5f. WORK UNIT NUMBER | |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Pittsburgh Medical Center | | | | 8. PERFORMING ORGANIZATION REPORT NUMBER | |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) | | | | 10. SPONSOR/MONITOR'S ACRONYM(S) | |
| | | | | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) | |
| 12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited. | | | | | |
| 13. SUPPLEMENTARY NOTES | | | | | |
| 14. ABSTRACT | | | | | |
| 15. SUBJECT TERMS | | | | | |
| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT UU | 18. NUMBER OF PAGES 179 | 19a. NAME OF RESPONSIBLE PERSON |
| a. REPORT unclassified | b. ABSTRACT unclassified | c. THIS PAGE unclassified | | | |



UPMC | University of Pittsburgh
Medical Center

Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government: A Summary of Key Findings and Conclusions

**Cooperative Agreement Research Study between
Defense Advanced Research Projects Agency (DARPA)
and University of Pittsburgh Medical Center (UPMC),
July 2007 – March 2009**

**BAA 06-19, Cooperative Agreement
HR0011-07-2-0003**

The views, opinions, and/or findings contained in this paper are those of the authors and should not be interpreted as representing the official views or policies, either expressed or implied, of the Defense Advanced Research Projects Agency or the Department of Defense.

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Abbreviations & Acronyms

| | |
|-----------|--|
| ASEAN | Association of Southeast Asian Nations |
| BAA | Broad Agency Announcement |
| BARDA | Biomedical Advanced Research and Development Authority |
| BDS | Bulk Drug Substance |
| BLA | Biologics License Application |
| BSL | Biosafety Level |
| BU | Boston University |
| CBER | Center for Biologic Evaluation and Research |
| CBMS | Chemical Biological Medical Systems |
| CBRN | Chemical, Biological, Radiological and Nuclear |
| CDC | Centers for Disease Control and Prevention |
| cGMP | Current Good Manufacturing Practice |
| CIA | Central Intelligence Agency |
| CMO | Contract Manufacturing Organization |
| COCO | Contractor-Owned, Contractor-Operated |
| CRADA | Cooperative Research and Development Agreement |
| CRISP | Computer Retrieval Information on Scientific Projects |
| DARPA | Defense Advanced Research Projects Agency |
| DCA | Demand Capacity Assessment |
| DHS | Department of Homeland Security |
| DoD | Department of Defense |
| DOE | Department of Energy |
| DTRA | Defense Threat Reduction Agency |
| EUA | Emergency Use Authorization |
| FAR | Federal Acquisition Rules |
| FDA | Food and Drug Administration |
| FFRDC | Federally Funded Research and Development Center |
| GAO | Government Accountability Office |
| GE | General Electric |
| GMP | Good Manufacturing Practice |
| GOCO | Government-Owned, Contractor-Operated |
| GOGO | Government-Owned, Government-Operated |
| GSA | General Services Administration |
| HHS | Department of Health and Human Services |
| HLCD | High Level Capability Design |
| IND | Investigational New Drug |
| IP | Intellectual Property |
| JPEO-CBMS | Joint Program Executive Office for Chemical Biological Medical Systems |
| JRO | Joint Requirements Office |
| JRO-CBRN | Joint Requirements Office for Chemical, Biological, Radiological and Nuclear Defense |
| JSTO-CBD | Joint Science and Technology Office for Chemical and Biological Defense |
| MCM | Medical Countermeasure |
| Mfg FFRDC | Manufacturing Federally Funded Research and |

| | |
|----------------|--|
| | Development Center |
| MOU | Memorandum of Understanding |
| MTA | Material Threat Assessment |
| MTD | Material Threat Determination |
| NASA | National Aeronautics and Space Administration |
| NATO | North Atlantic Treaty Organization |
| NBL | National Biocontainment Laboratory |
| NEIDL | National Emerging Infectious Disease Laboratories |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NPO | Nonprofit Organization |
| OPM | Office of Personnel Management |
| PAHPA | Pandemic and All Hazards Preparedness Act |
| PATH MVI | Program for Appropriate Technology in Health Malaria Vaccine Initiative |
| PRV | Priority Review Vouchers |
| PTA | Population Threat Assessment |
| R&D | Research and Development |
| RBL | Regional Biocontainment Laboratory |
| RCE | Regional Center of Excellence |
| RFP | Request for Proposal |
| rPa | Recombinant Protective Antigen |
| rProtein | Recombinant Protein |
| R _x | Therapeutic |
| S&T | Science and Technology |
| SEB | Staphylococcal Enterotoxin B |
| SIP | Special Immunization Program |
| TFF | Tangential Flow Filtration |
| UPMC | University of Pittsburgh Medical Center |
| USAMRIID | U.S. Army Medical Research Institute of Infectious Diseases |
| USG | United States Government |
| VPF | Vaccine Production Facility |
| VRC | Vaccine Research Center |
| V _x | Vaccine |
| WHO | World Health Organization |

Demand Capacity Assessment, High Level Capability Design, Operating Model: Executive Summary

Medical countermeasures (MCMs) are urgently needed to protect military and civilian populations against a chemical, biological, radiological, and nuclear (CBRN) attack and naturally occurring outbreaks of emerging infectious diseases. However, the United States Government (USG) does not have the capability to rapidly develop, license, and manufacture MCMs and many USG requirements for MCMs remain unmet.

Ensuring the rapid development, licensure, and cost-effective production of MCMs — especially biologics¹-based vaccines and therapeutics,— is crucial to building a balanced portfolio of MCMs at the Department of Defense (DoD) and the Department of Health and Human Services (HHS) to protect national security and public health. Consequently, the Defense Advanced Research Projects Agency (DARPA) entered into a cooperative agreement with the University of Pittsburgh Medical Center (UPMC) to study the best means for creating and sustaining this critical capability.²

At the request of DoD and in coordination with HHS, the UPMC study examined the scientific advantages, technical feasibility, and economic savings related to building a centralized capability for advanced development and manufacture of MCMs to support the approximately 80 biodefense innovators (biotechnology companies, academia, and research & development [R&D] labs) currently funded by DoD and HHS. To this end, the study first determined current USG demand for biologics manufacturing and identified the collective strengths and weaknesses of the current MCM development and acquisition model as articulated in interviews with multiple interagency and industry experts. The study then examined ways in which to leverage advances in biomanufacturing technology and regulatory guidelines for flexible manufacturing and combine advance development and production of biologics in a multi-product facility focused on satisfying USG needs. Finally, the study identified various operating models for structuring the capability and managing its operations.

Demand Capacity Assessment (DCA)

To assess the MCM needs of both DoD and HHS, an extensive survey was conducted. This included a review of all published requirements, the biodefense R&D portfolio, and stated requirements of USG organizations, and interviews of over 40 experts from various agencies throughout the USG. Together, DoD and HHS have requirements for 17 biologic MCMs to counter CBRN threats. Of these, DoD and HHS have joint requirements for eight products specific to shared threats. Additionally, DoD has specific requirements for seven products in small quantities when compared to drugs produced commercially. Similarly, HHS has two unique requirements for a much larger number of doses, when compared to DoD requirements.

A major challenge facing the development and procurement of MCMs is the need for a warm- base operation and ability to respond to new threats or attacks. Because biologic MCMs are extremely complex to produce, the FDA typically requires that at least one batch per year of each MCM be successfully manufactured in order to maintain the license to procure the MCM.

¹ Biologics are a class of vaccines and drugs that are produced by bacteria and other living organisms. Biologics are difficult to manufacture and are heavily regulated by the Food and Drug Administration (FDA). Biologics form the bulk of government-required MCMs currently under development and are the focus of the UPMC study.

² *Ensuring Biologics Manufacturing Capacity for DoD*, Defense Advanced Research Projects Agency Cooperative Agreement No. HR0011-07-2-0003 [hereinafter the *UPMC study*].

Current procurement by the USG has not fully addressed this need to sustain the ability to manufacture even current MCMs over the long term. In addition, current demand is based solely on current threats facing the USG. As new threats emerge, the demand for MCMs will rise accordingly. When this occurs, a manufacturing facility must have the ability to “surge” production levels of MCMs designed to meet the new threats. A flexible capability able to produce multiple products would have unique advantages over the current system in meeting this surge requirement.

High Level Capacity Design (HLCD)

The HLCD examines the attributes that a facility must have to conduct advanced development and manufacture of the MCMs described in the DCA. Although there are 17 different biologic MCMs listed in the DCA, their manufacture requires only approximately seven core production technologies. Core production technologies are standardized ways of producing a biologic MCM, e.g., growing a recombinant protein in *E. coli*. Incorporation of these core production technologies in a flexible, multi-product manufacturing facility could reduce cost and other constraints by creating the ability to produce MCMs for both stockpiling and surge production.

Recent technological advances in disposable manufacturing equipment and changes to the regulatory environment greatly facilitate the implementation of a multi-product capability by reducing the overall capital costs and time necessary to change over from one product to another. An analysis of the production methods and yields to fulfill USG MCM demand suggests that a facility resembling current pilot scale facilities in the commercial biopharmaceutical sector (e.g., 2,000 liter microbial reactors and 400 liter cell culture reactors) could fulfill the demand with eight dedicated manufacturing “suites.” Each suite would be composed of approximately three segregated rooms that would allow the growth of cells to generate the active ingredient along with space to purify the material to final bulk drug product, ready for fill, package, and finish. (Filling, packaging and finishing capabilities were outside the scope of the UPMC study and therefore not examined.)

Ultimately, the facility should be viewed as a prototype for a multi-product approach to MCM production for the USG. More than one facility may be required to provide redundancy and flexibility in MCM manufacture as USG demand changes or grows and new MCMs are added to the portfolio.

Operating Model

A successful operating model for a flexible multi-product facility is based on its operations, the resources required to perform those operations, and the public and private partners necessary to provide those resources. A dedicated capability’s operations must focus on functional areas that are highly specialized for advanced development and manufacture of MCMs and strategically aligned with the capability’s mission. The key resources needed to perform these operations can be grouped as management, technical expertise, products, and financing. Neither the USG nor private industry can provide these resources alone; rather, it requires a combination of both.

To fulfill its mission, a dedicated capability must be able to perform advanced development and manufacture of MCMs to meet USG demand requirements in a reliable and cost-effective manner. The current path for USG MCM acquisition relies on industry to develop

MCMs through FDA licensure, followed by USG procurement on an MCM-by-MCM basis as products become available. This strategy has resulted in limited success. Successful MCM acquisition requires the participation of both biodefense innovators and biopharmaceutical firms. Biodefense innovators have researched promising early-stage MCM candidates, yet lack the advanced development expertise to produce FDA-approved products. Biopharmaceutical firms have this expertise, but have avoided the noncommercial MCM market because of perceived low profitability and high risk. Therefore, a successful dedicated capability must leverage the development expertise of biopharma while retaining the innovation of biotech and other innovators. The USG must participate by demonstrating a long-term commitment to MCM demand, which would strengthen the economic rationale for all industry partners to become engaged and remain involved.

Success can be achieved through a range of options for structuring and operating the facility. These options range from a wholly private sector approach to a wholly public sector approach (i.e., a government owned and operated entity). The UPMC study concludes that a set of options with mixed public and private participation both reduces long-term cost and mitigates risk in the advanced development and production of required MCMs. Of these options, a public-private partnership (PPP), defined as a not-for-profit organization that both licenses early-stage MCM candidates from biodefense innovators and leverages biopharma expertise, is recommended. It is further recommended that the PPP be created with the objective of attracting and retaining an industry-competitive workforce that would successfully complete product development and manufacture the resulting MCMs for USG stockpile and use.

In response to the work performed under the DARPA/UPMC cooperative agreement, it is proposed that a flexible, multi-product advanced development and production facility—located domestically and operated as a PPP—would yield numerous scientific, technological, and economic benefits over the current system.

1 Introduction

1.1 Historical Background

Rapid advances in biotechnology and the emergence of state and non-state players capable of producing bioweapons have significantly increased the threat of a CBRN attack. In parallel, advances in biotechnology have increased the potential efficacy and safety of available MCMs to protect against the threat.

The USG threat assessment is more acute since the end of the Cold War. Once the Soviet Union collapsed, defectors and bilateral inspections revealed that the Soviet regime had an extensive offensive biological weapons program. During the 1990s, it was known that Iraq and possibly other countries possessed a biological weapons program.¹ The potential for American troops to be exposed to bioweapons during the Persian Gulf War demonstrated to DoD that the private sector was not providing a reliable and sustainable source of biodefense MCMs. Consequently DoD formed a task force—Project Badger (“Tri-Service Task Force for the Expansion of the Industrial Base for Production of Biological Defense Vaccines”)—to study the shortage of MCMs for anticipated threats.² Continuing concerns over the lack of a stable pipeline of MCMs to protect troops led to the creation of another task force to focus on assessing the need for a Vaccine Production Facility (VPF). This additional task force was to determine a solution for DoD biodefense MCM manufacturing.

In 1993, this VPF task force recommended a government-owned, contractor-operated (GOCO) facility that could manufacture a variety of MCMs and could surge production in times of crisis.³ The task force recommendation reflected the view that the private sector lacked the means to provide MCMs to the military on its own without adequate incentives. The choice of a GOCO model also reflected a then common DoD acquisition strategy to procure military equipment (e.g., ammunition, tanks) from GOCO facilities. MCMs were considered analogous to equipment. The paradigm held that a dedicated government facility could be built to guarantee an industrial base and a contractor could be found to manage the facility and produce required amounts of MCMs, just as would be done for ammunition, aircraft, and other equipment that could not be sourced from purely commercial markets.

A high-level conceptual design of the facility proposed by the task force was completed also.⁴ DoD concluded at that time the VPF concept was too costly to implement. DoD vaccine acquisition strategy then evolved to a prime systems contractor approach, one in which a single contractor is dedicated to the development and licensure of a biologic product. This was executed in anticipation of the biopharmaceutical industry ultimately supporting DoD production requirements. Over time, however, very little commercial interest in producing biodefense MCMs emerged, thus DoD still had no assurance that existing producers would provide vaccines and novel MCMs.

¹ S/1995/1038. United Nations. Tenth report of the Executive Chairman of the Special Commission. December 17, 1995. <http://www.fas.org/news/un/iraq/s/s1995-1038.htm>

² Chronology of Project Badger (Long Term). October 24, 1990. CMAT Control # 1998337-0000036.

³ DoD Vaccine Production Facility Task Force Final Report, U.S. Department of Defense, 1991 (draft), 1993.

⁴ DOD Vaccine Production Facility. LF-0445.00. *Conceptual Design Submittal*. Life Sciences International. November 27, 1993.

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Consequently, the prime systems contractor approach proved insufficient. Biopharmaceutical companies were discouraged from MCM development by such factors as low profit margins, the risk of liability for adverse reactions to the products, marginal federal funding for MCM programs, and inconsistent USG priorities for MCM acquisition. Examples of that troubled process include the loss of availability of Wyeth Laboratories' adenovirus vaccine in 1996, which caused an increase of respiratory disease in military trainees; the loss of the Greer Laboratories' plague vaccine in 1997, which had proven extremely effective in Vietnam against bubonic plague; and temporary loss of Bioport's (now Emergent Biosolutions) anthrax vaccine in 1997.

DoD remained concerned with resolving difficulties related to acquiring safe and effective MCMs. In July 2001, an independent panel of experts released the *Report on Biological Warfare Defense Vaccine Research and Development Programs* to the Deputy Secretary of Defense.⁵ The report recommended the overhaul of DoD biodefense program management and the construction of a GOCO VPF, advising integration with the industry and the national scientific community. Once again, the concept was not implemented: concerns persisted regarding the ability of a biopharmaceutical contractor to operate under the paradigm of military contracting and the facility was again considered too costly for DoD to manage alone. Questions also arose regarding whether DoD was the appropriate long-term USG sponsor for the program.

1.2 Current State of Biodefense and MCM Acquisition

The events of September 11, 2001 heightened the awareness of the need for MCMs, not only for the military but also for civilian populations. Current efforts are two-fold: (1) HHS is currently funding development of prioritized MCMs and is procuring a variety of MCMs to protect the civilian population and (2) DoD funding development of MCMs is accessing products from HHS' Strategic National Stockpile. The convergence of needs for MCMs to protect the American population and soldiers deployed to high-threat areas suggests that a dedicated capability should be revisited to determine how it might contribute to the effective development, licensure, and stockpiling of MCMs for the USG. As illustrated by a recent Government Accountability Office (GAO) report, reliance on multiple small companies dependent on venture capital or other private funding to support MCM development can be problematic to the success of MCM development and licensure.⁶ Advances in manufacturing technology over the past 20 years, however, have proven that producing multiple products in a single, flexible facility is a successful development, one which would dramatically reduce the size and scope of a facility to manufacture MCMs for the USG portfolio of requirements.

In recent years, the biodefense industry has progressed in significant ways. Advances in biotechnology have fueled R&D into biologic vaccines and therapeutic drugs. Manufacturing technology has followed suit, with biotech companies and contract manufacturers improving processes for producing biologics. In 1995, FDA released a ruling paving the way for validation of a multi-product approach to biomanufacturing. These technology and regulatory changes have made flexible, multi-product manufacturing of MCMs possible in ways that did not exist in the early 1990s.

⁵ Report on Biological Warfare Defense Vaccine Research and Development Programs.

⁶ GAO, "PROJECT BIOSHIELD: Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing the Stockpile of Licensed Vaccine," October 2007, GAO-08-88.

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Since the 2001 anthrax mail attacks, the awareness of the threat posed by bioterrorism has grown even more acute. HHS, for instance, began to consider how to increase the number of MCMs stockpiled for biodefense to protect the civilian population. The means by which the government acquired equipment and technology has also evolved, with increased use of private contractors for research and manufacturing activities.

The pharmaceutical industry has also undergone business strategy changes. Once reliant on an integrated approach to researching, developing, and manufacturing new products internally, the industry has begun to seek alliances with small biotech firms, academia, and public-sector organizations to bolster product pipelines. The growth in the number and capabilities of small biotech firms, university labs, and government facilities has provided a rich source of options for new product candidates that biopharmaceutical firms can turn to for innovative ideas.

Over the next decade, large biopharmaceutical companies will face a growing number of maturing products, including blockbuster commercial drugs. Patent expiration of these drugs over the next decade threatens future revenues. Given the inherent risks of drug development, biopharmaceutical companies have begun to consider external sources of new drug candidates to broaden the portfolio of potential products in their pipelines through acquisitions and strategic alliances.⁷

Biodefense MCMs face similar drug development challenges as commercial products as well as unique market risks due to the noncommercial, USG-only demand. As alliances become more common in commercial drug development, they may play a role in biodefense and the development of new MCMs.

1.3 UPMC study

Based on the unmet need for an innovative biologic production capability for both DoD and first responders to a crisis, DARPA funded a cooperative agreement with UPMC to examine the requirements for a national capability to produce biodefense biologics. During the initial phases of the UPMC study, UPMC identified a convergence of MCM requirements for DoD and HHS; thus the study was expanded to include HHS requirements.

Drugs are typically divided into two general groups. The first group is small molecule chemical substances that can be defined by chemical tests that prove purity, potency, and identity. The second group—biologics—refers to large molecule substances produced by bacteria and other living organisms. Biologics and their manufacture are complex, and so it is difficult to test their purity, potency and identity. Thus, biologics need to be defined not only by the testing of the final product but also by the facility and processes that are used to manufacture them. This integrated view of product/facility/process requires unique and substantial systems to ensure that a biologic is manufactured to standards acceptable to FDA.

The UPMC study involved understanding the breadth, depth, and scale of the current situation in the advanced development and manufacture of biodefense MCMs. A DCA model was created to forecast the development pipeline and MCM demand over a 15-year time horizon. The intent of the model has been that of developing the best available view of the USG demand for MCMs—both currently and in the future—based on the portfolio of products in development. The goal has been to define what production technologies a dedicated capability might need to encompass to manufacture such a portfolio. The next phase of the project involved development

⁷ “New Biotech-Pharma Partnership Models That Retain Greater Value”, Michael McCully, Presented at BIO2008 meeting, San Diego, June 17, 2008. http://www.recap.com/consulting.nsf/ANB_tab_slides?openform

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of a HLCD that assesses the approximate scale and capabilities required to manufacture the pipeline of MCM products. The last phase examined options for an operating model for the facility and also includes a recommendation as to which model should be pursued.

1.4 *An Innovative Capability Design Approach*

The DCA provides the first comprehensive data collection of USG requirements for biologic MCMs. Because these MCMs have no viable commercial market, the private sector cannot be relied upon to develop, license and produce these MCMs. The question remains as to who will produce these much needed MCMs and how it will be done.

The USG has no plans to develop, license, and produce these MCMs independently, despite past DoD recommendations to do so in a dedicated facility. Small biotech companies (in many cases the innovators) desire to participate but often have limited experience in the areas of advanced development (clinical trials), licensing, and production. Lack of experience in these areas means that the risk of failure is high; this ultimately affects the ability of small biotech companies to raise capital and build a sustainable financial model. Biopharmaceutical companies usually have much more profitable options available, but the opportunity costs of engaging in biodefense activities are considered too high for biopharmaceutical companies.

The USG's current procurement strategy is an incremental approach, whereby it identifies the highest priority threat and issues a request for proposal (RFP) to purchase doses. As more funding becomes available, additional RFPs targeting other threats may be issued. Recent history has shown, however, that smaller biotech companies that are eager to respond to these RFPs face many challenges in moving products through both clinical trials and the complex, time-consuming, and costly FDA licensure process. In December 2006, HHS canceled its contract with VaxGen under Project BioShield for the procurement of a recombinant protective antigen (rPa) anthrax vaccine. A subsequent GAO investigation found that three critical problems led to the failure of this effort: the contract was awarded to VaxGen while its product was at a very early stage of development; VaxGen took unrealistic risks in accepting the contract; and important FDA requirements for emergency use authorization were not known at the outset of the contract.⁸ The current USG strategy clearly leaves the country at risk.

An alternate strategy exists: both the 1995 changes in FDA regulations stating that pilot scale manufacturing facilities could be licensed to manufacture products and the subsequent proliferation of disposable biologics production technologies now make it possible to employ a flexible facility to support advanced development and production of multiple required MCMs. Although each MCM is different, the technologies used to produce them can be categorized into a core set of technologies. For example, a facility capable of manufacturing recombinant protein (rProtein) in *E. coli* could easily produce other products that share the same platform production technology (e.g., a future anthrax vaccine and also future plague, ricin, and Staphylococcal enterotoxin B (SEB) vaccines). Commercial vaccine companies use this approach in smaller-scale pilot plants that produce batches of vaccines for use during clinical trials. Further, the National Institute of Health's Vaccine Research Center (VRC) pilot production plant demonstrates the success of flexible and modern smaller-scale production facilities. Products manufactured in the VRC facility include vaccines against Ebola virus, HIV, and pandemic influenza.

⁸ GAO, "PROJECT BIOSHIELD: Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing the Stockpile of Licensed Vaccine," October 2007, GAO-08-88.

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1.5 *An Innovative Operating Model Approach*

Both the 1993 and 2001 DoD studies recommended a GOCO solution to reliably supplying MCMs to the government.^{9,10} Recent changes to both the USG approach to biodefense and the biotechnology industry warrant a renewed assessment of appropriate operating model options for a dedicated capability. Many factors now challenge the assumption that a GOCO is the only viable option for structuring a dedicated capability.

First DoD no longer faces the responsibility of solely developing and acquiring MCMs. A dedicated capability for the advanced development and manufacturing of MCMs would interact with multiple USG departments, including DoD, HHS, and possibly the Department of Homeland Security (DHS). Procurement contracts would likely come from both DoD and HHS. This suggests that a dedicated capability must be adequately nimble and flexible to supply MCMs under different types of contracts.

Also, the failure of recent MCM procurement contracts with small biotech firms, such as the \$877M VaxGen contract to supply a next-generation anthrax vaccine,¹¹ demonstrates that while biotech firms can manage the early-stage development process (i.e., discovery through Phase I clinical trials), they struggle with the advanced development phase of bringing biologic MCMs to market (Phase II clinical trials through FDA licensure). Biopharmaceutical firms have the experience with advanced development, and it is important to engage this expertise in order to realize new MCMs for the USG to acquire.

The enactment of Project BioShield in 2004 and the creation of the Biomedical Advanced Research and Development Authority (BARDA) in 2006 have demonstrated a stronger USG commitment to biodefense. BioShield provided \$5.6 billion in funds for research into new MCMs, and BARDA was established to assist industry with developing new MCM candidates. However, additional measures need to be taken to fully engage biopharma and thereby overcome the challenges of advanced development of biologics.

To fill the role of successfully developing and manufacturing biologic MCMs, a dedicated capability must have an industry competitive workforce. For the facility to attract and retain top scientific and engineering talent, it must be able to compensate talent on a private sector basis in ways above and beyond the means of the USG Office of Personnel Management regulations and government pay scales.

2 Demand Capacity Assessment

2.1 *Methodology*

To define the inputs to the demand capacity model in the absence of a consolidated source of information, the UPMC study used a three-phase approach.

Information was first obtained from the USG on current demand requirements. This included documents provided by DoD and HHS in addition to published RFPs on products under development. In conducting the study, all publicly available information on MCMs currently FDA-licensed or in development was researched also. This phase involved researching R&D funding agencies—HHS, National Institute of Allergy and Infectious Diseases (NIAID), Defense

⁹ DoD Vaccine Production Facility Task Force Final Report, U.S. Department of Defense, 1991 (draft) 1993.

¹⁰ Report on Biological Warfare Defense Vaccine Research and Development Programs, U.S. Department of Defense, 2001.

¹¹ The requests for proposal for the VaxGen contract are NIH-NIAID-DMID-02-26 (in 2002) and NIH-NIAID-DMID-03-29 (in 2003).

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Threat Reduction Agency (DTRA), and Chemical Biological Medical Systems (CBMS)—to ascertain what types of MCMs are under development for possible future procurement.

Secondly, the study consolidated public domain companies' R&D pipelines as well as academic literature on early-stage through licensed MCMs. Figure 1, below, illustrates the staged process for new drug development. As shown, there are three key review actions to be completed by the FDA Center for Biologic Evaluation and Research (CBER). The first is an Investigational New Drug (IND) application which is required to start Phase I human testing. The second is an Emergency Use Authorization (EUA), a relatively new review process for drugs that are still in development but have advanced to a stage where they would be appropriate to use during an emergency (as declared by the Secretary of HHS). The final milestone is the submission of the Biologics License Application (BLA) which is required for distribution and sale of final product.

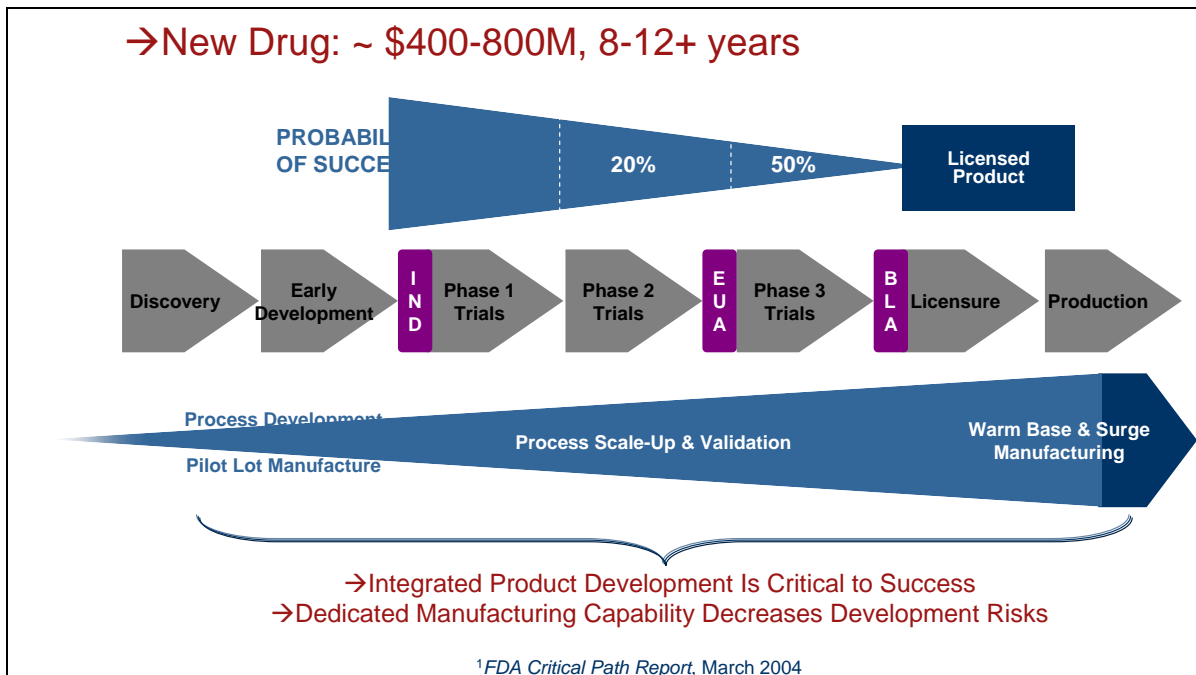


Figure 1: Stages of New Drug Development

During the latter stage of the DCA, a comprehensive set of interviews with over 40 stakeholders in the MCM development process was conducted. The interviews were designed to provide feedback and identify gaps in the information gathered. The interviews also shaped a consensus view of MCM development. Stakeholders included representatives from HHS, DoD, DHS, the Department of State, the White House, academia, and industry. The interviews provided a comprehensive view of MCM development as well as current trends and challenges in the field.

The study concludes that there is a substantial convergence of HHS and DoD demand around a set of shared requirements, as indicated in Figure 2.

The demand reflected in Figure 2 represents the USG MCM requirements as of December 2007. When modeling government MCM requirements, the most conservative figures were used in terms of both the number of different MCMs as well as the dose requirements that were articulated by open source documents, government-approved documents, and interviews. For example, HHS demand is constrained by available funding. Therefore, conservative estimates

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were used to model the MCM demand with the result being that the ultimate demand levels may be substantially higher.

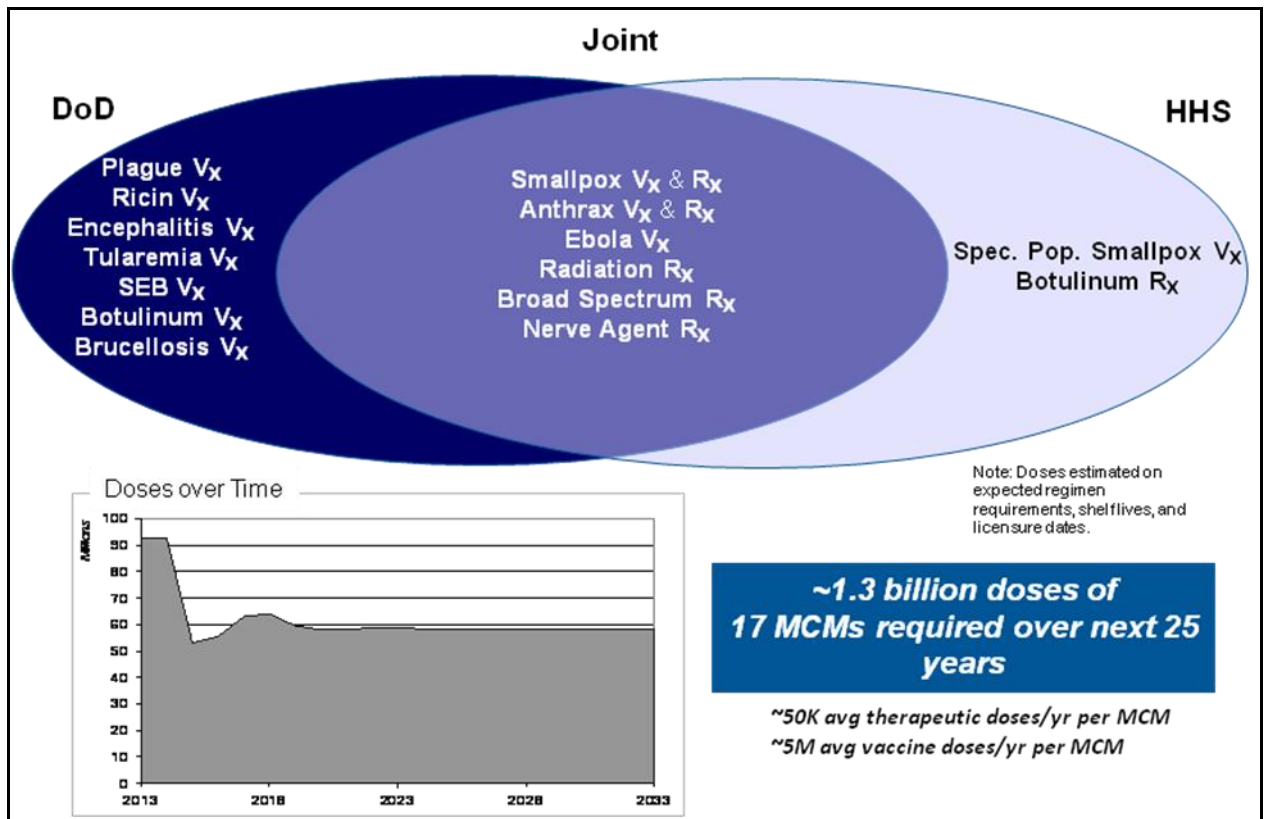


Figure 2: Convergence of MCM Needs for DoD and HHS.

2.1.1 Assumptions

The UPMC study is an assumption-driven exercise to estimate the capability necessary to manufacture the current MCMs required by the USG. Where applicable, assumptions are described in the sections where they are utilized. In addition there were several general assumptions utilized in the development of this DCA model and they are as follows:

- Prioritization of threat agents and associated MCM requirements will not change over the 15-year span of the DCA;
- One single product will be licensed at any given time for each MCM;
- A focus on the manufacture of products will occur after the estimated five-year development time for the facility;
- No animal-derived products will be manufactured (e.g., equine hyper-immune globulin, transgenic animals);
- Although important in any analysis of MCMs, veterinary MCMs are not included in this analysis;
- Only products with no commercial interest outside biodefense are considered;
- Only biologic products are considered;

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- Production of materials is at the bulk stage, and final filling is assumed to occur as needed in time for use; and
- Reliable access to raw source materials is assumed.

Assumptions were utilized to develop the DCA model. The facility is defined by three bounding assumptions. The first assumption is the size and specifics of the demand: this demand is defined by the number of doses necessary for production, the warm-base demand, the date of licensure/EUA when production starts, and any surge demand that may occur for that MCM. The second assumption is the product technology: the method of production determines what unit operations are necessary to be included in the facility and if there are unique requirements for the manufacture of the MCMs (e.g., equipment, biosafety levels [BSLs], materials, etc.). The final assumption is the available facility technology: this boundary determines what types of technologies are appropriate to include in the facility and what should be excluded. Capabilities such as process development, disposable technologies, and aseptic filling are all areas that still must be examined.

The timelines for licensure were determined based on DoD- or HHS-proposed timelines, if available. Otherwise, development timelines were determined using industry benchmarks to project licensure dates. The demand for an MCM was assumed to start at the EUA stage of approval, approximately two years prior to final FDA licensure. The model assumes only one licensed MCM at a time would be manufactured for a given threat and product (e.g., vaccine or therapeutic). When second-generation products are licensed, the first-generation product would no longer be manufactured. Based on the current portfolio, it is not believed that biologic therapeutics will be entirely replaced by small molecule products for either agent-specific or broad-spectrum applications. The lower estimate of all baseline products stockpiled was utilized. The production of new MCMs is assumed to initiate two years prior to the BLA after EUA approval and with two years to manufacture sufficient material for the stockpile. In subsequent years, a minimum of a single lot of material will be manufactured up to an amount sufficient to replenish any expired materials in the stockpile. A shelf life of 10 years is assumed for smallpox vaccine and five years for all other MCMs based on the likely distribution of shelf life for products in development. A minimum of one lot per year must be manufactured as part of the warm-base to maintain FDA license and, if necessary, sufficient material to replace any expiring product in the stockpile.

2.1.2 Forecasting Product Demand and Production Requirements

Once the demand was established, each product in the portfolio was reviewed and categorized by its production technology, e.g., rProtein in E.Coli, monoclonal antibody, or viral vector in cell culture. This information was gathered from patents, package inserts, publications, and industry presentations. Where available, human dose information was collected also. Production technologies were utilized to help size the facility required to manufacture the MCMs.

The expected licensure date for each MCM in the portfolio was evaluated also. For some products, the projected licensure date was presented by the funding agency (DoD or HHS), but the majority of products did not have specified licensure dates. For these products, industry benchmarks were used for development times and added onto the current stage of development

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for the products.^{12, 13} In assessing the demand, it was assumed that products are initially manufactured under EUA for inclusion in the stockpile requirements. EUA was assumed to occur two years prior to final licensure of the product based on draft EUA requirements under discussion in the field. Please refer to Table 1 below for a summary of drug development timeline benchmarks.

| Period | Years | | | | | |
|---------------------------------------|-----------|------------|------------|------------|------------|------------|
| Preclinical to Phase I: 2.4 | 2.4 | | | | | |
| Phase I to Phase II: 2.0 | 2 | 2 | | | | |
| Phase II to Phase III: 1.8 | 1.8 | 1.8 | 1.8 | | | |
| Phase III to Pre-registration: 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | | |
| Pre-registration to Registration: 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | |
| Registration to Launch: 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 |
| Total: | 10 | 7.6 | 5.6 | 3.8 | 2.4 | 1.3 |

Table 1: Drug Development Benchmarks

The final information needed to determine product requirements was warm-base production. Warm-base is driven by two factors: replenishment of expired material in the stockpile and regulatory requirements to demonstrate the capability to retain the license. Based on generally accepted practices with biologics, it is expected that at least one lot of material will be required to be made annually to sustain FDA license for manufacture. In addition, each biologic was assigned an approximate shelf life as a bulk product. Given the extensive commercial capability for final fill/finish, the output of the facility would be anticipated to be largely bulk drug substance (BDS), rather than final drug product which would be in the final delivery container. This is consistent with the current strategy for the HHS pandemic flu stockpile, which holds product at the BDS stage for filling in the event of a pandemic flu outbreak.¹⁴

2.2 Stakeholder Landscape Assessment

2.2.1 Introduction

To complete the DCA, over 40 experts from industry and defense, civilian, and international health constituencies were consulted. The interview questions posed were both general and technical in nature, yet focused on issues concerning current and future MCM requirements for defense, civilian and special immunization populations, product development and production technologies, national preparedness, and the value of establishing a biologics

¹² Struck, MM, "Vaccine R&D Success Rates and Development Times," *Nature Biotechnology*, 14(5):591-3, 1996.

¹³ DeMasi et al, "The price of innovation: new drug estimates of drug development costs," *Journal of Health Economics* 22, 2003, p. 151-185.

¹⁴ Information from CDC interviews conducted for the UPMC study.

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manufacturing capability in and for the United States.

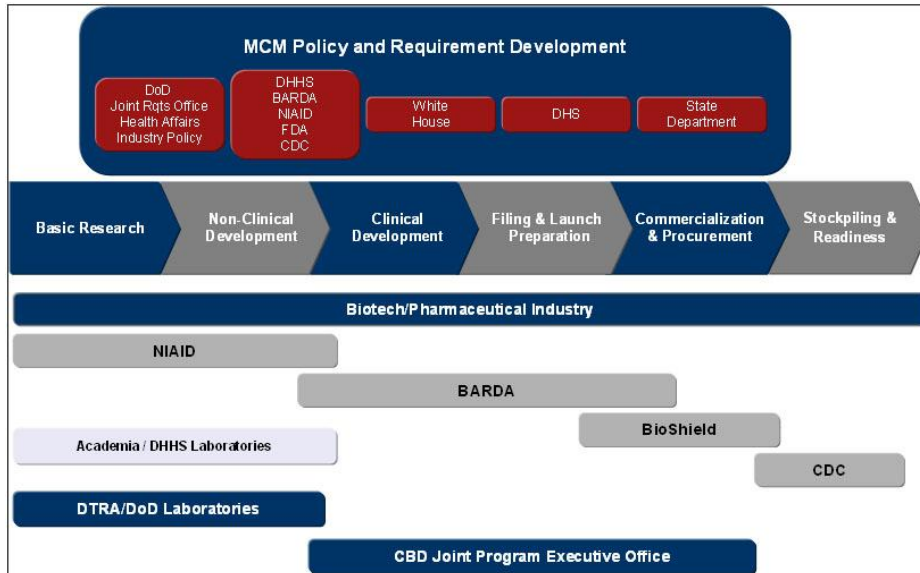


Figure 3: Interviewees' Areas of Expertise and Influence

In addition to representatives from scientific communities and the biotechnology and biopharmaceutical industries, representatives from several federal agencies were consulted for the DCA. Figure 3 provides an overview of the interviewees' areas of expertise.

2.2.2 Sustainability of Supply is Important in Biodefense

There exists an encouraging level of agreement among the interview participants that a reliable and sustainable capacity for biologics products can ensure adequate MCMs for our soldiers, civilian population, and global allies, rendering the nation more secure at home and abroad. The interviewees' concern about sustainability in biodefense reflects the need to ensure a reliable supply of safe and effective MCMs, to advance new products and technologies, and to protect the nation and its troops against CBRN threats in, ideally, a more affordable and adaptable fashion.

Some shared opinion among interviewees was expressed that a facility dedicated to advancing and manufacturing biologic MCMs should have been developed many years ago. This opinion seems to mirror a general belief among the interviewees that the nation is neither adequately nor robustly prepared for the myriad of scenarios and homeland security threats which make conceivable a catastrophic biological attack or infectious disease outbreak.

The concept of a facility that can make multiple different MCMs and that can surge production in the event of an emergency was viewed as a compelling idea both within the defense and civilian communities.

Collectively, the interviewees revealed that sustaining a capacity for MCMs and creating a domestic facility for manufacturing MCMs is as significant as sustaining a national interest in biodefense. Many interviewees acknowledged specific challenges that the USG and its private sector partners continue to face in building defenses for biological threats. Such challenges include—but are not limited to—moving products toward advanced development, ensuring manufacturing capacity for products granted licensure, handling various liability issues,

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managing a portfolio of products against uncertain threats, and foreseeing the USG’s needs in the future. Sustaining interest among companies in the biodefense market is essential to developing a flexible mix of MCMs that can respond to a diversity of threats.

Interviews with regulatory officials confirmed that time and budget constraints have made the product approval process longer and more taxing than desirable. Both the ease and affordability of attaining product licensure and the assurance of having manufacturing capacity post-licensure were identified as critical factors in sustaining industry’s interest in biodefense. Over the years, constraints of time and budget have limited the private sector’s interest and thus the number of MCMs brought to market, leaving gaps in the nation’s ability to protect troops and civilians against a range of CBRN threats. Furthermore, the biologics manufacturing capacity for MCMs has been trending overseas, as evidenced by the list of current products procured under BioShield in which a substantial number of products manufactured outside the United States is detailed (see Table 2).

| Material Threat | Product | Company (Country) | Award Date |
|--------------------------|---------------------------------|-----------------------------|-----------------|
| Smallpox | ACAM2000 | Acambis (UK) | 9/04 |
| | MVA | Bavarian Nordic (Denmark) | 6/07 |
| | Vaccinia Immune Globulin | Cangene Corp. (Canada) | 8/07 |
| Anthrax | rPA vaccine | VaxGen (USA) | Cancelled 12/06 |
| | AVA vaccine | Emergent Biosolutions (USA) | 5/05 and 5/06 |
| | ABthrax | Human Genome Sciences (USA) | 6/06 |
| | Anthrax Immune Globulin | Cangene Corp (Canada) | 7/06 |
| Botulinum Toxin | Botulinum Antitoxin Heptavalent | Cangene Corp (Canada) | 6/06 |
| Radiological and Nuclear | Potassium Iodide—Liquid | Fleming & Company (USA) | 3/05 and 2/06 |
| | Ca-DTPA | Akorn (USA) | 2/06 |
| | ZN-DTPA | | |

Table 2: Current State of Advanced Development Contracts Under BioShield and Before BioShield

Despite a favorable opinion among interviewees toward establishing a domestic facility for MCMs, most confirmed that such a facility cannot be viewed as the “cure-all” for existing challenges in MCM development and manufacture. Although notable progress and collaboration has been achieved across the government since the anthrax attacks of 2001, many interviewees agree that some issues of leadership, policy, and FDA regulations continue to restrain absolute success in national biodefense.

In addition, the interview participants explained that sustainability in national biodefense is not limited to ensuring an adequate supply of, for example, anthrax and smallpox vaccines for defense and civilian populations. The requirements of biodefense have become much broader

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and more robust, some notionally extending beyond the need for traditional MCMs. Efforts to sustain interest in biodefense are rendering new understandings of what products and capabilities “biodefense” should encompass today. Within the defense, civilian, and international health communities, there is a growing concern about emerging diseases, especially those which threaten military, Foreign Service Officers and relief workers stationed overseas. One interviewee advised that the DCA model should identify a more robust application implying that biodefense is hedging toward a steady state. In practice, this idea supports the views of several interviewees about developing a domestic capability not only to ensure a reliable supply of known MCMs, but also to manufacture MCMs for emerging threats and advance technologies that may target “unknown” threats.

2.2.3 Forecasting National Demand

For purposes of the DCA, open source data and the expertise of over 40 interviewees were relied upon to determine for what the nation is—and should be—preparing. The purpose of the DCA is to model and forecast the demand for MCMs during the next five to fifteen years. The DCA also assesses MCMs of most importance today and, to the extent possible, tomorrow so as to depict the appropriate set of production technologies.

Many interviewees commented on the extensive collaboration among federal agencies in leveraging civilian and defense capabilities. The convergence in technologies required to manufacture MCMs for defense and civilian populations makes the notion of a joint-manufacturing capacity not only conceivable but also practical. A degree of collaboration is imperative between DoD and HHS to ensure that requirements are met. Defense and civilian representatives verified that, at present, their joint needs cover a MCM portfolio that includes anthrax, smallpox, filoviruses, radiological/nuclear agents, and botulism countermeasures as well as broad spectrum antibacterials and antivirals. These products of joint importance to the nation were, therefore, the primary drivers in forecasting and modeling demand.

Due to differing missions and requirements, military and civilian MCM requirements are not always aligned. In general, DoD interviewees focused on prophylactic treatments for force protection while HHS focused on treatments post-exposure. However, both require stockpiled MCMs to meet stated requirements.

A consistent theme in forecasting the national demand was an acknowledgement that financial constraints for MCM development limit the choices that can be made. These financial constraints greatly impact the requirements that have been shared publicly for MCMs. It is a common view, though impossible to quantify, that USG-published MCMs requirements represent only a very small fraction of the true needs based on the threat. If one looks at all possible threats, a wide diversity of MCMs are required. The array of threats has been further defined in the classified Material Threat Determinations (MTD) done by DHS. As the MTDs are classified, they were not reviewed or utilized in this analysis. The scientific community also could define those MCMs that could likely be developed given current technology. Both DoD and HHS maintain a basic research portfolio as well as development portfolios that are a subset of those that are currently scientifically feasible. Finally, there are published requirements and procurement from the USG. These procurements are limited to current DoD budgets and the HHS Special Reserve Fund of \$5.6 billion to be utilized over 10 years. Relatively speaking, interviewees indicated that these published requirements are a small fraction of the needs based on the portfolio in development and the threat analyses.

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Another evident theme in the interviews was how to respond to the threats given limited funding constraints. Two fundamental philosophies emerged. The first, referred to as “broad-spectrum,” concludes that given the number of potential threats and limited funding, a “one-bug-one-drug” strategy is too costly. This group believes that the most cost-effective strategy would be that of focusing on the development of “broad-spectrum” products that would provide protection against a variety of threats. The example of antibiotics is cited as a model for how these broad-spectrum agents could be used in bacterial, viral, and general immune enhancement applications. The second philosophy is termed “prioritize agent specific.” This group points out that there are a wide variety of relatively low-risk products that could be developed against the agents and given the funding constraints, high-priority threats should be addressed first, and then new MCMs could be added as funding becomes available. It is pointed out that “broad-spectrum” development costs are high risk, and it is unknown if a broad-spectrum treatment can be developed from this strategy given the technical hurdles. Clearly, these opposing views represent two important strategies in MCM development, and the balance between them must be carefully considered as the funding of both is an important risk mitigation strategy.

2.2.4 International Needs and Countermeasures for Emerging Threats

One of the key conclusions and lessons learned from the *Atlantic Storm* exercises of January 2005, led by the Center for Biosecurity of UPMC, was the criticality of developing an adequate supply of MCMs. “The current lack of MCMs to infectious diseases and the inability to quickly increase global production of those that do exist may force leaders to employ disease control options such as border closures that could be socially, politically, and economically destabilizing and serve to turn a crisis into a catastrophe.”¹⁵ It is evident that the need and demand for biodefense MCMs is global in measure. A consideration of the UPMC study has been the ability to surge production of MCMs at home and for global allies; yet quantifying the precise amount of MCMs that could be needed globally remains imperfect. Attempts were not made to determine population demands as part of the DCA.

As clarified by one interviewee, there are no existing international agreements that require the USG to share MCMs in the event of a biological attack, although it is without doubt the intent of the USG to share, if possible, MCMs in the event of an attack against a global ally. There are some broadly defined mutual aid treaties of interest, yet no specific aid agreements are in place with respect to MCMs. With this factor one among many other uncertainties, the DCA does not incorporate a precise global demand for MCMs. One interviewee, however, did suggest that the USG consider some multinational agreements to share MCMs. Some resources have already been committed via virtual stockpiles and through the World Health Organization (WHO). As the manufacturing base for biologics becomes more global, it is also important to consider opportunities for synchronized production with allies as well as the requirements under the Geneva Convention that suggest an occupying force would be required to provide available treatments to local populations.¹⁶

¹⁵ *Atlantic Storm: Analysis and Lessons*. Center for Biosecurity, University of Pittsburgh Medical Center. <http://www.atlantic-storm.org/conclusions.html>.

¹⁶ Article 56 of The Geneva Convention requires “To the fullest extent of the means available to it, the public Occupying Power has the duty of ensuring and maintaining, with the cooperation of national and local authorities, the medical and hospital establishments and services, public health and hygiene in the occupied territory, with particular reference to the adoption and application of the prophylactic and preventive measures necessary to combat the spread of contagious diseases and epidemics. Medical personnel of all categories shall be allowed to carry out their duties.”

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Within the defense and civilian communities, there is a growing interest in targeting emerging threats: such as Dengue, yellow fever virus, SARS, Rift Valley Fever virus, West Nile virus, Japanese encephalitis, Chikungunya, adenoviruses, malaria, Junin, Q fever, Nipah virus, Tularemia, and Hantaan.

This focus on emerging threats and the need to build new response capabilities spans from the international relations community to United States civilian, scientific, and defense communities. The defense community, which has a target profile different than that of commercial interests or the needs of the developing world, has voiced specific concerns about developing MCMs for emerging threats. One interviewee explained that some biopharmaceutical companies in the business of developing products against emerging threats (e.g., malaria) are targeting the prevention of disease for populations, rather than the blocking of infection, and this concerns DoD in its efforts to protect soldiers. It remains unclear what defense and civilian needs for each of the emerging threats identified will be in the future. Yet based on the expertise of the interviewees, MCMs for emerging threats are apt to become a more significant issue in protecting United States citizens who are soldiers, Foreign Service Officers, relief workers, and/or travelers throughout Africa, Asia, and the Middle East. If there is no commercial market for products that target emerging threats, a domestic manufacturing capacity may need to play a role in providing new MCMs. Although the DCA does not forecast a demand within this new and relatively unknown market, its model includes technologies that could facilitate the production of additional products beyond joint civilian and defense—or purely defense—MCM needs.

2.2.5 The Special Immunization Program

Another demand for MCMs that was identified during the interview process was the DoD Special Immunization Program (SIP). SIP currently utilizes vaccines developed under IND and produced more than 10 years ago using technologies developed in the 1970s and 1980s. This program was established to protect laboratory workers researching the agents on the demand list by using investigational vaccines. Since 2001 there has been a dramatic growth in the number of BSL-3 and BSL-4 laboratories in the United States and there are significant concerns about the laboratory staff. As illustrated in a recent GAO report, as the number of laboratories grows, so does the potential for a laboratory exposure incident.¹⁷ Several interviewees highlighted the need for vaccines to protect laboratory workers who are working with these agents while researching next-generation vaccines and therapeutics. A recent review of the SIP program at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) showed that despite extensive use of barrier methods for protecting workers, vaccination remained the most effective approach.¹⁸ The current SIP program utilizes vaccines manufactured at the Salk Institute in Swiftwater, PA, which was closed in the mid-1990s. These vaccines remain in storage, yet DoD is increasingly unable to continue use as they lose potency. Given the technologies used to develop these products, it was the consensus of those interviewed that the SIP products cannot be further developed into licensed vaccines. It is believed that a new capability could play a critical role in a next-generation SIP program by becoming a stable and high-quality manufacturer of investigational products for use in laboratory workers where there

¹⁷ GAO, “High-Containment Biosafety Laboratories: Preliminary Observations on the Oversight of the Proliferation of BSL-3 and BSL-4 Laboratories in the United States,” October 2007, 08-108T.

¹⁸ Rusnak JM, Kortepeter MG, Hawley RJ, Anderson AO, Boudreau E, Eitzen E, “Risk of occupationally acquired illnesses from biological threat agents in unvaccinated laboratory workers,” *Biosecur Bioterror* 2004; 2(4):281-93.

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are insufficient requirements or funding to further develop these vaccines. Currently, there is no alternative manufacturing program established to address this research community need.

2.2.6 Warm-Base Capacity

The production of biologics requires routine production of product to maintain FDA license. Although there is no explicit requirement in FDA regulations, it is generally agreed during licensing negotiations with FDA that at least one lot of product is made per year. Discussion with industry experts suggested that for complex viral products this may, in fact, be insufficient and at least 2 lots per year should be planned. Currently there is no consistent strategy articulated by USG procurements on how warm-base will be addressed for MCMs. The current appropriation of funds on a year-to-year basis precludes multi-year contracts for MCMs.

Interviewees at both DoD and HHS highlighted the lack of a consistent strategy for maintaining warm-base requirements for MCMs. This concern was also articulated in the Pandemic and All-Hazards Preparedness Act (S. 3678) which grants HHS the authority to contract for warm-base and surge-production capacity for pandemic influenza vaccine. As new MCMs are licensed by individual companies, the USG will need to ensure continued availability to maintain the stockpile. Such a strategy will require long-term contracts with individual companies. In many instances, these companies may not be able to manufacture other products in these facilities and will, therefore, require financial compensation to maintain production for the USG. Acambis is currently negotiating a warm-base contract for the ACAM2000 smallpox vaccine which will ensure both its continuing domestic operations and access to its smallpox vaccine.¹⁹ Given the evolving nature of the product pipeline, it has been noted that there may be instances where the USG does not support a warm-base if a second-generation product will become available in a relatively short period of time. As pointed out in the GAO report on anthrax, however, development of new MCMs can be significantly delayed and the transition from one warm-base to another can be fraught with difficult technical, procurement, and financial implications.²⁰

2.2.7 Leadership and Human Capital

A final theme of the interview process was that the current system was not working well in the development of new and novel MCMs. A key component highlighted in this shortcoming was the lack of dedicated human capital necessary to develop novel biologics. The development of biologics involves an extremely complex and lengthy process that is best done by individuals who have completed the entire process previously. The establishment and cultivation of this human capital, regardless of where it resides, was often cited in the interviews as an essential step in the development of MCMs. Several interviewees also noted the critical shortage of highly qualified personnel and the competitive environment for recruiting them, requiring significant compensation packages to attract staff and retain them, even in industry.

¹⁹ Acambis press release “CDC Agrees to Place \$30 Million Order for Acambis PLC (ACAM)’s ACAM2000 Smallpox Vaccine 9/13/2006 8:43:27 AM,” www.acambis.com.

²⁰ GAO report “Project BioShield: Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing the Stockpile of Licensed Vaccine,” October 2007, GAO-08-99.

2.3 *Published Requirements and Current MCM Stockpile*

2.3.1 Military

The Joint Requirements Office for Chemical, Biological, Radiological and Nuclear Defense (JRO-CBRN) is responsible for the planning, coordination, and oversight of joint CBRN defense operational requirements. The JRO represents the Services and Combatant Commanders in the capabilities generation process and acts as their proponent for coordinating and integrating CBRN-operational capabilities. In addition, DARPA and DTRA manage and direct basic research and early advanced development to identify and demonstrate innovative solutions to address warfighters' needs. Similarly, USAMRIID conducts basic and applied research on biological threats, focusing on medical solutions for the warfighter. The Joint Science and Technology Office for Chemical and Biological Defense (JSTO-CBD) receives input from the JRO and prioritizes the R&D of MCMs. The Joint Program Executive Office for Chemical Biological Medical Systems (JPEO-CBMS) manages and directs advanced development leading to FDA licensure and stockpile of MCM products. During this project, CBMS was able to provide by approval through JRO a list of DoD requirements for MCM development, both funded and unfunded.

2.3.2 Civilian

DHS is charged with determining and prioritizing the threats that require development of MCMs for civilians. As a component of the development of response plans, DHS conducts integrated assessments of the risks posed by threat agents and issues MTDs to determine which agents pose a material threat sufficient to affect national security.^{21, 22} The Secretary of Homeland Security has issued MTDs for threat agents and has conducted Population Threat Assessments (PTAs) to estimate the number of individuals who may potentially be exposed to each threat in plausible, high-consequence scenarios. HHS has developed an implementation plan for stockpiling MCMs to address the MTDs and PTAs.

Similar to its military counterparts, NIAID focuses on basic and applied research to “better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases.”²⁵ The Centers for Disease Control and Prevention (CDC) is involved in preparedness and response to infectious disease outbreaks.

2.3.3 Sources of Requirements

The published output of both HHS and DoD MCM processes was used to develop a comprehensive view of the joint requirements. The stakeholder interview process was used to further refine the published requirements in order to reach a reasonable demand requirement. Where ambiguities in requirement levels exist, the most conservative estimates were used.

²¹ Federal Register/Vol 72, No. 77, Monday, April 23, 2007, Notices pp 20117-20128.

²² MTDs are authorized under section 319F-2(c)(2) of the Public Health Service Act and are a legally required precursor to procurement under that authority.

2.4 *Portfolio of MCMs in Development*

As previously discussed, the funding of R&D products by HHS and DoD drives a significant portion of the demand. Material Threat Assessments (MTAs) are the basis for this R&D, and thus give a view of the demand not possible without access to classified MTA documents. To ultimately determine what manufacturing facility is needed to deliver these critical MCMs to the government, the production technologies utilized for current MCMs—as well as those in development—were examined. The products were divided into three groups. “1st generation” products are those that are currently licensed or likely to be licensed within five years (by 2012). This interval was chosen as the development of any new manufacturing facility would take at least five years to begin to produce new MCMs. “2nd generation” products would be licensed in the six–ten year time horizon. These products, along with those already licensed, will provide the basis for determining the size and scope of the manufacturing facility necessary for this project. “3rd generation” products are not likely to be licensed for at least 10 years and are in the early phase of development. Additionally, most utilize technologies not currently used in licensed products. Overall, the manufacturing facility should be designed in a way to accommodate future products. However, given the timeline for development and new technologies, it is not assured that all products examined will be licensed.

As an example, Figure 4 describes the portfolio for the three top threats: smallpox, anthrax, and Ebola/Marburg viruses. These representations were derived from published literature, company websites, and RFPs from DoD and HHS. Licensure dates were used, when available, to determine if they were first-, second-, or third-generation products. Where no licensure dates were estimated, industry benchmarks were used from the current state of development to project potential licensure dates. Products were also categorized as to what basic production technology they utilized. These production technologies included live viruses (typically manufactured in cell culture), protein-based recombinants (bacterial or cell culture based), nucleic acids (DNA plasmids or replication incompetent viral vectors), antibodies, or small molecules manufactured by chemical synthesis.

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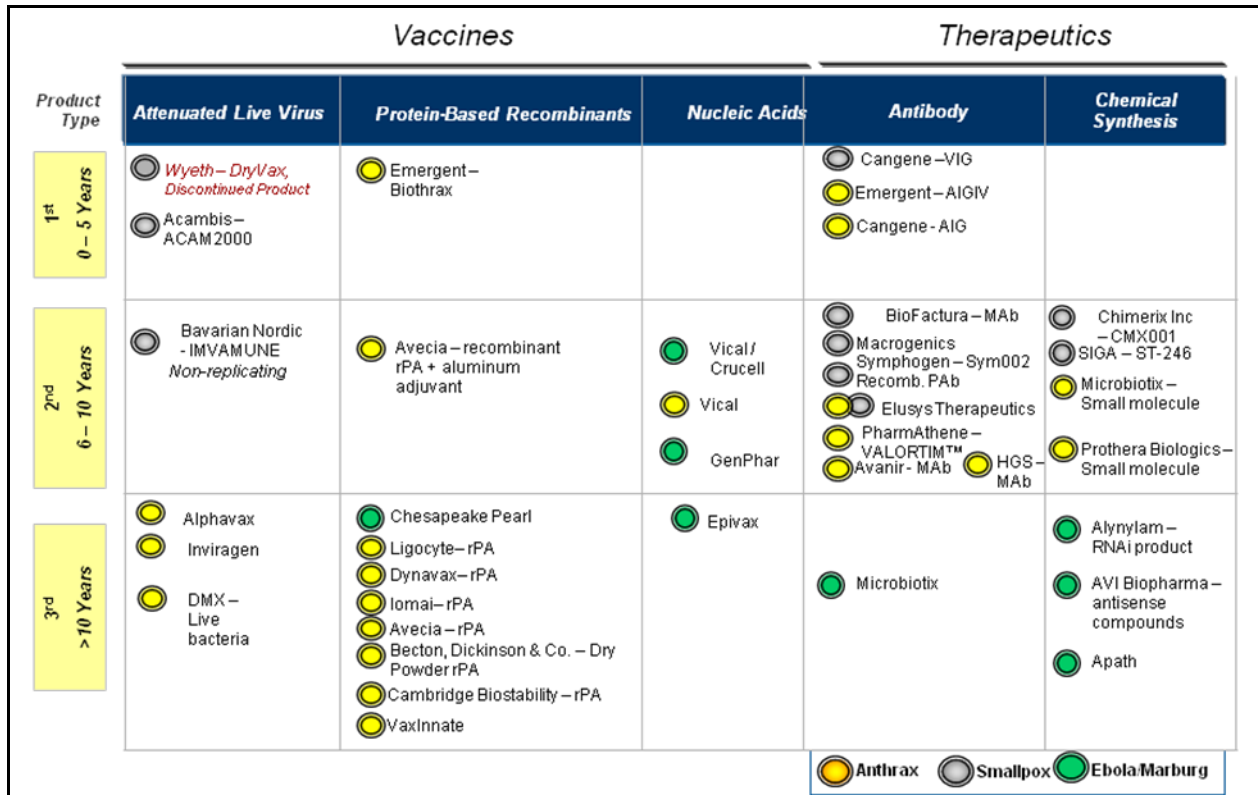


Figure 4: R&D Portfolio of Products for Anthrax, Smallpox & Ebola/Marburg Viruses

2.5 Demand Capacity Assessment Model

The intent of the DCA model is to inform the design of a new capability to deliver MCMs to DoD and HHS. The inputs to this model are the licensed MCM, the production technology used to manufacture it, and the number of doses required each year for production. Table 3 provides a summary of the DCA model for the threats described previously and the parameters used in the model.

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| Agent | Class | DoD (Regimens / TED) | HHS (Regimens) |
|--|-------------|---------------------------------|---------------------------------|
| Anthrax | Vaccine* | No Requirement (B) ¹ | 25,000,000 (A) ² |
| | Therapeutic | Shared Requirement (B) | 20,000 (B) ³ |
| Botulinum | Vaccine* | 2,600,000 (A) | No Requirement (C) |
| | Therapeutic | No Requirement (A) ⁴ | 200,000 (B) ⁵ |
| Broad Spectrum Viral Inhibitor | Therapeutic | 100,000 (C) ⁶ | 100,000 (C) ⁶ |
| Brucellosis | Vaccine* | 2,600,000 (A) ⁷ | No Requirement (C) ⁸ |
| Ebola/Marburg | Vaccine* | 2,600,000 (A) ⁷ | 1,000,000 (C) ⁹ |
| Encephalitis (VEE,EEE,WEE) | Vaccine* | 2,600,000 (A) ⁷ | No Requirement (C) ⁸ |
| Nerve Agent | Therapeutic | 90,000 (A) ¹⁰ | 90,000 (C) ¹¹ |
| Plague | Vaccine* | 2,600,000 (A) ⁷ | No Requirement (C) ⁸ |
| Radiation | Therapeutic | 500,000 (A) ¹² | 100,000 (C) ¹³ |
| Ricin | Vaccine* | 2,600,000 (A) ⁷ | No Requirement (C) ⁸ |
| SEB | Vaccine* | 2,600,000 (A) ⁷ | No Requirement (C) ⁸ |
| Smallpox, Smallpox Vaccine (special population) | Vaccine | Shared Requirement (A) | 300,000,000 (A) |
| | Vaccine | No Requirement (A) | 10,000,000 (B) |
| | Therapeutic | No Requirement(A) | 100,000 (B) |
| Tularemia Vaccine | Vaccine | 2,600,000 (A) ⁷ | No Requirement (C) ⁸ |

Key:
(A): Fully defined requirement
(B): Partially defined requirement, lack of consensus during interviews
(C): No defined requirement, partial information provided during interviews

*Specific requirement for this vaccine exist and were used for the DCA and HLCD models. The numbers presented here are the average requirements across all 8 vaccines noted as such and do not represent individual requirements.

¹ DoD requirements for Anthrax vaccine will likely be drawn from the HHS stockpile.
² RFP from HHS on procurement of recombinant anthrax vaccine with Vaxgen.
³ HHS contract with Cangene for procurement of AIG. Assumption is that a monoclonal will replace this product by 2014. (<http://www.cangene.com/biodefense2.htm#ebola>).
⁴ DoD does not have requirement based on strategy which relies on prophylactic vaccine.
⁵ BioShield contract with Cangene for Botulinum anti-toxin to deliver 200,000 doses (<http://www.cangene.com/biodefense2.htm#ebola>).
⁶ Demand is modeled on products like Baviximab under development by Peregrine Pharmaceuticals Inc. This monoclonal product targets aminophospholipids exposed on surface of host cells infected with enveloped viruses. Minimum estimated requirement for broad-spectrum biologic derived anti-viral based on PHEMCE implementation plan prioritization of broad-spectrum, DoD R&D funding priorities, and interviews with HHS and DoD personnel. It is likely the demand would be higher, but estimate is based on the consensus of the interviewees.
⁷ DoD requirements provided by JRO.
⁸ No HHS demand was found, but several interviewees pointed out that HHS demand is limited by current funding levels and does not represent threat scenarios.
⁹ HHS Public Health Emergency Medical Countermeasure Enterprise Implementation Plan for Chemical, Biological, Radiological, and Nuclear Threats. April 2007. Plan lists requirement for anti-Radiation product procurement greater than \$100 million. Estimated demand as approximately 100,000 doses.
¹⁰ CBMS Annual Report to Congress 2007 cites program and PharmAthene press release cites contract for procurement of 90,000 doses of Protexia for DoD (<http://www.pharmathene.com>).
¹¹ HHS requirement assumed to be comparable to DoD. No anti-nerve agent is in PHEMCE plan, but licensure date of 2013 will allow several iterations of plan to develop prior to procurement.
¹² CBMS Annual Report to Congress cites licensure date and procurement contract with Cleveland Biolabs to procure 500,000 regimens if CBLB502 developed. (<http://www.cbiolabs.com>).
¹³ HHS Public Health Emergency Medical Countermeasure Enterprise Implementation Plan for Chemical, Biological, Radiological, and Nuclear Threats. April 2007. Plan lists requirement for anti-Radiation product procurement greater than \$100 million. Estimated demand as approximately 100,000 doses.

Table 3: Shared DOD and HHS requirements

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3 High Level Capability Design

How large a flexible, multi-product facility would need to be to satisfy USG MCM demand is a key factor in determining the feasibility of such the multi-product approach. The facility must be large enough to accommodate the baseline demand. This requirement involves producing initial doses for the stockpile, sustaining a warm-base of products, and replenishing doses as they expire over time. Another important capability of a flexible facility is its ability to surge production of MCMs should a threat or outbreak occur. Determining how much surge capacity the nation requires is ultimately a decision for policy makers, but the analysis performed while sizing this facility helps to inform the discussion. Finally, several qualitative arguments for making the facility either larger or smaller are discussed.

The scope of the facility is shown in Figure 5 in the context of the overall end-to-end development process for MCMs.

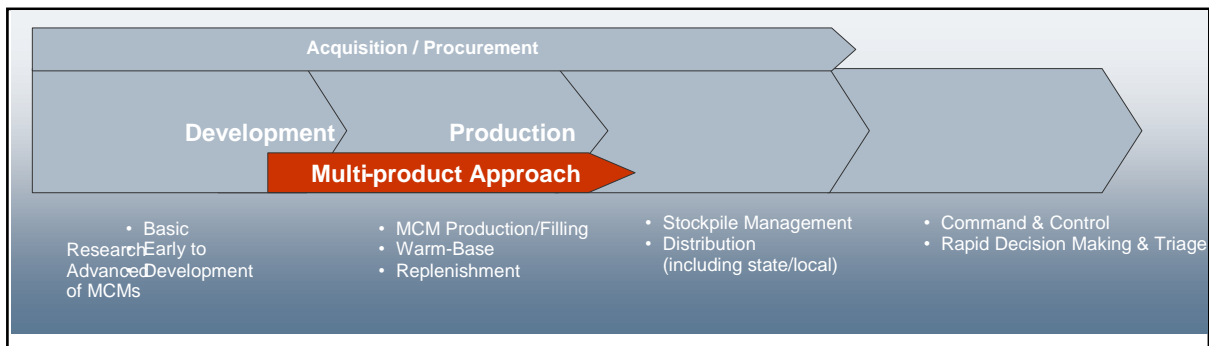


Figure 5: Dedicated Facility and the End-to-End Product Development Process

3.1 Methodology

The critical piece of information required to accurately size the facility is the *yield* achieved by each production technology. The yield, usually expressed in grams per liter (g/L), is a measurement of how much usable product comes out of each production cycle or batch. In a commercial setting, yields are generally considered trade secrets and are not published. Because of this, research was conducted from several different angles to determine the best estimate of yields. In some instances, companies or researchers publish the yields, or range of yields, that have been achieved. Yield information may also be specified in presentations at conferences. In other cases, patents were reviewed to determine a specific, most often minimum, yield. Finally, the team used its collective experience (over 40 years in the biologics manufacturing field) to fill in any gaps remaining after literature searches were conducted. All yields were then vetted through the experts serving on the project Steering Team. In all cases, conservative estimates were used when a precise answer was not identified. Sensitivity analysis was also performed to evaluate how large an impact yield estimates had on the final facility size estimate.

Once yields were established for each production technology, a spreadsheet model was created to analyze the required facility size. As shown below in Figure 6, the major model inputs included elements of expected demand, production technologies, and surge scenarios.

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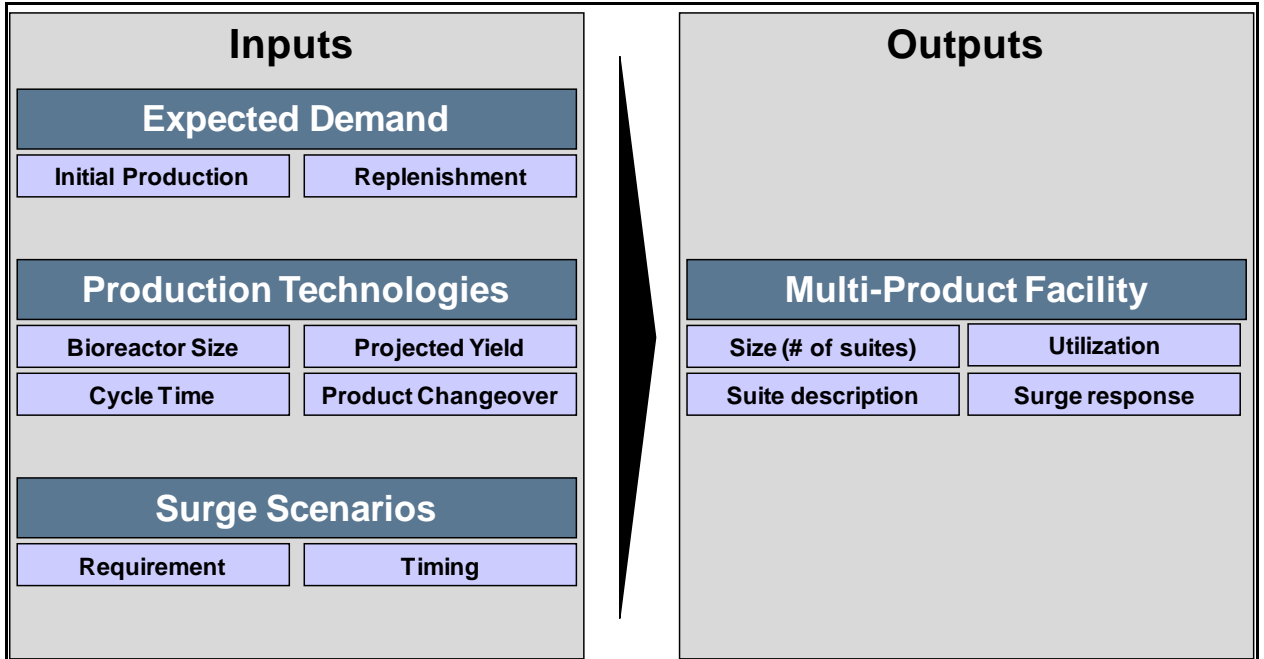


Figure 6: Facility Sizing Model

The key output of the model is the number of suites required to satisfy minimum USG demand. Additionally, the model is flexible, allowing for criteria, such as the maximum utilization and time required between changeovers, to be adjusted for the purpose of quickly assessing what the impact might be on overall facility size. Surge production can also be modeled to inform policy discussions on the required size of the facility.

Finally, research was conducted regarding employable manufacturing technologies supporting this flexible, multi-product approach. Research was focused mainly on disposable bioreactors as this is the most mature step in the production process in terms of disposable technologies. This was done although there are a growing number of examples of disposable technologies that are also in use in the isolation and purification steps.

3.1.1 Assumptions

Similar to the DCA, the capability design analysis is based on data as well as a series of assumptions. When applicable, assumptions are described in the sections where they are utilized; additionally, there are several general assumptions used in the facility modeling. These assumptions are as follows:

- Dose requirements outlined in the DCA represent the baseline demand;
- Licensure dates projected in the DCA will be met;
- Required stockpile is established over a two-year period;
- Stockpile begins with EUA, assumed to be two years prior to licensure;
- Bioreactor size has been limited to ensure flexibility (400L for eukaryotic cells and 2,000L for prokaryotic cells). As additional technologies are developed in the field, bioreactor sizes could be increased to accommodate them. For example, eukaryotic bioreactors of 1,000L size are currently entering the marketplace; and
- Production suites can operate a maximum of 40 weeks per year, with remaining weeks dedicated to maintenance (e.g., changing filters, changing seals, etc.).

3.2 Flexible, Multi-Product Approach

3.2.1 Enabling Rules and Regulations

Traditional manufacturing of biologics involves the design, build, and validation of a dedicated production facility for each licensed product. Pilot plants produced small lots of different types of MCMs for use during research and trials, but pilot plants and the products produced were not licensed. In 1995, however, FDA's Center for Biologics Evaluation and Research (CBER) released guidance stating that pilot scale manufacturing facilities could be licensed to manufacture products.

“An application for establishment licensure can be made for any facility (regardless of the scale of manufacture) that has been fully qualified and validated, that operates under cGMP's, and that otherwise complies with applicable laws and regulations.”²³

Companies quickly took advantage of this regulatory change as well as of a new array of disposable technologies that enabled smaller scale; flexible manufacturing was introduced to the market. The facility envisioned is of the same scale as existing pilot plants.

3.2.2 Enabling Technologies

Disposable sterile components in drug delivery and medicine have been evolving for many years (Figure 7). One example is the replacement of glass intravenous containers with plastic bags. A dramatic increase in acceptance of disposable biologics manufacturing equipment has greatly expanded over the past ten–fifteen years, due to innovation within industry. Since the invention of the Wave bioreactor in 1998, many companies take advantage of the opportunities that disposable biologics equipment offers.²⁴ As biopharmaceutical and biotech companies shift from blockbuster drugs to more individualized, smaller scale gene therapies, disposables, as described later, will become the only practical way of achieving success. In addition, as multi-product facilities are developed to support such changes, the value of disposable equipment will increase.

²³ FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products, July 11, 1995, Federal Register, Vol. 60, p. 35750.

²⁴ Anonymous. “The Wave Biotech Story.” http://www.wavebiotech.com/pdfs/press/WaveStory_FINAL.pdf

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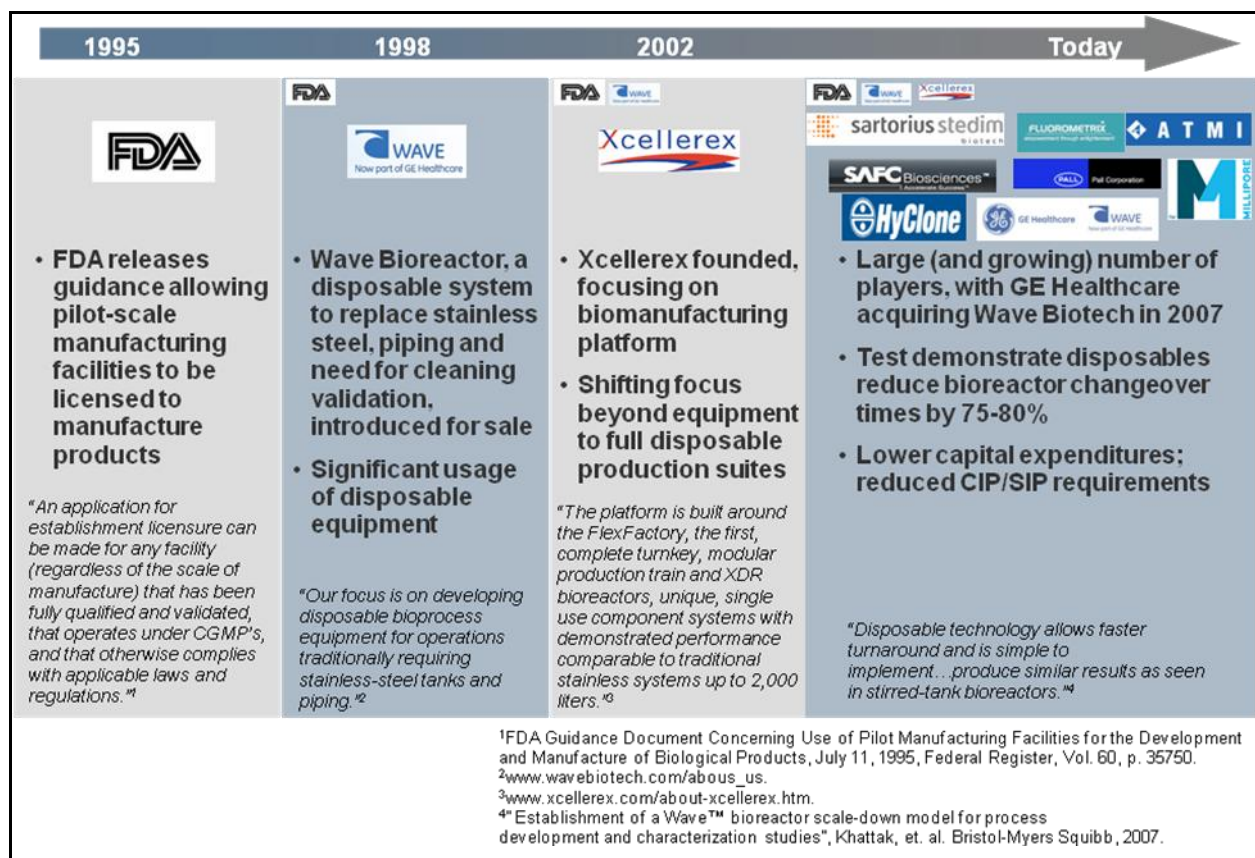


Figure 7: Growth of Disposable Technologies

Until recently, the necessary flexibility to achieve this shift was bottlenecked by the high cost of building and operating manufacturing facilities, as well as the lack of FDA certification for multiple products in a single facility.²⁵ The closed nature of disposable manufacturing reduces the potential for contamination that exists in traditional manufacturing facilities. Additionally, disposable manufacturing substantially mitigates the risks associated with multi-product development and manufacturing within a single facility. Specifically, the need to clean and sterilize equipment when switching between products can be virtually eliminated through the use of disposables. FDA's 1995 decision to permit the licensing of pilot scale manufacturing facilities to manufacture products continues to have an impact on the biotech and biopharmaceutical industry by creating a niche in which many innovative companies, like Wave and others, now specialize.

Companies have developed disposable products that have replaced every part of equipment involved in the biologics manufacturing process. The advantages that these products offer are numerous and include the ability to easily scale up from disposable equipment in R&D and trials to disposable equipment in bulk drug manufacturing.²⁶ The use of the same technology in both phases affords a significant risk mitigation opportunity. The fully automated nature of manufacturing using disposable equipment also reduces the opportunities for errors or failure.²⁷

²⁵ FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products, July 11, 1995, Federal Register, Vol. 60, p. 35750.

²⁶ Anonymous. "Viral Vector Technology for Gene Therapy." <http://www.virxsys.com/pages/the-technology/viral-vector-technology-for-gene-therapy.php>

²⁷ Pendlebury D et al. "Disposable." Future Pharmaceuticals. March 2007.

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With the same conditions during both processes, companies are no longer faced with the unintended consequences resulting from chemical interactions with steel bioreactors or particulate residue.

Beyond the complicated outcomes of chemical processes, disposable equipment offers other significant advantages over traditional biologics manufacturing equipment. Facilities employing disposable technologies offer reduced operating and capital expenditures, as well as elimination of clean-in-place or steam-in-place requirements.²⁸ Validation, an expensive step in facility construction, is no longer necessary for capital equipment, as all disposables come pre-validated by the manufacturer.²⁹ This is an important point because it shifts the financial, personnel, and capital requirements necessary to maintain regulatory compliance from the biologics producer to the equipment provider/manufacturer.

Finally, there are cost advantages to employing disposable materials. Non-disposable components of a disposable system (e.g., heating units, holders, and computers) cost approximately one-third to one-fourth the amount of fully non-disposable units.³⁰ Disposable components, according to one source, cost significantly less than the cost of cleaning, sterilizing, maintaining, and validating a steel bioreactor.³¹ These financial advantages are coupled with the decreased need for the high-quality utilities—gas, purified water—that are required to operate large-scale bioreactors. Additionally, fewer necessary HVAC capabilities are required as a result of the self-contained nature of disposable equipment (though this primarily pertains to the Xcellerex system).³²

Traditional large-scale, bulk manufacturing processes also pose a significant challenge to the emerging necessity for flexibility in the biologics industry. The ability to quickly change production lines is gaining importance. In the case of the biodefense industry, the need to respond to an attack or outbreak in a timely fashion is challenged by the changeover burden. Biopharmaceutical companies may be forced to discontinue a drug and require significant efforts to gear up production of a more profitable or successful alternative. The time required to clean, sterilize, and validate fixed bioreactors significantly impacts the capacity of companies to respond to market demands. Manufacturing capacity in disposable equipment can be easily changed over to respond as necessary. Instead of necessitating weeks of cleaning, disposable equipment can be thrown away and replaced in a matter of hours.³³

The continuing acceleration of disposable manufacturing has had a significant impact on the industry. Large firms including Baxter and Genentech, and the USG have become active in the industry.³⁴ Contract manufacturing organizations (CMOs) have yet to fully adopt disposable technologies, but as they upgrade and develop additional facilities, it is likely that disposables will play a central role for CMOs as well.³⁵

²⁸ Matthews T and Wolk B. “The Use of Disposable Technologies in Antibody Manufacturing Processes.” Process Development Engineering, Genentech, Inc. South San Francisco, CA, USA.

²⁹ DePalma A. “Bright Sky for Single-Use Bioprocess Products.” Genetic Engineering & Biotechnology News, 1 Feb. 2006. <http://www.genengnews.com/articles/chitem.aspx?aid=1319>

³⁰ Ibid.

³¹ Ibid.

³² Xcellerex. “Xcellerex, FlexFactory, and the Future of Biomanufacturing.” www.xcellerex.com

³³ Shahidi A J. “Major Benefits of Single Use Systems in the Biopharmaceutical Industry: An Evolving Technology.” BayBio 2008.

³⁴ Anonymous. “Cell Culture Advances Enable Better Biology.” Genetic Engineering & Biotechnology News, 1 Jan. 2006. www.genengnews.com/articles/chitem.aspx?aid=1217

³⁵ Anonymous. “CMO’s Aim to Boost Production Efficiency.” Genetic Engineering & Biotechnology News, 1 Oct. 2006. www.genengnews.com/articles/chitem.aspx?aid=1905

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With proven successes, large companies such as General Electric (GE) have sought to strengthen their portfolios of disposable equipment by acquiring smaller, niche manufacturers. In 2007, GE acquired Wave, the maker of the Wave bioreactor.³⁶ Other firms have either merged or similarly acquired other companies to develop an almost end-to-end portfolio of disposable manufacturing equipment. This consolidation is not complete, and independent niche players within the disposables market still exist.

3.3 Sizing the Multi-Product Facility

3.3.1 Overview

The DCA phase of the study described the size of the “market” for biologic MCMs. The timing of the demand was determined based on industry benchmarks for product development timeframes. Shown in Figure 8, the annual demand for vaccines (red) is ~60M doses while the annual demand for therapeutics (blue) is ~250,000 doses. For perspective on the scale of biodefense MCM demand, consider that the 2007–2008 flu vaccine requirement was 132M doses, and the total number of CDC-recommended childhood immunization vaccines for 2008 is 196M doses. This number was estimated by taking the United States birth cohort of approximately four million births per year multiplied by the childhood recommendations for universal immunization obtained from the CDC website.

With the demand for the 17 MCMs defined, the MCMs were then grouped into core production technologies. These are standardized ways of producing a biologic, e.g., growing a recombinant protein in *E. coli*. Each of the production technologies included in such a facility uses a bioreactor to grow cells and produces a different yield³⁷ or amount of usable material generated during a production cycle.

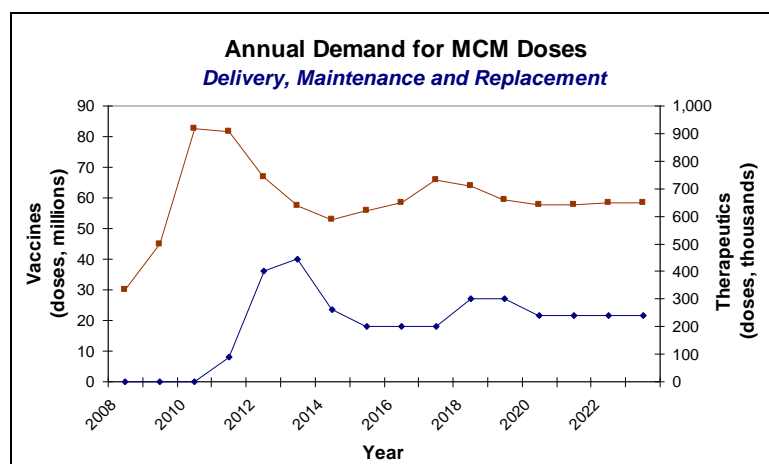


Figure 8: Biologic MCM Demand over Time

Table 4 shows the 17 MCMs defined during the DCA, the assigned production technology, and the projected licensure date. One of the MCMs, the hemorrhagic fevers vaccine, consists of two parts: a plasmid DNA-based prime given in two doses, followed by an rAdenovirus-based

³⁶ Wave Biotech. “About Us.” www.wavebiotech.com/about_us/about_us.php

³⁷ As more effort is focused on process development, yields can be increased over time. A vaccine maker will carefully consider the cost/benefit tradeoffs when deciding how much to invest in process development improvements.

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boost several months later.

| Agent | Class | Production Technology | Licensure |
|------------------------------|----------------------------|------------------------------|------------------|
| Anthrax | Therapeutic | Monoclonal Antibody | 2014 |
| | Vaccine | rProtein in E. coli | 2012 |
| Botulism | Therapeutic | Monoclonal Antibody | 2015 |
| | Vaccine | rProtein in Yeast | 2013 |
| Broad Spectrum | Therapeutic | Monoclonal Antibody | 2020 |
| Brucellosis | Vaccine | rProtein in E. coli | 2024 |
| Encephalitis (VEE, EEE, WEE) | Vaccine | Alphavirus Replicon | 2019 |
| Hemorrhagic Fevers | Vaccine (prime) | Plasmid DNA in E. Coli | 2014 |
| | Vaccine (boost) | rAdenovirus in Cell Culture | 2014 |
| Nerve Agent | Therapeutic | rProtein in Cell Culture | 2013 |
| Plague | Vaccine | rProtein in E. coli | 2011 |
| Radiation | Therapeutic | rProtein in E. coli | 2014 |
| Ricin | Vaccine | rProtein in E. coli | 2019 |
| SEB | Vaccine | rProtein in E. coli | 2018 |
| Smallpox | Therapeutic | Monoclonal Antibody | 2015 |
| | Vaccine (Spec. Population) | Virus in CEF | 2011 |
| | Vaccine | Virus in Cell Culture | 2007 |
| Tularemia | Vaccine | Bacterial Pathogen | 2020 |

Table 4: MCMs and Production Technologies

Using these and other inputs, a model was developed to calculate the space requirements for a multi-product facility. Size is described by the number of production suites within the facility. The facility size was first modeled based upon meeting the minimum USG demand expressed in the DCA. Additionally, the surge capability of the facility was evaluated to determine if additional capacity would be needed to respond to likely surge requirements. Under a surge scenario, the facility would convert all production suites to single use, producing large quantities of a particular MCM. Model inputs include:

- | | |
|--|--|
| <p><i>Expected Demand</i></p> <ul style="list-style-type: none"> ▪ Required MCMs ▪ MCMs licensure timeline | <p><i>General</i></p> <ul style="list-style-type: none"> ▪ Product changeover times ▪ # of production weeks per year |
|--|--|

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- # of years to build initial stockpile
- Shelf life
- Maximum overall utilization

Production Technologies

- Bioreactor size
- Bulk yield
- Cycle time

Based on these inputs, the model determines the size—or number of suites—of the facility, how many of the suites use 400L vs. 2,000L bioreactors, what the facility’s utilization rate is and the facility’s ability to respond to surge requirements.

Figure 9 describes the required steps to determine how many suites are needed in the facility. First, the demand for each individual MCM (Biologic A, B, C, etc) is evaluated based on a projected yield. The projected yield, provided in “human doses/L of bioreactor,” determines how many liters of bioreactor are required. In keeping with the flexible design, the bioreactor size was capped at 400L for eukaryotic cells and 2,000L for prokaryotic cells. This limiting factor enables the calculation of the number of required “batches,” or production cycles. The number of batches is then evaluated against the time horizon—40 production weeks in a year—to determine the minimum number of suites needed to meet the USG minimum demand. As the total demand will vary over time, so too will the necessary number of suites needed to meet the demand. As shown in the diagram below, the facility will be sized at a particular level. It is not a practical consideration to scale down a facility over time.

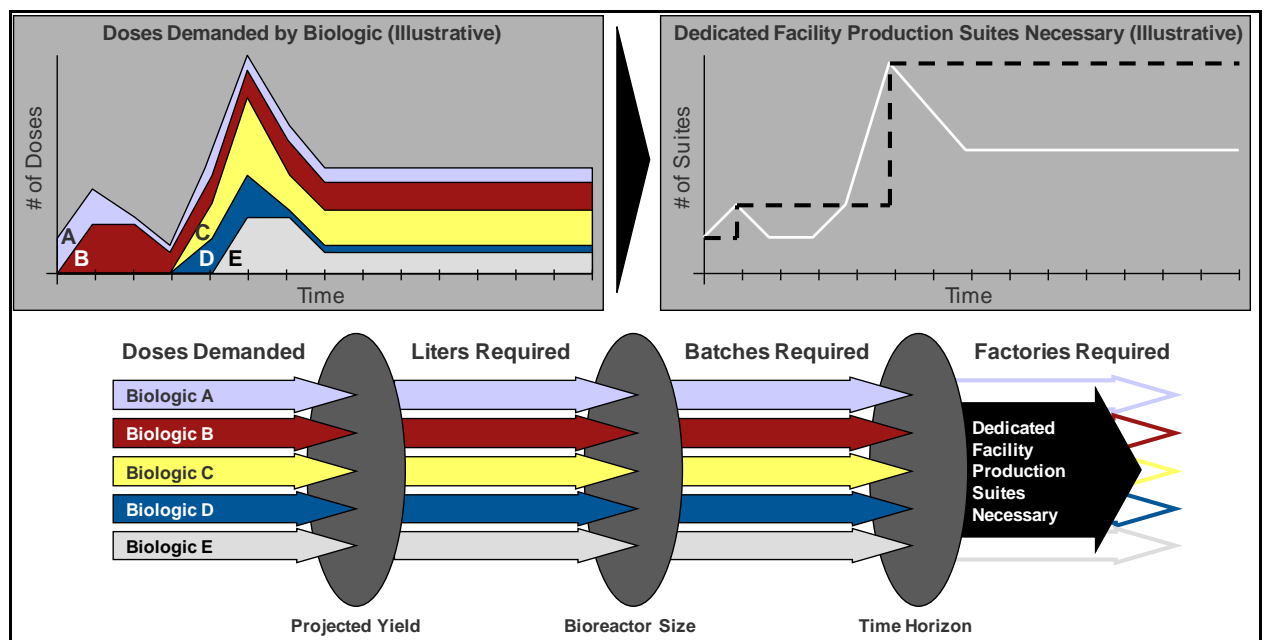


Figure 9: Facility Sizing Illustration

3.3.2 Baseline Production

The first step in sizing the facility is to determine how many production suites are required to satisfy the baseline production requirements specified in the DCA. These

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requirements consist of an initial buildup of the stockpile over a two-year period, followed by annual replenishment using the equation:

$$annual_replenishment = \left(stockpile_doses \right)^* \frac{1}{shelf_life}$$

The shelf life for most MCMs is five years. See the DCA report for a full discussion of other inputs. The production yield assumptions discussed are shown in Table 5.

| Class | MCM | Production Technology | Yield (doses per L) | Yield (doses per L per day) | |
|----------------------------|-----------------------------------|-----------------------------|---------------------|-----------------------------|--|
| Vaccine | Encephalitis (VEE, EEE, WEE) | Alphavirus Replicon | 1,000 | 36 | |
| | Tularemia | Bacterial Pathogen | 1,000 | 71 | |
| | Hemorrhagic Fevers (Ebola; DNA) | Plasmid DNA in E. coli | 150 | 11 | |
| | Hemorrhagic Fevers (Ebola; adeno) | rAdenovirus in Cell Culture | 1,000 | 36 | |
| | Anthrax | rProtein in E. coli | 1,000 | 71 | |
| | Plague | | | | |
| | Ricin | | | | |
| | SEB | | | | |
| | Brucellosis | | | | |
| | Botulism | rProtein in Yeast | 1,000 | 71 | |
| Smallpox | Virus in Cell Culture | 5,000 | 179 | | |
| Vaccine (Spec. Population) | Smallpox | Virus in CEF | 5,000 | 179 | |
| Therapeutic | Anthrax | Monoclonal Antibody | 333 | 12 | |
| | Smallpox | | | | |
| | Botulism | | | | |
| | Broad Spectrum | | | | |
| | Nerve Agent | rProtein in Cell Culture | 83 | 4 | |
| | Radiation | rProtein in E. coli | 33 | 2 | |

Table 5: Production Technology Yields

Additional assumptions include:

- Facility comes on line in 2013
- Bioreactor Size: 400L for eukaryotic; 2,000L for prokaryotic
- Cycle Time: Between two and four weeks
- 40 weeks of production time per year
- ~80% cap on utilization to provide margin for unsuccessful runs/equipment failures/unforeseen interruptions in operation
- Product changeover times:
 - Two weeks between different MCMs
 - One week between different components of the same MCM
 - No changeover between batches of the same MCM
- Two years to build up initial stockpile

Using this input data, the model calculates the number of “batches” or production cycles necessary to produce the required number of doses. The appropriate number of changeover weeks is added in order to generate a total number of production weeks required to meet the demand. Figure 10 shows how the demand for vaccine and therapeutic MCMs translates into a

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requirement for a certain number of suites in a given year. An eight-suite facility is large enough to accommodate the minimum demand specified in the DCA.

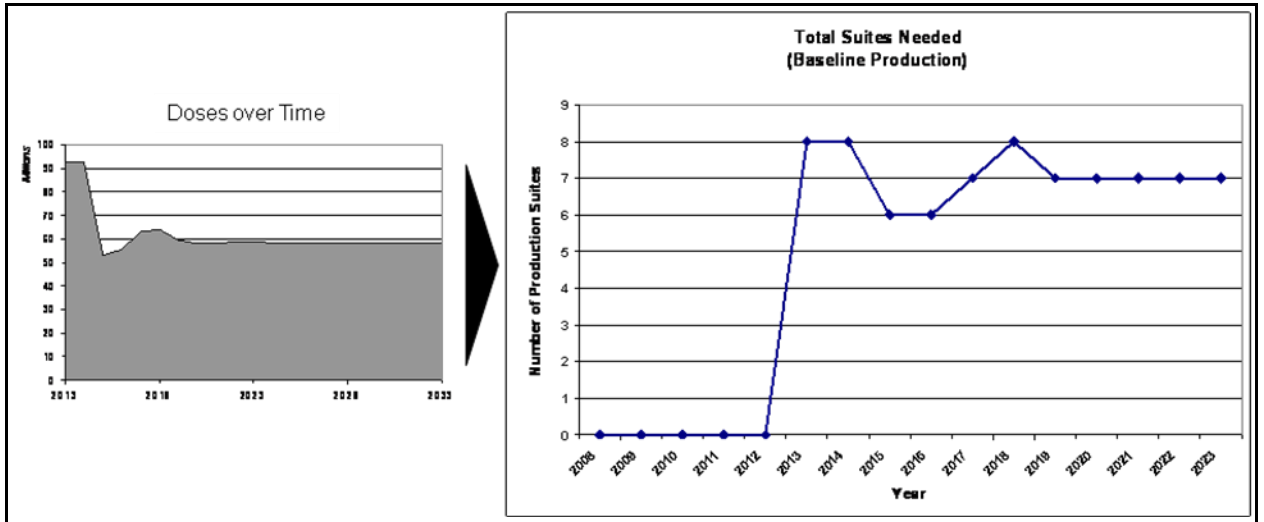


Figure 10: Facility Sizing

Because of the large number of products that need to be produced for the stockpile during the facility’s first two production years, the 80% utilization constraint was relaxed so as not to build in too much excess capacity. Table 6 shows the facility utilization over time.

| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 |
|-------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Utilization | 87.5% | 87.5% | 59.7% | 61.6% | 76.6% | 79.7% | 70.9% | 70.3% | 70.3% | 71.6% | 71.6% |

Table 6: Facility Utilization over Time

As MCM production is campaigned through the suites, each suite is likely to be used to produce multiple MCMs within a year. Figure 11 illustrates the suite utilization based on the 40-week operating limitation and displays clearly the manner in which MCM production is campaigned through the suites as well as the required changeover periods. The figure is illustrative and does not represent an actual production strategy.

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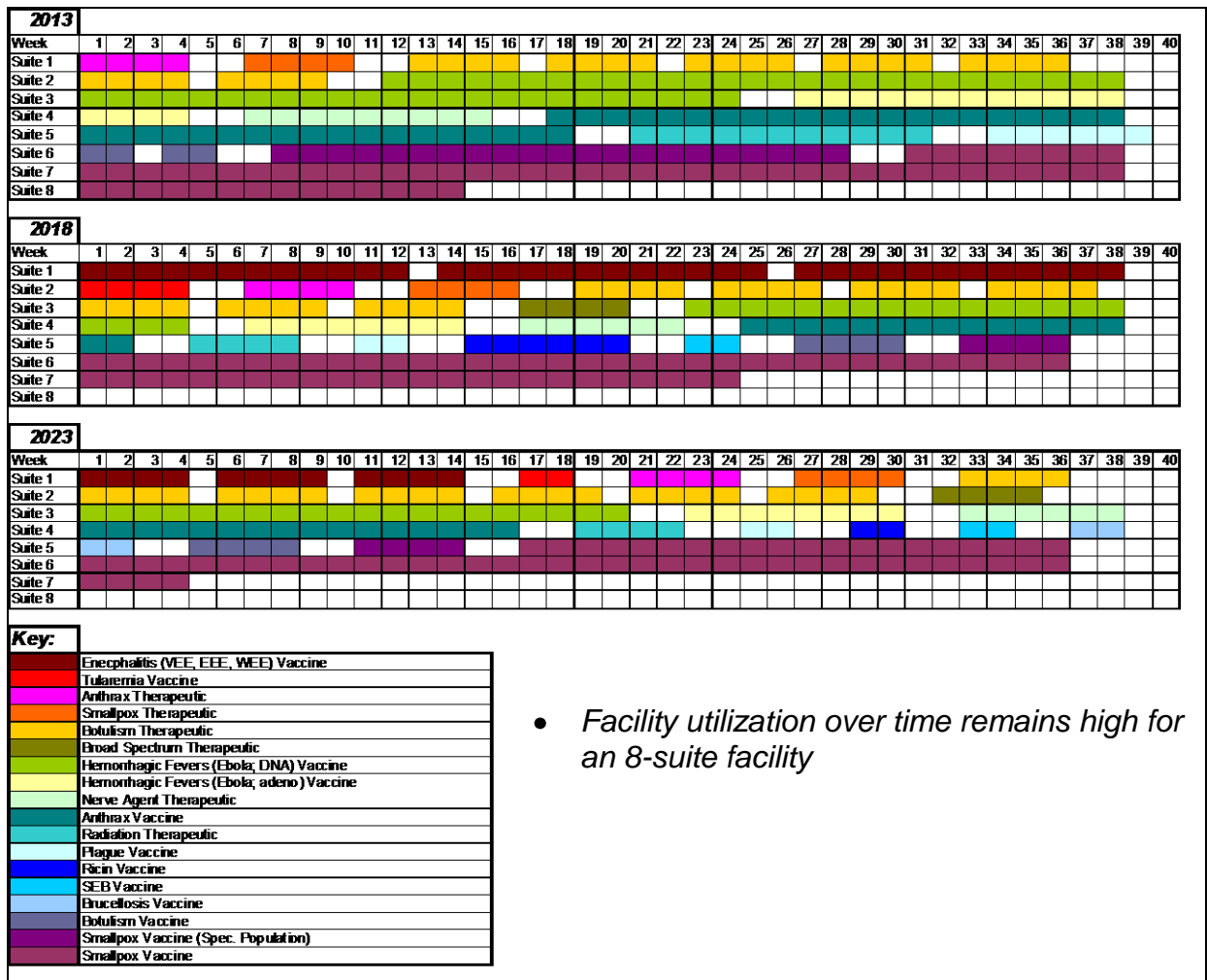


Figure 11: Suite Utilization

During the replenishment phase for each MCM, the facility will annually produce at least one batch to satisfy FDA regulatory requirements. Additionally, the facility will provide stockpile replenishment required to maintain the number of non-expired doses. It is common practice for commercial companies to invest time and resources into process development improvements that will lead to higher yields and more doses produced in each production cycle. For many of these MCMs, the stockpile replenishment requirement is so low that there is no incentive to invest in product development, i.e., the single batch required by FDA produces enough (or more than enough) doses to replenish expiring stockpile doses.

However, depending on the terms defined in the operating agreement, the entity operating the facility may have an incentive to invest in process development for particular MCMs. For example, if this entity were able to improve the yield for the anthrax vaccine by 650%, it would free up an additional six production weeks in the facility. Such an improvement is not unreasonable, given the typically low yields achieved when using relatively “new” production technologies. Benchmark comparisons show that CMOs typically rent out their suites for ~\$580K per week. Were the operating entity able to rent excess capacity as a CMO would, this would create a \$4.3M annual incentive to invest in the process development necessary to improve the yield.

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To estimate productivity a conservative approach was taken. For many of the products, published yields from research processes were used. These yields would ultimately increase if process development work was performed to optimize the manufacturing process. Process development work is typically done with relatively large teams of engineers and scientists that perform much of their work at substantial scale, which can be expensive. Process development is usually undertaken with a goal of a productivity level that either minimizes facility size, cost of production, cycle time, or other constraining factors. The analysis presented provides an opportunity to highlight which current production technologies should have additional product development to minimize their impact on the facility size and provide the best return for that investment.

One way to analyze the need for process development is to examine how many batches are required to maintain the warm-base for each product from the perspective of replacing the expired material in the stockpile. FDA requirements require at least one lot per year to be manufactured to maintain licensure. It would be most productive if only one lot were needed.

3.4 Surge Response

A key benefit of the multi-product, flexible facility is its ability to respond to a surge requirement. In the event of an outbreak, attack, or change in MCM requirements, all production suites could be quickly transitioned over so that the entire facility could manufacture required MCMs. The eight-suite facility designed to handle baseline production requirements can produce tens of millions of bulk regimens of most of the vaccines within a six-month timeframe. Therapeutics are made with less productive technologies, so fewer doses can be made in the same timeframe. A larger facility could produce more but at the marginal expense of an additional production suite, validation, and associated capital equipment.

Figure 12 shows the number of bulk regimens the eight-suite facility can produce within six months. This assumes an initial two-week changeover for preparation and four weeks at the back end to allow time for fill and finish.

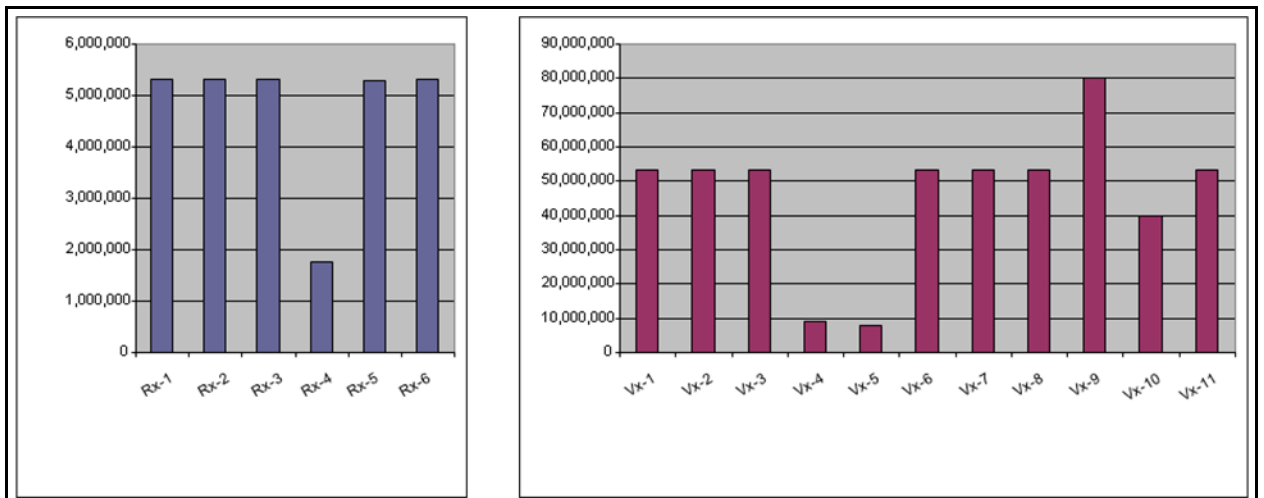


Figure 12: Six-Month Surge Capability

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3.5 *Other Considerations*

In addition to the quantitative analysis regarding the facility sizing, many qualitative assessments exist. These qualitative assessments are divided between those that would *increase* the size of the facility and those that would *decrease* the size of the facility.

The arguments to increase the facility size include:

- *Demand specified is truly the minimum.* The argument is that the specified demand is artificially limited by the actual ability of the government to procure the specified doses.
- *Excess capacity could be an incentive for commercial partners.* One possible incentive to attract an industry partner would be the flexibility to allow rental of unused capacity in the facility for clinical product manufacture. CMOs typically charge ~\$580K per week to rent out a single production suite.
- *Advanced product development space.* Depending on the exact terms of the operating agreement, the facility is likely to be managing a relatively large portfolio of products going through clinical trials and other regulatory requirements. Additional production space could be used to produce these pilot lots.
- *International markets of allied countries exist that could raise demand.* Although traditional commercial markets do not exist for these MCMs, there are other allied countries that may have a desire to purchase doses, thereby increasing the demand.

The arguments to decrease the facility size include:

- *Licensure dates might slip.* The MCM demand is based on estimated licensure dates for products in the R&D pipeline. Although these estimates are based on industry benchmarks, it is possible that these MCMs may take longer than estimated to reach a phase where EUA is possible. In addition, the full development costs of most of the MCMs are currently not budgeted in either DoD or HHS fiscal plans.
- *Initial ramp-up schedule is aggressive.* The highest utilization levels occur during the first two years when the facility comes on-line. Beginning production of a new MCM is a complex process, and the facility may not be able to begin production on all of the MCMs required immediately. This slower ramp-up period would lead to lower utilization.
- *The DCA demand assumes the government is prepared to purchase the required doses over a 25-year analysis period.* The government's commitment to long-term purchases of the MCM doses specified is a critical component of the analysis.

Each concern outlined has the ability to significantly alter the size of the facility. However, these arguments offset each other and the most prudent course of action is to size the facility based on the analyses of the required baseline production and surge capabilities to meet current minimum requirements. Analyses show that an eight-suite cGMP facility can both accommodate the baseline production requirements and provide an acceptable level of surge response.

The facility will require support areas that allow it to fulfill its mission in the production of bulk drug components. The most important of these will be process development laboratories that use the same equipment as the cGMP production areas but without cGMP restrictions. These

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laboratories will likely cover the same square footage as two production suites and require support laboratories for assay development and process development.

The facility will also require process utilities, quality control laboratories, administration space, and warehouse space. One of the most critical areas for product development would be high-containment animal facilities necessary for product development studies under the animal rule and potentially required for lot release. The recommendation is that such areas should be out-sourced to a separate partner and not necessarily housed on-site. Such functional areas would best be done at a location with such expertise and ongoing operations (e.g., Battelle, Lovelace Laboratories, academic institutions, USAMRIID, CDC, NIAID).

The UPMC study focuses on bulk manufacturing, but clearly integration with fill/package/finish capability is critical for the ultimate success of the overall mission to deliver MCMs to the stockpile and distribute MCMs to the field. In general, it is recommended that fill/package/finish capability be obtained through agreements with contract filling organizations as this capability is well established.

Two gaps, however, have been identified. The first is in the filling of viral materials. The consensus in terms of this being that currently there are very limited capabilities in the field for these types of products, and this capability may need to establish filling using technologies such as barrier/isolator. Second, in the event of surge or even routine production, the supply chain for syringes, vials, stoppers, and other components might quickly become rate-limiting and result in a bottleneck that prevents the delivery of MCMs to the field.

4 Operating Model

4.1 Methodology

The operating model describes the operations, resources, and partners necessary to fulfill the mission of advanced development of new MCMs and the manufacturing of them for the USG.

The methodology for planning the operating model is grounded in a data-driven process focused on fulfilling the USG mission. First, the operations needed to deliver the mission (i.e., product development, clinical, manufacturing operations) are defined. Those operations are then assessed in greater detail to determine which functions will reside within the dedicated multi-product facility and which will be either contracted out or accomplished through a strategic alliance. Next, the internal functions are examined to determine the resources necessary to fulfill the mission, as well as what kinds of partners are needed to provide such resources. Finally, a series of partnership structures are evaluated as to their ability to provide resources while offering partners the proper incentives, all while managing risk and cost.

4.1.1 Assumptions

The operating model is a high-level assessment of the operational framework and organizational structure of a dedicated multi-product facility for the advanced development and manufacturing of biologic MCMs to meet USG biodefense requirements. The economic modeling and risk analysis used to evaluate partnership structure options are based on high-level assumptions. These assumptions will be discussed in greater detail in subsequent sections. The resources and incentives are informed possibilities, based on the best information currently available and the guidance of multiple subject-matter experts. A comprehensive biologics

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industry survey would supplement this analysis by identifying the necessary conditions to allow for an alignment of USG and industry needs to create mutually beneficial outcomes as partners in a multi-product approach. The survey would enrich the range of options for engaging biopharma while retaining the participation of biotech companies. Such a survey was, however, outside the scope of the UPMC study.

Generally, the following was assumed:

- The dedicated facility will focus on developing biologic MCMs required by USG, as defined in the DCA, through advanced development and manufacturing for USG procurement;
- The advanced development goal of the facility will be to develop MCMs from post-Phase I through FDA licensure. The facility will be developing MCMs for the Strategic National Stockpile and military use. In doing so, the facility will develop products through BLA and FDA approval, in order to incorporate safe and effective MCMs into the national stockpile;
- The facility will utilize flexible manufacturing platforms and disposable technology to take advantage of horizontal economies of scale, as defined in the HLCD; and
- The facility will seek to leverage existing assets through partnerships and alliances to accomplish its mission.

4.2 **Mission**

4.2.1 **Overview**

Mission Statement:

To perform advanced development and manufacturing of MCMs to fulfill USG demand requirements in a reliable and cost-effective manner.

4.2.2 **Market Environment**

The mission stated above will be accomplished in a unique market environment.

- **Many low-volume requirements:** USG demands more than 500M MCM doses over the next 15 years, but that demand is spread across 17 different MCMs. Depending upon the year, the MCM, and its shelf life, this demand can translate into an annual requirement as low as 4,000 doses based on current minimum requirements. This amount is substantially below the typical demand for a vaccine, even for the United States population. The birth cohort in the U.S. is approximately 4M, and most childhood vaccines require three–four doses to complete the series.³⁸

³⁸ CIA, “The World Factbook,” (<https://www.cia.gov/library/publications/the-world-factbook/geos/us.html>)

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- **Dynamic demand:** Moreover, the MCM demand is dynamic; it will vary depending upon changing threat determinations and other unpredictable factors. USG requirements may change, new products may emerge from breakthrough research, licensure dates for MCM candidates may change, and the definition of demand may broaden to include emerging public health threats.
- **Fractured R&D environment:** USG requirements are being researched and put through early-stage development by dozens of biopharmaceutical innovators, including small biotech, large biotech, and regional centers of excellence (university and other research laboratories so designated by the USG, known as RCEs). These innovators have varying market requirements, depending upon the size and stage of their organization.
- **Monopsony:** The USG represents the sole buyer of MCMs within the United States, making ventures into any stage of research, development, and manufacturing highly risky. Suppliers (MCM developers) develop MCM candidates without an alternative market and rely on a dynamic USG demand that may change in unpredictable ways. Suppliers are thus developing products for which there is no certainty regarding how much will be purchased and, in some cases, whether the market for a particular product will remain stable once the product is licensed. In the future, other governments closely allied to the United States may become additional buyers.
- **Stringent regulation:** Biologics are difficult to manufacture and are highly regulated by CBER, a division of FDA. Vaccine and drug developers who lack the required expertise face high risks to success of product development.

4.3 *Operations*

4.3.1 Operational Stages

Operations to fulfill the dedicated facility's mission include establishing the capability and then conducting continuing operations. Establishing the capability refers to the one-time action of setting up the organization, workforce, and facility. In accordance with standard practice in the biopharmaceutical industry, implementing the capability consists of three stages.

- Stage 1 formulates the concept for the facility and studies its feasibility. This stage is represented by the UPMC study along with additional proposed activities, such as comprehensive industry outreach and a detailed regulatory strategy for setting up and validating manufacturing operations.
- Stage 2 develops a conceptual facility design and more detailed plan for management and operations. This stage would include engagement of an architecture and engineering firm.
- Stage 3 builds and validates the facility and establishes the organization and operating agreements. Depending on the facility scale, this stage could cost on the order of hundreds of millions of dollars. Continuing operations refer to ongoing activities to operate the facility and supply MCMs. These activities include product development, manufacturing, and maintenance of the facility. For each MCM, continuing operations occur in two stages: advanced development and lifecycle management. Advanced development refers to all actions required to bring vaccine or drug MCM candidates to FDA licensure. Lifecycle management refers to all actions involved in the manufacture of

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approved MCMs for stockpile or use, replenishment of stockpiles, maintenance of a warm-base for production, and provision for surge production in case of a crisis, change in demand, or heightened threat assessment.

Figure 13 depicts a timeline for establishing the facility and conducting continuing operations. As indicated in the diagram, some overlap occurs between building the facility and operating it. For example, the first MCM product candidate to be licensed into the facility will be selected before the facility is complete. If this candidate requires advanced development, some of these activities can begin before the facility is fully operational. As described in the HLCD, the facility could be built in a modular fashion, and some advanced development and manufacturing capacity could be made operational before the entire facility was complete.

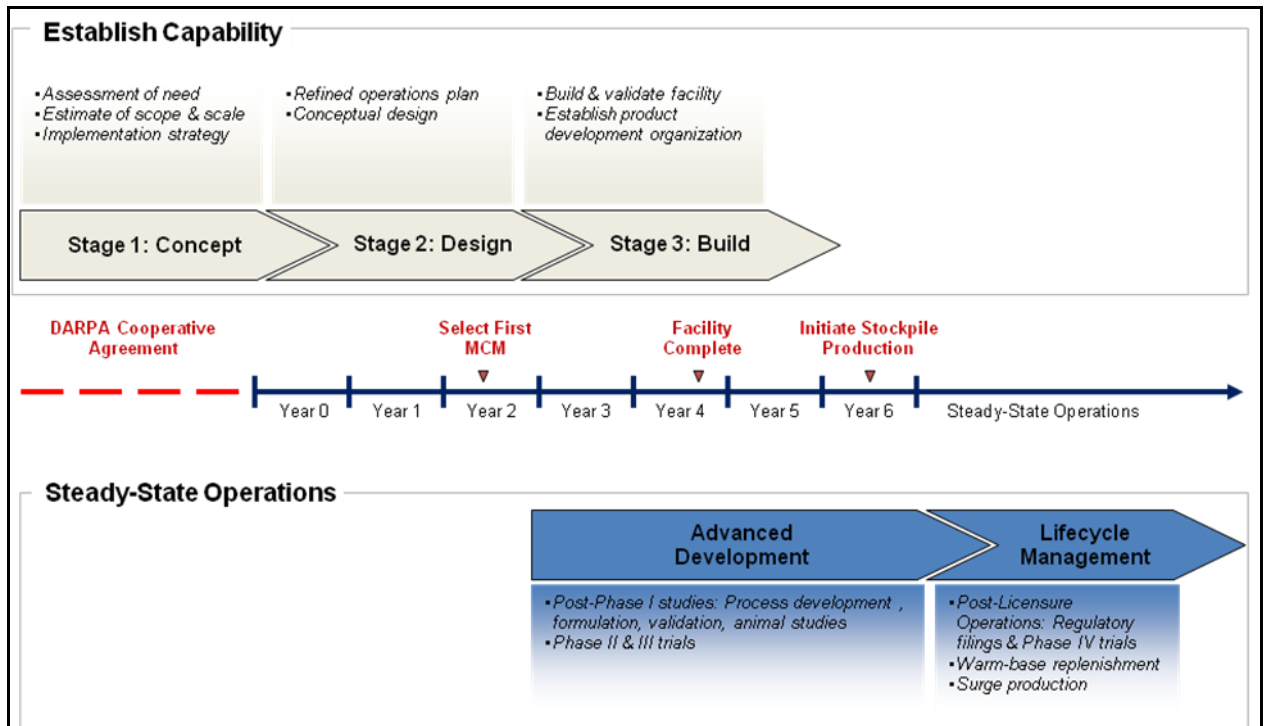


Figure 13: Timeline for Development and Operations of the Capability

Within the scope of the UPMC study, emphasis is on continuing operations. While designing and building the facility are considered as part of the analysis, the operations, resources, and partners involved in the dedicated facility are assessed primarily with the ongoing mission of supplying MCMs in mind.

4.3.2 Functional Areas for Continuing Operations

Continuing operations are fulfilled by a broad array of multi-disciplinary functional areas. The functional areas are the detailed operations that span advanced development and lifecycle management. They reflect at a high level the would-be organizational chart of the dedicated facility. Functional areas are listed in Table 7. They are outlined at three levels of granularity to determine the decision point where functions can be differentiated in terms of either those performed internally or those accomplished through external alliances and contractors.

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| Level I | Level II | Level III | Level I | Level II | Level III | |
|------------------------|----------------------------|---------------------------------------|------------------|-------------------------|-------------------|-----------------------------|
| Admin | Licensing/BD | | Operations | Quality Control | Wet Chemistry | |
| | Portfolio Management | | | | Manufacturing | Animal Potency |
| | Legal | | | | | Microbiology/ Immunology |
| | Finance | | | Bulk | | |
| | Human Resources | | | Formulation/Fill/Finish | | |
| | Information Technology | | | Supply Chain | | |
| | Contracting | Commercial USG | | Engineering | Process Equipment | |
| | Security | | | | Facility | |
| | Executive-Level Management | | | | Maintenance | |
| | Project Management | | | Technical Services | | |
| Clinical | Clinical Design | | Plant Management | | | |
| | Pharmacovigilance | | Safety | | | |
| | Operations | | Regulatory | | | |
| | Employee Health and Safety | | QA/Regulatory | QA | Compliance | |
| Product Development | | | | | Regulatory | Lot Release |
| Clinical Assays | Non-Clinical | Animal Study Program Management | | | | Validation |
| | | Model Development | | Training | | |
| Animal Facility | | | | | | |
| Scientific Design | | | | | | |
| Toxicology | | | | | | |
| Analytical Development | | | | | | |
| Process Development | | Formulation | | | | |
| | | Bulk Manufacture | | | | |
| | Clinical Manufacture | | | | | |

*Derived from comparative analysis of existing biopharmaceutical operating structures

Table 7: Functional Areas for Continuing Operations

The functional areas were determined through a comparative analysis of existing operating structures in the biopharmaceutical industry for advanced development and manufacturing.

4.3.3 Defining Functions by Specialization and Strategic Alignment

The facility will not perform all functions directly. It will have “core competencies” in certain areas, such as process development and flexible, multi-product biomanufacturing. The facility could also outsource some functions, forming strategic alliances with external parties that already demonstrate best practices in specific areas and are available for a business alliance or vendor relationship. For example, some specialized research skills differ significantly from product development skills. While both skill sets are critical to developing MCMs, particular research skills are already established and do not need to be accomplished at the facility. Animal model studies, for instance, are functions that the facility itself could try to perform but which outside parties are as well or better positioned to provide.

To delineate which functions the facility would perform internally and which it would outsource through external relationships, a framework was established to assess each function as to its specialization in terms of product development and manufacturing as well as its strategic alignment with the facility’s mission. Functions were differentiated in terms of four categories:

- Internal functions that the facility can best perform;
- Strategic alliance functions that are best fulfilled through agreements with specific, expert organizations. These functions require close communication, coordination, and long-term agreements;
- Contract functions to be provided through routine vendor agreements; and

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- Service offering functions that the facility is positioned to provide but which are not central to fulfilling its mission. Such services could be offered to other organizations on a consulting basis, as long as they do not distract from core mission functions.

In terms of specialization for product development and strategic alignment with the facility, the categories are oriented as follows:

- Internal functions—high specialization, high strategic alignment;
- Strategic alliance functions—high specialization, low strategic alignment;
- Contract functions—low specialization, low strategic alignment; and
- Service offering functions—low specialization, high strategic alignment.

Figure 14 summarizes the framework for determining which functions the facility will provide internally.

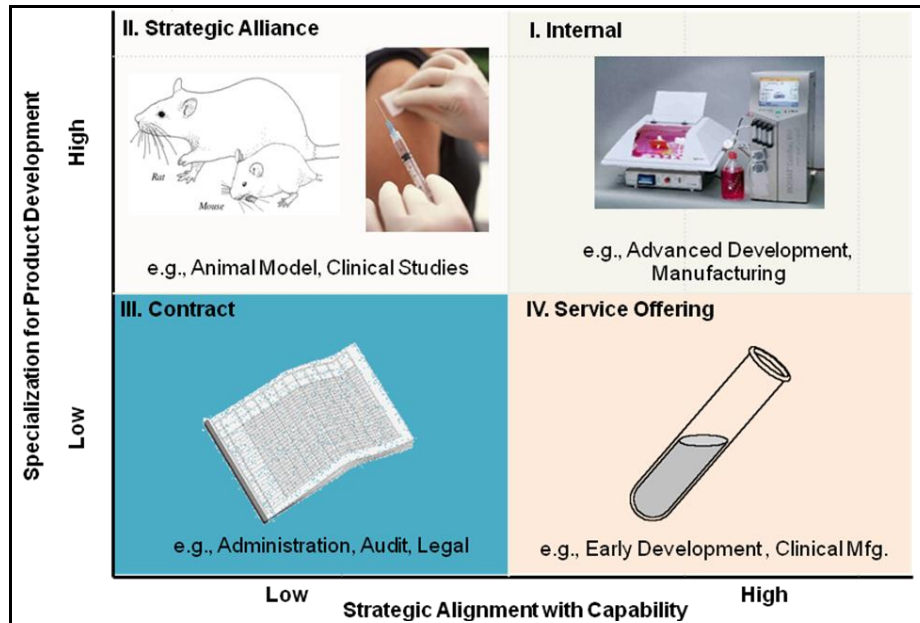


Figure 14: Selecting Internal Activity and External Relationships

4.3.4 Defining Internal Functions and External Relationships

Internal functions include advanced development, manufacturing, project management, and executive leadership. These activities are all highly specialized for product development and aligned with the capability’s “core competencies.” Strategic alliance functions include clinical studies and animal model work that could most effectively be conducted with existing facilities. Contract functions include routine administration, finance, and legal services and are best contracted to outside vendors who specialize in these non-strategic tasks. Service offering functions include early development and clinical manufacturing, which the capability is well positioned to do but which are not central to its mission. The capability will most likely be able to assist and guide early development but will not concentrate on such efforts internally.

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4.4 Resources

4.4.1 Resources that Provide Internal Functions

The facility's internal functions will require resources, which can be categorized into four areas: products, expertise, financing, and management.

4.4.2 Products

Products consist of Phase 1 candidate vaccines and therapeutic drugs that address the 17 MCMs specified by USG biodefense requirements. These products are currently in various phases of discovery and development, and most of them have no commercial market. Potential MCM candidates usually originate with a broad array of biodefense innovators, including small biotech companies and academic and USG labs that are researching biodefense products.

Biodefense innovators excel at researching new vaccines and drugs but do not have in-depth experience with the challenging process of process development, formulation, and clinical trial management necessary to achieve FDA licensure. Biodefense innovators also usually lack manufacturing assets and the ability to scale up a manufacturing process to produce large quantities of product. The result is that biodefense innovators are capable of providing the product, but they are unable to provide the expertise and management resources needed by the facility.

4.4.3 Expertise

The expertise required for a multi-product approach includes the technical skills in bioprocessing and biomanufacturing to bring biologics to market. This expertise can be acquired as both human capital (workforce) and intellectual property (IP) that includes process development and manufacturing platform technology. Human capital must be highly specialized in biologics development and must have the multi-disciplinary training necessary to excel in a facility developing and manufacturing multiple products simultaneously. For a dedicated capability to acquire such expertise, much of such talent will have to be recruited to work internally at the facility. IP must consist of standard operating procedures and a quality system.

Expertise, as outlined above, resides in the biopharmaceutical industry, which has extensive experience bringing vaccine and drug products to market.

4.4.4 Financing

A significant amount of financial capital will be required to establish and operate the facility. Based on the model, the estimated upfront investment in the facility approaches \$750M. The annual operating capital needed is currently estimated at approximately \$250M per year. In order to attract the biopharmaceutical industry to participate in a program of this scale, the USG must make a substantial capital contribution up front. This contribution would make a statement of USG commitment to the venture and allow private money to obtain the attractive borrowing rates (less than 35%) that they would need to be involved for start-up and ongoing operations.

Financing a dedicated capability will require a long-term investment horizon and consistency of purpose and funding from the USG. Funding could involve equity (cash) or debt

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(e.g., instruments such as bonds or project finance) and would require transparency of activities as appropriate for a public initiative.

4.4.5 Management

Management resources of the facility are comprised of the human leadership and management systems necessary to direct a biopharmaceutical enterprise and command a public-private partnership. Management must be able to navigate the complex scientific, technological, and political environment of the dedicated capability, including the strict regulatory environment governing the development of biologics. It must have the authority and flexibility to engage in dynamic, agile practices to balance and satisfy both public relations needs as well as the requirements of USG and industry. Management systems also must be agile in order to recruit and retain a talented workforce in a competitive labor market and ensure the transparency of operations that sustain such a public-private enterprise.

4.4.6 Resources Provided by Partners

Senior leadership should be recruited from industry as well as the not-for-profit sector. Industry recruitment is essential to guarantee experience in product development and manufacturing. Expertise from the not-for-profit sector should be engaged to provide guidance on how to do business under a public service mandate. Management resources also must be developed organically over time. As discussed in Section 4.5, human capital growth will be an important component of a dedicated capability. Management and other resources will be provided by institutional partners, including USG, the biopharma industry, the biotechnology community, and non-profit public health or life science organizations. Management resources are a particularly valuable commodity at these institutions, and a dedicated capability's ability to expand the pool of biopharmaceutical talent will play an important role in ensuring partner participation.

Figure 15 illustrates an example of how different partners could provide the resources necessary for the success of a dedicated capability. There are many different possible formulas for matching resources with the providing partners, and the exact provisions would be determined through proposals for implementing the facility and agreements between partners. Figure 15 defines one possible scenario. The biopharma industry is well positioned to provide the expertise in advanced development and manufacturing. Small biotechnology companies and other biodefense innovators such as RCEs and USG labs would provide most of the products and early-stage development expertise, such knowledge being important for transitioning the products to advanced development. In order to demonstrate commitment to its demand for MCMs and allow for the facility to be built with lower borrowing costs when compared with entirely private funding, the USG should be positioned to provide much of the initial capital.

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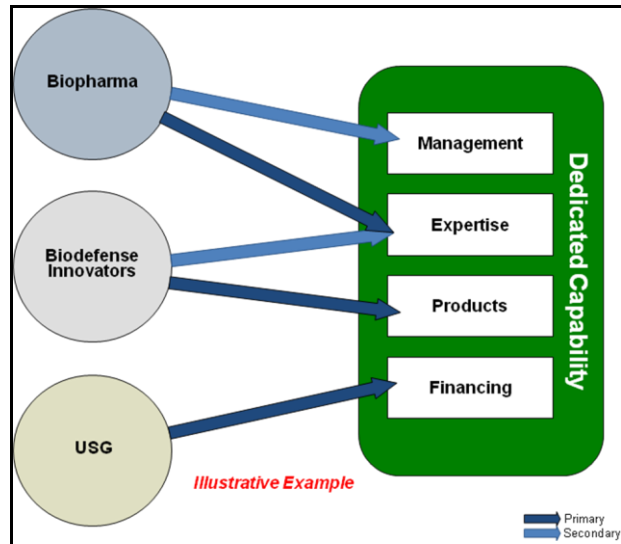


Figure 15: Illustrative Example of Partners and Resources

4.5 Partners

4.5.1 Aligning the Interests of Public and Private Partners

Both public and private partners are critical to providing the resources required to fulfill the mission and internal operations of a dedicated capability. This analysis and those of the prior USG studies in 1993 and 2001 support this conclusion.^{39, 40} The remaining question is how to engage and align interests of these partners to ensure they bring appropriate and best practices to any collaboration.

The USG and biodefense innovators already engage in partnerships for research and development of new MCMs.⁴¹ The challenge lies in providing incentives to retain and expand biodefense innovator participation—and to engage biopharma—without alienating innovators who may be reluctant to allow biopharma access to products and IP. In the process, the USG commitment to the market must be maintained by ensuring the advantages a dedicated capability could offer in mission fulfillment.

A comprehensive understanding of the incentives and barriers facing each partner requires an extensive industry outreach; however, limited outreach suggests that there are a number of ways partner participation could be ensured.

4.5.2 Partner Incentives and Barriers

Biodefense Innovators' Incentives and Barriers

A traditional business strategy for a small biotech company is to retain control of product development through FDA licensure and independently build or contract its manufacturing capacity to another party. The goal under the flexible, multi-product approach is for the company to integrate development and manufacturing as it grows, emulating the model set by large,

³⁹ DoD Vaccine Production Facility Task Force Final Report.

⁴⁰ Report on Biological Warfare Defense Vaccine Research and Development Programs.

⁴¹ See DCA report survey on USG R&D pipeline for MCM development.

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successful biotech firms such as Amgen (NASDAQ: AMGN) and Genentech (NYSE: DNA). These two firms built success upon blockbuster commercial products. Small biotech companies focused on biodefense require a different strategy in order to grow. Developing MCM products may build a biotech's expertise and demonstrate a track record of success, but MCMs against bioterrorism threats do not offer the outsized returns on investment of blockbuster products.

The collaboration implied by a dedicated capability, where innovators would contribute MCM candidates for co-development at the advanced stage, would allow innovators to focus on their core competency: research and early-stage development. Once MCM candidates have been transferred into the facility for advanced development, the innovators can pursue new products. Innovators can transition to commercial product development or remain primarily MCM developers, but either way reliance on transferred MCM product for success is no longer needed. Should a dedicated capability be implemented, innovators must be provided with incentives to justify what will in some cases be a strategic shift and must continue to develop new MCM candidate products to be brought to the facility.

Incentives for participation by biodefense innovators include the following:

- *Reduced Reliance on Capital Markets*—Innovators would not need venture capital and other private investment to fund an MCM candidate's development through licensure;
- *Increased Probability of Success*—Biopharma expertise would enhance biodefense innovators' ability to complete advanced development;
- *Milestones and Royalties on Technology Transfer and Delivered Products*—Financial compensation would reward the risk of researching new MCMs by and provide a return on investment to private investor capital from innovators;
- *Access to Data and Proof of Concept for Commercial Products*—Knowledge gained in process development through developing an MCM candidate at the facility could be leveraged by the innovator in future public and private sector products;
- *Focus Resources on New Innovations*—Innovators are allowed to concentrate on what is arguably their strength, researching new biologics, instead of diluting scarce resources on scale-up and manufacturing expertise.

These and other incentives must be put in place to overcome barriers to biodefense innovator participation and retention. Barriers to biodefense innovator participation include the following:

- *Reduced USG Subsidization*—The availability of fewer grants and other funding with which innovators finance operations; and
- *Less Independence*—Innovators would relinquish control over MCM product development after Phase I, contradicting common business strategy to control product through licensure, manufacturing, and sales and marketing.

For financial incentives to overcome barriers to biodefense innovator participation, innovators must be compensated for private investments that support MCM R&D through Phase I. Typically, innovator R&D are supported by a mix of USG funding and private capital (e.g., angel investors, loans, or venture capital). For innovators participating in a dedicated capability, when the capability takes on advanced development of an MCM candidate, the innovators' early-

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stage private investors must be compensated for the risk assumed through their initial support of R&D. For a commercial product, this occurs when investors sell their stake for a multiple of the initial investment, which often occurs three–five years after investment.

For MCMs, a dedicated capability, through a system of milestone payments and royalties, must provide that return on investment in place of the commercial market. The timeline for these payments is longer than under a commercial arrangement; it typically requires eight–ten years for an MCM to complete clinical trials, be licensed, and begin production. For compensation to remain proportional to that of commercial investment, the return of investment over time will have to be significantly higher. For example, if a commercial investment requires a 5x multiple after three–five years, a biodefense MCM investment would require a 10–15x multiple after eight–ten years. This return on investment would be limited to only the private sector portion of the original investment.

Figure 16 illustrates an example of biodefense innovator return on private investment to compensate for significant risk in innovation. Many scenarios are possible for mixed USG-private funding of R&D through Phase I. The example in Figure 16 uses an illustrative scenario of 75% USG funding and 25% private funding, five biodefense innovators with candidate MCMs to address a particular threat agent, and \$20 million in total cost of early stage development, from research through Phase I.

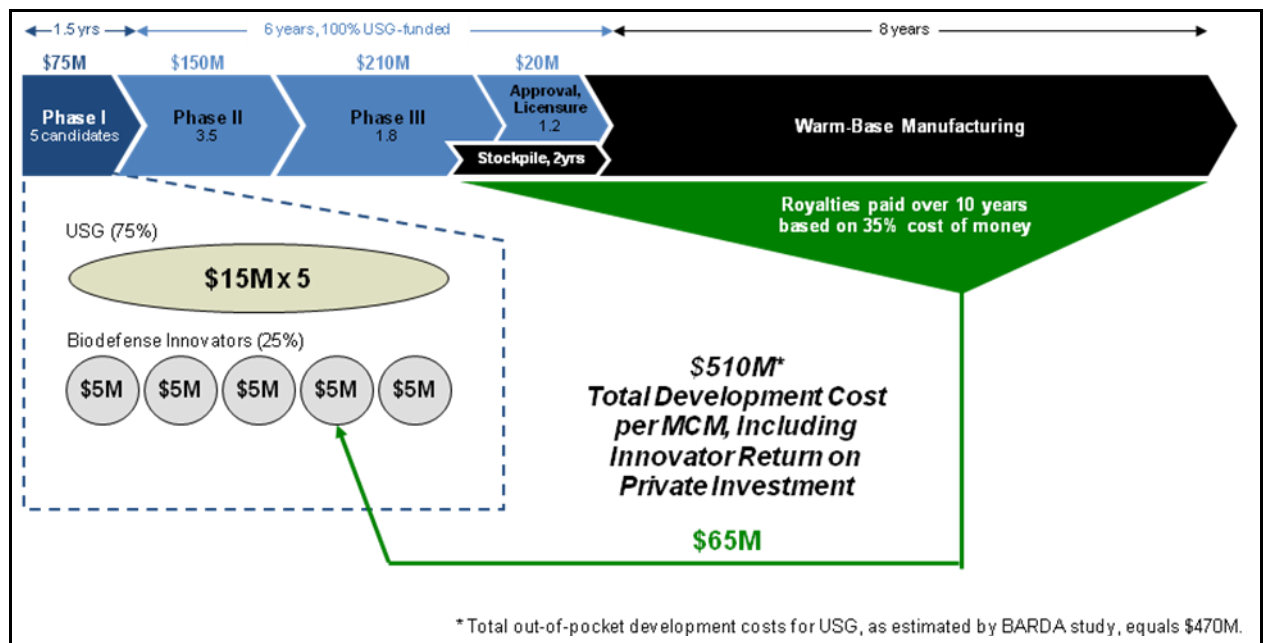


Figure 16: Example of Biodefense Innovator Return on Private Investment

In this scenario, each of the five innovators invests five million dollars of private equity into the development of a product that reaches Phase I clinical testing. Biotechnology companies make investment in products in the hope that they will be successful and ultimately provide a return to their investors. This is acknowledged as a high-risk venture, where the probability of success is low but the potential for a high return creates the incentive to invest. Any model for the development of MCMs must ensure that incentives for the participation of biodefense innovators remain. In the economic model developed, we assumed that only one innovator’s MCM candidate is successful in ultimately reaching licensure (out of the five that reach Phase I).

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The compensation back to the innovator, in the form of milestone payments and royalties, would be paid out over ten years while the product is being delivered to the USG stockpile. Given the high failure rate of drugs during their development (for example less than 20% of products that are in Phase 1 clinical testing will ever make it to licensure), companies seek a return of approximately 35% on their investment knowing that more than 80% of the time they will get no return. At these returns, the return to the biodefense innovator would be approximately sixty-five million. Ultimately, there are many options for developing the necessary incentives for biodefense innovators; this particular return was used as a place-holder in the economic analysis to capture this concept.

USG Incentives and Barriers

As discussed above, USG participation in a dedicated capability would take the form of a long-term commitment to the demand for biodefense MCMs.

Incentives for participation by the USG include the following:

- *Cost Savings and Reduced Risk*—A strategic approach to MCM acquisition would be acquired at a lower total cost over time and with improved probability of success in MCM development;
- *Reliable Supply of MCMs*—A reliable operating model would be put in place for the success of MCM development and manufacturing;
- *Accelerated Development*—Advanced development knowledge and expertise would be applied across products to bring MCMs to licensure on an accelerated timeline in comparison to multiple developers acting independently;
- *Increased Return on Investment (ROI) on Research Dollars Spent*—USG investment in R&D and early development would be better spent if the advanced development and manufacturing challenges were overcome; and
- *Support for National Competitiveness in Bioscience/Biomanufacturing*—USG investment in a dedicated capability would grow the human capital required to maintain a healthy domestic biomanufacturing industry.

These and any other incentives must be sufficient to overcome barriers to USG participation such as:

- *Long-term Commitment*—The USG, facing a dynamic policy environment, may struggle to maintain a long-term commitment to biodefense MCMs in regard to which both threat and technologies may change suddenly;
- *Oversight Requirements*—Heavy USG oversight requirements may undermine the flexibility required for a dedicated capability to succeed;
- *Contracting Inflexibility*—The USG may be limited in the type of contracts it can engage in to build a dedicated capability and procure MCMs; and
- *Perceived Commercial Interference*—USG support for a dedicated capability, if not focused on noncommercial products, risks being perceived as interfering in the commercial sector and unfairly supporting particular companies over others.

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Biopharma Incentives and Barriers

Incentives for participation by biopharma include the following:

- *Goodwill*—Marketing benefits could be acquired for participation in a program that serves national security and the public interest;
- *Access to New Manufacturing Platforms*—Through a dedicated capability, a biopharma partner could experiment with new technologies for process development and manufacturing that it could not otherwise afford to experiment with for its commercial products;
- *Unused Capacity Use*—Participating biopharma could use a dedicated capability’s excess capacity for clinical lot production of commercial products or advanced development;
- *Liability Protection*—Indemnification could be provided for legal liability in MCM development, if needed, above and beyond that provided by BioShield and SAFETY and PREP acts;
- *Priority Review Vouchers (PRVs)*—Legislation could allow regulatory rewards, such as vouchers for FDA priority review of commercial product applications, to be available in exchange for development of biodefense MCMs. The precedent for PRV use has been established for neglected tropical diseases;⁴²
- *Tax Credits*—Participating biopharma could be ensured tax credit eligibility for orphan drugs and other development work for biodefense MCM candidates in the facility; and
- *Human Capital Growth*—Workforce trained at a dedicated capability could become an important source of multi-disciplinary talent for biopharma.

These and any other incentives must be sufficient to overcome barriers to biopharma participation. Barriers for participation by biopharma include the following:

- *Distraction to Core Business*—Biopharmas, operating in extremely competitive commercial markets, may be reluctant partners out of concerns that involvement could distract management and expertise and divert resources from commercial business;
- *Opportunity Cost*—Participation in a dedicated capability would substitute for employing resources elsewhere, whether that be commercial activities or charitable endeavors that also would provide goodwill, tax credits, and other incentives; and
- *Understanding USG Business Practices*—Unfamiliarity with government contracting practices could deter biopharmas, which may be inexperienced with evaluating risk and cost of pursuing government business.

4.5.3 Partnership Structure Options

There are a number of different ways to structure a partnership among biodefense innovators, the USG, and biopharmas. Partnership structure options fall along a spectrum of public and private approaches to ownership and operational control. On the public end of the spectrum lies the government owned and operated option with innovator participation as a source of MCM candidates and biopharma participation as a potential source of human or intellectual

⁴² The use of PRVs has been authorized for tropical diseases (diseases that are infectious or parasitic and typically affect large populations in poor developing nations) by FDA Amendments Act (FDAAA) of 2007.

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capital but with otherwise no direct innovator participation. On the private end of the spectrum lies the current path of contracting with private companies on a contract-by-contract basis to develop and produce individual MCMs. In such arrangements, the government’s role is primarily that of a customer.

Along the continuum between these two options are a diverse range of options for public-private collaboration with ownership and operations divided between the USG and industry. For the purposes of this analysis, these options have been grouped within discrete categories. The categories are artificial in the sense that they do not capture all possibilities; however, they do reflect the fundamental boundaries along which USG and industry participation can be allocated. The categories are:

- Current Path of Multiple Independent Contractors (single-product approach);
- Contractor-Owned, Contractor-Operated (COCO);
- Public-Private Partnership (PPP);
- Federally Funded Research and Development Center (manufacturing capable) (Mfg FFRDC),⁴³
- Government-Owned, Contractor-Operated (GOCO); and
- Government-Owned, Government-Operated (GOGO).

Figure 17 summarizes these options and how they are defined for this report’s analysis.

| Option | Summary Description |
|--------------|--|
| Current Path | Multiple Independent Companies, Each Manufacturing One Product |
| COCO | Single Independent Company |
| PPP | Single Independent Not-For-Profit with USG Investment, Can Compete for Commercial Business Dependent on Charter |
| GOCO | Government Facility Turn-Key Operations by Contractor |
| Mfg FFRDC | Government Facility & Operations, Staffed by Contractor, Requires Special Provision to Compete for Commercial Business |
| GOGO | Government Facility, Operations & Staff |

Figure 17: The Spectrum of Partnership Structure Options

Existing initiatives are each uniquely set up to fulfill a particular mission, emphasizing the point that partnership structure is more a spectrum than discrete buckets of options. Even in the case of FFRDCs, which are defined by the USG, there is variation within certain accepted

⁴³ FFRDCs require special authorization from their sponsoring USG agency, if they plan to engage in manufacturing. The FFRDC approach is included here under the assumption that a manufacturing FFRDC would be authorized to manufacture noncommercial MCMs, since doing so would not interfere with commercial markets.

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guidelines. For example, some FFRDCs are non-profit organizations while others are nonprofit but wholly owned by a for-profit parent company.⁴⁴

Key distinctions between these options lie in the type of contract used to supply MCMs, the profit status of the entities, and the nature of facility and operations investment. Figure 18 shows how the options differ in these terms.

| Option | Contract Type for MCM Purchase | Business Economics | Facility Investment | Operations Investment |
|---------------------|---------------------------------------|--------------------------------|----------------------------|------------------------------|
| Current Path | Fixed Price | For Profit | Private | Private |
| COCO | Fixed Price | For Profit | Private | Private |
| PPP | Fixed Price | Non-Profit / For-Profit | Public / Private | Private |
| GOCO | Fixed Price | Non-Profit / For-Profit | Public | Private |
| Mfg FFRDC | Cost Reimbursement | Non-Profit / For-Profit | Public | Public |
| GOGO | N/A | N/A | Public | Public |

Figure 18: Business Attributes of Partnership Structure Options

Fixed price contracts generally allow a higher operating margin to the contractor as compensation for the increased risk borne by the contractor. Under a fixed price contract, the contractor would be paid upon delivery of MCMs. If the contractor failed to deliver on a batch of MCMs (a realistic scenario for biologic products, which suffer from batch variation) the contractor would not be paid for that batch. Conversely, cost reimbursement contracts are lower margin because the contractor bears less risk: the USG would pay for contractor effort, regardless of success.

Generally, the current path of multiple contractors as well as a multi-product capable COCO model both involve for-profit commercial enterprises that would finance, build, and operate a dedicated capability privately based on expected business from USG contracts for MCMs. Given the substantial up-front USG investment necessary to establish the facility, the structure must ensure that it will be focused on biodefense and broader public service. A pure private-sector organization with the demands of return to shareholders would provide neither the flexibility necessary to respond to changes in demand for MCMs nor the extensive interface necessary with the USG. Given these unique aspects of the mission, the USG may prefer a non-profit or not-for-profit⁴⁵ corporation in order to better satisfy USG contracting provisions.

⁴⁴ Nonprofit organizations (NPOs) are entities whose mission is to engage in activities of public or private interest without commercial or monetary profit. They are a broad legal category that includes U.S. Code 501(c)3 tax exempt organizations and not-for-profit corporations (defined in the next footnote). The main distinction between NPOs and for-profit entities is how they handle profits generated by activities. NPOs are regulated in how they may use surplus income; they usually spend the funds to serve their mission or improve their capabilities to do so. For-profit entities generally return net income to owners or shareholders.

⁴⁵ Not-for-profit organizations are nonprofit organizations that are registered as corporations but do not issue stock. The main difference lies in how not-for-profits are set up as business entities akin to for-profit corporations but do not return retained earnings (equity) to shareholders. The use of the not-for-profit corporation often involves generating income in order to serve a public interest.

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4.6 Analysis and Recommendations

To determine which options are viable for a dedicated capability’s operating model, each was evaluated in terms of risk of failure related to fulfillment of mission, total cost to provide an advanced development and manufacturing solution, and qualitative business and legal characteristics.

4.6.1 Risk Analysis of Partnership Structure Options

To evaluate risk of failure to fulfill mission, the options were scored in terms of risk of failure to provide the necessary experience to succeed, to supply required MCMs over time, and to sustain a dedicated capability’s operations over the long-term. Scores closest to 1 represent best case scenarios. This risk assessment—summarized in Figure 19—shows that both the current path and a completely government solution are both highly risky alternatives for partnership structure (higher numbers signify greater risk).

| Option | Risk Summary | TOTAL |
|--------------|--|------------|
| Current Path | <ul style="list-style-type: none"> • Cannot leverage knowledge across products • Limited surge capacity | 5.0 |
| COCO | <ul style="list-style-type: none"> • Unlikely to attract the substantial capital investment required to establish capability | 2.3 |
| PPP | <ul style="list-style-type: none"> • Shared investment from public and private sector provides incentive to sustain capability and fulfill mission • Less risk to USG if MCM demand does not materialize | 1.7 |
| GOCO | <ul style="list-style-type: none"> • Government-owned facility requirements reduce flexibility to rapidly address operational and technology challenges | 2.3 |
| Mfg FFRDC | <ul style="list-style-type: none"> • Flexibility required to attract and retain top talent reduced • Less procurement flexibility for GMP and technology compliance | 2.3 |
| GOGO | <ul style="list-style-type: none"> • Inability to attract and retain top talent, • Inflexible procurement practices | 3.7 |

Figure 19: Risk Analysis of Partnership Structure Options

The current path cannot leverage knowledge across products through a single-product approach and has limited surge capacity. The GOGO option likely would be unable to attract the requisite talent from industry and offers inflexible procurement practices that would be unable to adapt to the dynamic market environment for MCMs.

Integrated public and private investment in a multi-product, flexible capability reduces risk. A Mfg FFRDC would have greater flexibility to attract talent than a purely government option, but would still be constrained in comparison to more private options. It also would have less procurement flexibility from Good Manufacturing Practice (GMP) and technology compliance. The multi-product COCO option has greater flexibility for hiring talent and supply, but is unlikely, due to the dynamic market environment, to attract the substantial capital investment required to establish the capability. As will be demonstrated in the cost analysis, the COCO option relies on high borrowing and opportunity costs—including borrowing costs of up to 35%—that deter contractors from assuming the risk of building and operating the capability in a risky market environment. The turnkey GOCO option enables the contractor to utilize industry

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competitive talent, but the government-owned facility requirements reduce the flexibility to rapidly address operational and technological challenges.

The remaining option, the PPP, provides the optimal risk profile because shared investment from both the public and private sectors provides the incentive for all partners to bring best practices to sustain a dedicated capability and fulfill its mission. A sizable USG investment would reassure industry partners and significantly reduce borrowing costs for the private portion of investment. Contractor ownership of a dedicated capability reduces risk to the USG if the demand changes.

4.6.2 Cost Analysis of Partnership Structure Options

A cost comparison of the structure options considers the total cost of building and operating a dedicated capability over 25 years, the expected life of the facility given the DCA scope. A cost model was developed that used a number of inputs—including allowable operating margin, cost of borrowed money, and level of private investment in both the facility and working capital of the facility—to determine required USG investment and total cost over time.

The operating margin was determined based on standard assumptions considering the contract type concerned. Options that use fixed price contracts are assumed to have 20% operating margins to compensate for high operational risk. Cost reimbursement is assumed to use a “cost-plus” approach with a 10% margin. Government operations are assumed to be fulfilled at cost.

The cost of borrowed money depends on contractor risk profile and level of government investment. The current path, or single-product approach, concentrates risk and thus requires a higher return on any privately borrowed money. The COCO option has a lower cost of money because it assumes a reliable contractor with diverse businesses and the ability to address a larger portion of the MCM market with a multi-product approach. Both the PPP and GOCO options involve substantial USG investment, which reduces the amount of private borrowing required and provides assurance to lenders. Both an FFRDC and a GOCO would be financed through USG appropriation and require no borrowing.

The level of private investment—in terms of building facility infrastructure and providing working capital—varies with how each structural option is defined. The current path and COCO options assume full private investment, and the GOGO and FFRDC options none at all. The GOCO option, as a turnkey arrangement, assumes private investment only as working capital to conduct operations. The PPP option assumes substantial public investment to build the facility, but private investment can vary and does not affect the analysis of this option at this stage. For the purposes of this analysis, private investment is assumed to range from 0% to 30%. Figure 20 illustrates the cost analysis.

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| Option | Operating Margin | Cost of Money | % Private Facility Investment | % Private Working Capital Investment | Initial USG Facility Investment (\$M) | Avg Yearly Procurement Cost to USG (\$M) | TOTAL COST 2008-2033 |
|--------------|------------------|---------------|-------------------------------|--------------------------------------|---------------------------------------|--|----------------------|
| Current Path | 20% | 25-35% | 100% | 100% | \$0 | \$1,700 | \$25B to \$35B |
| COCO | 20% | 15% | 100% | 100% | \$0 | \$490 | \$10 B |
| PPP | 20% | 5% | 0% to 30% | 100% | \$730 to \$510* | \$280 to \$310 | \$6.7B to \$7.1B |
| GOCO | 20% | 5% | 0% | 100% | \$730** | \$280 | \$6.7 B |
| Mfg FFRDC | 10% | 0% | 0% | 0% | \$730** | \$250 | \$6.1 B |
| GOGO | 0% | 0% | 0% | 0% | \$730** | \$240 | \$5.7 B |

Figure 20: Cost Analysis of Partnership Structure Options

Figure 20 demonstrates significant cost savings options compared to the current path. By choosing any of the other five options, which represent a dedicated capability with a multi-product approach, the USG would change the order of magnitude for MCM acquisition from \$25–\$35 billion to \$5–\$10 billion. This significant total cost savings demonstrates the value of a strategic approach to the challenge of developing and acquiring MCMs. Even in the case of a completely contractor owned and operated option that had USG commitment to acquisition, the savings reflect reduced borrowing costs. The adoption of an integrated facility also reflects the elimination of redundancies in having to support production in multiple single-product facilities.

The GOGO option would theoretically carry the lowest cost as there would be no need to borrow or pay margins on private terms. However, as the risk analysis concluded, whether a GOGO is even viable is an open question. Of the other options, a Mfg FFRDC, GOCO, or PPP minimize the cost to \$6-\$7 billion through their decreased reliance on private borrowing.

4.6.3 Recommended Options Based on Risk and Cost

Based on analyses of both risk and cost, a Mfg FFRDC, GOCO, PPP, and COCO are all viable partnership structure concepts for a dedicated capability and all offer significant advantages over both the multiple contractor, current USG single-product approach, and a government GOGO solution. In Figure 21, it is recommended that the USG focus on partnership structure options in the lower left quadrant of the chart, where both risk and cost are mitigated. Of these options, the PPP represents the best model for success. It must be remembered, however, that as indicated previously, these structure concepts are broadly defined. The USG should consider the business and legal characteristics of a Mfg FFRDC, GOCO, and COCO in order to craft requirements for a PPP option that would best fulfill the mission of developing and supplying MCMs.

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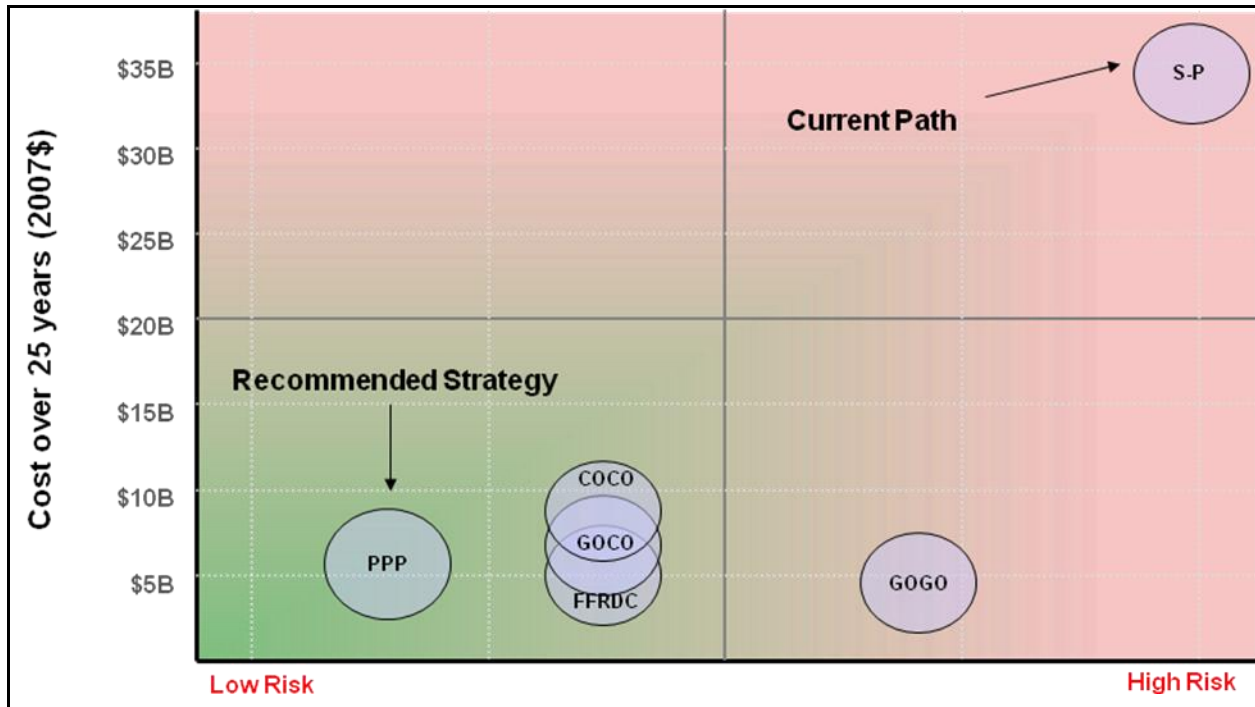


Figure 21: Partnership Structure Options Compared

4.6.4 Business and Legal Characteristics of Recommended Options

How GOCO, FFRDC, and COCO structural models interact with USG regulations and allow for industry incentives informs the viability of such options for a dedicated capability. A more detailed look at the characteristics of the options reveals the advantages and disadvantages of each model and highlights elements that should be characteristics of an innovative PPP model.

4.6.5 GOCO Characteristics

At a GOCO facility, the government furnishes the contractor with government property when the agency head or designee determines that a contract cannot be fulfilled by any other practical means or determines that it is in the public interest to provide the facilities.

GOCO contracts are not specifically defined in the Federal Acquisition Rules (FAR).⁴⁶ The FAR definition of “federally-controlled facilities” includes “government-owned, contractor-operated facilities.” Cost reimbursement contracts are often used for GOCO facilities, but the structure of GOCO facilities and the contracts that underlie them vary depending on the type of work undertaken. Since the term “GOCO” does not refer to one discrete legal structure, entities within this category not only vary widely but also overlap with FFRDCs, as will be discussed.

The Department of the Army’s GOCO ammunition manufacturing facilities and the Department of Energy’s (DOE) complex of national laboratories provide good examples of typical GOCOs. For instance, Lockheed Martin operates Sandia National Laboratories and

⁴⁶ The FAR were established to codify uniform policies for acquisition of supplies and services by USG executive branch agencies. The FAR is issued and maintained jointly under the statutory authorities granted to the Secretary of Defense, Administrator of General Services Administration (GSA) and the Administrator, National Aeronautics and Space Administration (NASA). Statutory authorities to issue and revise the FAR have been delegated to the procurement executives in DOD, GSA and NASA.

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Knolls Atomic Power Lab under the GOCO model on behalf of DOE. Department Of Energy GOCOs use cooperative R&D agreements, which will be discussed, to partner with private business both to achieve its R&D objectives and to provide opportunities for business partners to commercialize technology.

Advantages and Disadvantages

For a dedicated capability, the key characteristic in the GOCO option is government ownership. This serves as both an advantage and a disadvantage. Many government officials are wary of making a large infrastructure investment that the USG will later be obligated to support no matter how the need changes. For this reason, the USG is unlikely to desire retaining the ownership risk for a large MCM production facility. However, government ownership ensures that a dedicated capability would be available despite contractor turbulence. If the contractor goes out of business or decides to pursue other opportunities and leaves the vaccine market, the government would not lose access to advanced development expertise and manufacturing facilities. The USG would need to find a new contractor to operate the facility, instead of starting over and building new facilities. Although government ownership brings risk and may raise political concerns about long-term cost, it also provides the security of guaranteeing USG access to an industrial base that serves a critical national security function.

One clear advantage of the GOCO model is that, unlike other models that mainly focus on R&D, GOCOs are already used by the USG for manufacturing purposes. Using a GOCO model for a dedicated capability would leverage a clear precedent for such manufacturing.

A GOCO also provides existing authority for sharing intellectual property created at the GOCO with industry partners. GOCOs and other federal laboratories can enter into cooperative R&D agreements (CRADA), under the Federal Technology Transfer Act of 1986, in order to facilitate interaction with private sector industry. A CRADA enables the government to “grant, or agree to grant in advance, to a collaborating party patent licenses or assignments, or options thereto, in any invention made in whole or in part by a laboratory employee.”⁴⁷ Through a CRADA, a scientist employed by a GOCO contractor may share in royalties earned by commercial licensing of an invention, but the patent documentation must provide for the retention by the agency of a nonexclusive, irrevocable, government use license. CRADAs are often seen as a prerequisite to making significant corporate investment in a joint research project. CRADAs are usually multi-year agreements involving significant research projects under which the GOCO or federal laboratory in addition to the collaborator may both provide personnel, services, facilities, equipment, or resources.

CRADAs also provide means for a collaborator to transfer funds to the government, which is one of the few mechanisms through which government entities may receive non-appropriated private sector funds. There are, however, restrictions on how the private sector money can be used. CRADAs could be useful tools to examine further for use by a dedicated capability.

One potential disadvantage to a GOCO is political resistance to the model. GOCOs are frequently perceived as large, older, World War II-era initiatives that are costly over time and not particularly dynamic. The creation of a GOCO to produce vaccines for DoD has been recommended on two past occasions.^{48, 49} The lack of USG support for this recommendation may

⁴⁷ Federal Technology Transfer Act of 1986.

⁴⁸ *DoD Vaccine Production Facility Task Force Final Report*, 1993.

⁴⁹ *Report on Biological Warfare Defense Vaccine Research and Development Programs*, 2001.

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reflect a perception within the USG that the GOCO operating model retains certain drawbacks that a more flexible approach might avoid. Principally, these drawbacks are the inflexible long-term USG commitments both to MCM demand and supporting the infrastructure of the GOCO.

Figure 22 summarizes the key attributes of a GOCO, in terms of the four resource areas required by a dedicated capability.

| Government-Owned, Contractor-Operated (GOCO) | |
|--|---|
| Management | <ul style="list-style-type: none"> • No special access to USG resources • USG determines need to partner • Management flexibility not likely • Contractor-dependent |
| Expertise | <ul style="list-style-type: none"> • Contractor-dependent • No special USG access • FAR & OPM human resources restrictions |
| Products | <ul style="list-style-type: none"> • Cost reimbursement contracts • Manufacturing precedent • CRADA sharing of IP • Limited profit suppresses innovation • Supports use of single contractor |
| Financing | <ul style="list-style-type: none"> • Turnkey USG investment • Precedent with existing examples • Long-term costs may carry political risk • Subject to USG oversight • Perceived as costly |

Figure 22: Key Attributes of a GOCO

Federally Funded Research and Development Centers (FFRDC) Characteristics

Although FFRDCs also can be GOCOs, they are subject to more requirements and restrictions than most GOCOs because FFRDCs benefit from privileged access to the government (e.g., sole-source contracts, data access). Generally, FFRDCs are nonprofit organizations operated by a university, not-for-profit corporation, or a for-profit government contractor. They are usually financed on a sole-source basis, exclusively or substantially by a USG agency. FFRDCs operate according to a sponsorship agreement between the government and the FFRDC, which generally takes the form of a contract with a term no longer than five years that can be renewed after periodic review.

In order to establish an FFRDC, the sponsoring agency must determine that alternatives cannot effectively meet the agency’s special R&D needs and that sufficient government expertise exists to objectively evaluate the FFRDC’s performance. The FFRDC’s sponsor must also conduct a comprehensive review of its use of and need for the FFRDC prior to extending the sponsorship agreement.

FFRDCs have access to USG data, employees, and facilities beyond those which are commonly given to normal contractors. Due to the special long-term relationship with the government, FFRDCs are required to operate in the public interest with objectivity and independence, to be free from organizational conflicts of interest, and to make full disclosure of activities to the sponsoring agency. FFRDCs are established to conduct “unique” work that

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cannot be obtained readily from the private sector.⁵⁰ FFRDCs may perform work that is not for the sponsoring agency under the Economy Act.⁵¹ Thus, FFRDCs are not allowed to compete for federal or private sector contracts; most of their work comes from sole-source government contracts. However, this prohibition does not apply to an FFRDC's parent organization in its non-FFRDC operations. Moreover, an FFRDC may not perform quantity production or manufacturing, unless the sponsoring agency ensures authorization to do so by legislation.⁵²

FFRDCs are not subject to Office of Personnel Management regulations, although they may be subject to certain personnel and budgetary controls imposed by Congress or the sponsoring agency. FFRDC personnel are not considered federal employees but rather employees of the organization that manages and operates the center.

Prominent examples of FFRDCs include National Defense Research Institute (RAND), National Cancer Institute at Frederick (SAIC), and the IRS FFRDC (MITRE).⁵³ FFRDCs can be divided into four primary categories: basic research laboratories, R&D laboratories, study and analysis centers, and systems engineering/systems integration centers. FFRDCs can be structured in different ways. For example, the NIAID Vaccine Research Center pilot plant is sponsored by NIAID to develop biologic vaccines in conjunction with NIAID labs and manufacture small quantities for clinical trials, and was developed under the HHS' National Cancer Institute FFRDC. The land and shell building of its facilities is owned by the private sector, and the plant and equipment are owned by the USG. The center's operations are managed by SAIC-Frederick, Inc., a subsidiary of SAIC (NYSE:SAI). The employees are non-government staff, managed and paid by SAIC-Frederick under the National Cancer Institute FFRDC.

There are two key disadvantages to FFRDCs. First, they cannot perform quantity production or manufacturing unless the sponsoring agency secures authorization by legislation to do so. If the sponsor requires the FFRDC to do quantity production or manufacturing, those could be authorized on a case-by-case basis by FAR. Such authorization would be needed if the FFRDC model were to be used for a dedicated capability.

Second, FFRDCs may not compete with the private sector. This is consistent with the mission of a dedicated capability, but FFRDC restrictions that enforce this rule could make a partnership with industry more difficult to achieve. The sponsoring agency is responsible for monitoring the compliance of FFRDCs with FAR. GAO has also reviewed the use of FFRDCs, and, in the past, it has concluded that certain teaming arrangements with commercial companies resulted in FFRDCs competing improperly with commercial organizations.⁵⁴ The sponsoring agreement between a USG agency and an FFRDC contains termination provisions for how the USG agency may compete or remove an organization's FFRDC designation. Between 1992 and 2003, for example, the DOE terminated FFRDC status for six institutions, competing the activities for two institutions and reducing the scope of activities for the remaining four.⁵⁵

Although an FFRDC itself is not allowed to compete for federal or private sector contracts, this prohibition does not apply to an FFRDC's parent organization's non-FFRDC operations. For

⁵⁰ OFPP Policy Letter 84-1.

⁵¹ The Economy Act of 1982, 31 U.S.C. 1535, part 35.017.

⁵² OFPP Policy Letter 84-1.

⁵³ Master List of Federally Funded Research and Development Centers. www.nsf.gov/statistics/nsf05306/

⁵⁴ *Report of the Defense Science Board Task Force on Federally Funded Research and Development Centers and University Affiliated Research Centers*. January 1997.

⁵⁵ *Contract Reform: DOE's Policies and Practices in Competing Research Laboratory Contracts*. U.S. Government Accountability Office (GAO), GAO-03-932-T, July 2003. The two competed FFRDCs were the Knolls and Bettis Atomic Power Laboratories, and the four terminated FFRDCs were the Hanford Engineering Development Laboratory, Inhalation Toxicology Research Institute, Energy Technology Engineering Center, and the Oak Ridge Institute of Science and Education.

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example, the RAND Corporation operates three FFRDCs that conduct national security research for DoD: RAND Project AIR FORCE, RAND Arroyo Center, and RAND National Defense Research Institute. RAND also provides research services on a number of other public policy issues.⁵⁶ These activities arguably compete with other think tanks, consulting firms, and academia. Clients include the USG, foreign governments, and private sector firms.

However, this blurring of role between trusted unbiased government advisor and private sector competitor has drawn broad political criticism of FFRDCs and the potential conflicts of interest they create. Most FFRDCs were created in the 1950s and 1960s. In recent years, several FFRDCs have ceased to be listed on the government's master list, as several of them have been transitioned into private organizations. This may be because of the politically controversial nature of FFRDCs, which has led Congress to limit the power of the Secretaries of Defense, Army, Navy, Air Force, and the heads of some other agencies to create new FFRDCs.

Since FFRDCs can be GOCOs, they share some of the same advantages and disadvantages. For example, FFRDCs can also enter into CRADAs, as described earlier. However, similar concerns about government ownership risk and political resistance may arise. Like other GOCOs, personnel working at an FFRDC are not generally subject to Office of Personnel Management (OPM) regulations. As noted above, FFRDCs can be subject to some personnel and budgetary controls imposed by Congress and/or their sponsoring agency. Although these limitations are generally not as stringent as those imposed on federal agencies, such personnel restrictions could be a disadvantage if they limit the ability of a dedicated capability to retain highly qualified professionals in the competitive market for biotech and biopharma talent.

Figure 23 summarizes the key attributes of an FFRDC, in terms of the four resource areas required by a dedicated capability.

⁵⁶ RAND's research areas are the arts, child policy, civil justice, education, energy and environment, health and healthcare, international affairs, national security, population and aging, public safety, science and technology, substance abuse, terrorism and homeland security, transportation and infrastructure, and workforce and workplace.

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| Federally Funded Research and Development Center (FFRDC) | |
|--|--|
| Management | <ul style="list-style-type: none"> • Special access to USG resources • Restrictions on private sector teaming • Restrictions on budget & contracting • Barred from manufacturing without special legislation |
| Expertise | <ul style="list-style-type: none"> • R&D focus good for product development • Good at integrating expertise for R&D |
| Products | <ul style="list-style-type: none"> • Cost reimbursement contracts • Manufacturing requires mandate • R&D focus • CRADA sharing of IP • Cannot compete with private sector |
| Financing | <ul style="list-style-type: none"> • Sole-source funding • Restricted private funds • Precedent with existing examples • Long-term costs may carry political risk • Subject to USG oversight • Perceived as costly |

Figure 23: Key Attributes of an FFRDC

COCO Characteristics

COCO organizations can take many forms, but some relevant examples of facilities that are both owned and operated by contractors are the Program for Appropriate Technology in Health Malaria Vaccine Initiative (PATH MVI), the Salk Institute for Biological Studies, and Boston University’s (BU’s) National Emerging Infectious Disease Laboratories (NEIDL). Each of these examples provides a different framework for how a COCO can be structured. The PATH MVI operates as a nonprofit R&D contractor to facilitate development of a malaria vaccine with funding from government, industry, and other nonprofits. Before selling the facility to Connaught Laboratories in 1978,⁵⁷ the Salk Institute operated a vaccine production facility in Swiftwater, Pennsylvania for DoD from the 1960s to the 1970s. This report focuses on the BU NEIDL example because it involves a contemporary COCO biodefense research partnership between the university and the federal government. NEIDL was created through a \$120 million award from NIAID to build a National Biocontainment Laboratory (NBL). Boston University is being required to provide matching funds worth a minimum of one dollar for every three federal dollars to help construct the BSL-4 lab, which will be dedicated to the development of diagnostics, vaccines, and therapeutics to combat emerging infectious diseases. The university

⁵⁷ The U.S. government’s affiliation with MVI and the Salk Institute for Biological Studies is not as robust and enduring as with the other entities discussed. Although MVI receives U.S. government funding (20.9% in 2005) and Congress has appropriated money for the President to donate to MVI as a “voluntary contribution to international vaccine funds,” MVI was founded by PATH in 1999 through a grant from the Bill & Melinda Gates Foundation; the majority of its funding still comes from private sources. Similarly, the Salk Institute for Biological Studies was founded by the developer of the polio vaccine. The San Diego City Council gifted the land, and the March of Dimes, which has continued to support the Salk Institute over its history, provided the seed money. Although the Salk Institute has had numerous government contracts in recent years, such as its work with the Army and DoD, these relatively small “project grants” do not represent a substantial U.S. government relationship. Unlike the other quasi- government organizations discussed earlier, the federal government was not the impetus for creating MVI or the Salk Institute nor does it exercise significant control over them.

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was awarded a grant to build one of two NBLs based on a strategic plan developed by NIAID's 2002 blue-ribbon panel on bioterrorism.⁵⁸

The relationship between BU and the government was formed based on the university's successful RFP response to NIAID. The university competed with other applicants to build the NBL. In order to meet the RFP's requirements, BU had to commit to utilize the facility for "biomedical research purposes as determined by NIAID program needs for at least 20 years."⁵⁹ The university also must submit annual progress reports during the 20-year utilization requirement, and, if the university fails to comply with the utilization requirement, the government can recover the federal share of the facility's value. Thus, the contract requires BU to use its new biocontainment facility with the specific goal of supporting the NIAID biodefense research agenda, thus creating an important ongoing relationship between the university and the government.

The primary difference between a COCO and the previous models is that the contractor bears both the operating risk and the ownership risk. Since the USG would not own the facility, this could be an advantage in that the USG does not risk making a large infrastructure investment that it later will be obligated to support. However, this option could also lead to instability because the USG could lose access to the facility if contractor operations were disrupted due to production interruptions or loss of contract. It may be possible to structure a contract such that the USG has the right to buy the facility if the contractor loses the contract or if the contractor decides to exit the MCM market. However, the feasibility of such a contract provision is questionable. Contractors may be averse to bearing the ownership risk and less willing to invest in building a facility if they know the USG has the right to buy it back from them at a fixed price. Therefore, arranging a COCO relationship where a dedicated capability, as proposed in this report, would be available reliably to the government is likely to be costly, even if the USG does not directly own the facility itself.

Although the NEIDL example is not a manufacturing facility, many COCO operations engage in manufacturing. This is an advantage of the model over others that focus more on R&D.

Another disadvantage of COCOs is that they do not generally have the same close relationship with the government as FFRDCs do. COCOs, by definition, are more independent from the government than either GOCOs or FFRDCs.

Despite the looser connection between the USG and a COCO, there may still be IP issues related to the government's right to inventions at a COCO when discoveries are funded in part with federal money. The Bayh-Dole Act provides limited rights under which the recipient of the federal money can keep the rights to inventions. Bayh-Dole permits nonprofits and small businesses to elect to retain title to any "subject invention" made with federal R&D funds.⁶⁰ They must elect to retain title within a reasonable time and must commit to commercializing the invention within an agreed-upon timeframe. However, the government retains a nonexclusive,

⁵⁸ NIAID Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research. This panel was first convened in February 2002 to provide NIAID with objective expertise on the Institute's biodefense future research plans and help identify the highest priority areas. Among the panel recommendations was the creation of more laboratory space for working with dangerous pathogens than was previously available in the United States. In September 2003 and September 2005, NIAID announced the recipients of grants partially funding the construction of two National Biocontainment Laboratories (NBLs) and thirteen Regional Biocontainment Laboratories (RBLs), thus increasing BSL-4 and BSL-3 lab space nationwide.

⁵⁹ RFP: BAA-NIH-NIAID-NCRR-DMID-03-36. Only nonprofits were eligible to respond to the RFP.

⁶⁰ P.L. 96-517, sec. 200. Note that there is an exception under exceptional circumstances when it is determined by the agency that the restriction or elimination of the right to retain title to any subject invention will better promote the policy and objective of this chapter.

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nontransferable, irrevocable license for USG use for any subject invention.⁶¹ Nonprofit institutions are, however, subsequently permitted to assign title rights to another organization.⁶²

Figure 24 summarizes the key attributes of a COCO in terms of the four resource areas required by a dedicated capability.

| Contractor-Owned, Contractor-Operated (COCO) | |
|--|---|
| Management | <ul style="list-style-type: none"> • No special access to USG resources • Restrictions on private activities • Management practice flexibility • Contractor-dependent • Best practices |
| Expertise | <ul style="list-style-type: none"> • Contractor-dependent • No special USG access • Industry-competitive |
| Products | <ul style="list-style-type: none"> • Firm fixed price contracts • Manufacturing experience • Bayh-Dole Act IP sharing • Profit potential encourages innovation • Supports use of single contractor |
| Financing | <ul style="list-style-type: none"> • Matching funds from private sector • Subject to contractor turbulence • Less USG oversight • Price-performance based evaluation |

Figure 24: Key Attributes of a COCO

PPP—Characteristics of an Innovative Option

Quasi-governmental organizations such as GOCOs, FFRDCS, and COCOs are broadly defined in concept. Actual examples are uniquely designed to fit an institution’s mission and are often categorized after structural requirements have been determined. Therefore, it is recommended not to select one pre-existing model for a dedicated capability. Instead, it is recommended to design a hybrid organization—a public-private partnership—that fulfills the unique USG and industry operating requirements of such a capability.⁶³ The term public-private partnership (PPP) is broadly defined but usually refers to a privately owned entity that serves a public purpose and has a significant level of government investment and other participation.

For a dedicated capability, the optimal operating model of a PPP would draw upon the strengths of the GOCO, FFRDC, and COCO concepts. Figure 25 shows how desirable traits of the three existing models could be incorporated in a PPP.

⁶¹ P.L. 96-517, sec. 203. Note that the government also retains “walk-in rights” which are triggered when a determination is made that the contractor has not made efforts to commercialize within the agreed-upon time or that the “action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor.”

⁶² “The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology,” Congressional Research Service, Library of Congress, Oct. 5, 2007.

⁶³ Precedent exists for creating new types of hybrid organizations. For example, In-Q-Tel has many characteristics of an FFRDC but was created as a distinct new type of hybrid quasi-government entity.

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| | MFG FFRDC | GOCO | PPP | COCO |
|-------------------|---|--|-----|---|
| Management | <ul style="list-style-type: none"> • Special access to USG resources • Restrictions on private sector teaming • Restrictions on budget & contracting • Barred from mfg w/out special legislation | <ul style="list-style-type: none"> • No special access to USG resources • USG determines need to partner • Mgmt flexibility not likely • Contractor-dependent | | <ul style="list-style-type: none"> • No special access to USG resources • Restrictions on private activities • Management practice flexibility • Contractor-dependent • Best practices |
| Expertise | <ul style="list-style-type: none"> • R&D focus good for product development • Good at integrating expertise for R&D | <ul style="list-style-type: none"> • Contractor-dependent • No special USG access | | <ul style="list-style-type: none"> • Contractor-dependent • No special USG access • Industry-competitive |
| | <ul style="list-style-type: none"> • FAR & OPM HR restrictions | | | |
| Products | <ul style="list-style-type: none"> • Cost reimbursement • Mfg requires mandate • R&D focus • CRADA sharing of IP • Cannot compete with private sector | <ul style="list-style-type: none"> • Cost reimbursement • Mfg precedent • CRADA sharing of IP • Limited profit suppresses innovation • Supports use of single contractor | | <ul style="list-style-type: none"> • Firm fixed price • Mfg experience • Bayh-Dole Act IP sharing • Profit potential encourages innovation • Supports use of single contractor |
| Financing | <ul style="list-style-type: none"> • Sole-source funding • Restricted private funds | <ul style="list-style-type: none"> • Turnkey USG investment | | <ul style="list-style-type: none"> • Matching funds from private sector • Subject to contractor turbulence • Less USG oversight • Price-performance based evaluation |
| | <ul style="list-style-type: none"> • Precedent with existing examples • L/T costs may carry political risk | | | |
| | <ul style="list-style-type: none"> • Subject to USG oversight • Perceived as costly | | | |

Figure 25: Building an Innovative Partnership Structure Option

It is possible to create a PPP option without new legislative action. DoD already has special “other transactions” authority through DARPA which allows the department to enter into flexible, multi-party consortium agreements involving multiple sources of funding.⁶⁴ Other transactions authority is not subject to FAR and allows payments to be based on achievement milestones. It also gives DARPA flexibility regarding intellectual property. BARDA has been granted similar special authority by the Pandemic and All Hazards Preparedness Act (PAHPA).⁶⁵ However, as yet, HHS has not released regulations regarding the use of BARDA’s new other transaction authority. DoD and BARDA may be able to use this special authority to create a more flexible hybrid organization that is specifically tailored to the task of both developing and manufacturing MCMs.

4.6.6 Operating Model Recommendations

A PPP can take many forms. A dedicated capability, if developed as a PPP under the PPP option, can define its partnership, operations, and governance structure in ways that meet the requirements set out in this report.

⁶⁴ 10 U.S.C. 2371(a) (2000); see Participant Views of Advanced Research Projects Agency “Other Transactions,” available at www.darpa.mil/body/d1791.

⁶⁵ 42 U.S.C.A. § 247d-7e(c)(4)(B)(iv).

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Partnership Structure

The most successful partnerships between government and industry have effectively balanced efficiency and accountability. The USG gives such PPPs the flexibility and discretion to operate as a private business would while at the same time acknowledging that they are engaged in public functions and so accountable to the USG. The managers of successful PPPs balance multiple objectives. They tend to cultivate strong informal relationships with USG counterparts and develop non-contractual operating norms that complement formal contractual commitments. Over time, as PPPs prove reliable and trustworthy, some of the informal relationships may supersede the rigid, formal USG points of contact and allow for a more effective balancing of oversight and efficiency. Successful PPP managers also need to keep in close contact with the USG for purposes of ensuring that they do not unwittingly deviate from the USG's goals.

To this end, a dedicated capability should possess the following characteristics:

- Innovative incentives to attract the best minds and most sophisticated businesses to participate:
 - Authority to pay employees above government scale
 - For-profit participation
 - Protections for existing IP that participants bring to the initiative and provisions to allow those parties to own a portion of the new IP they shared in developing at a dedicated capability
 - Bonus compensation for biopharmaceutical and biotechnology participation⁶⁶
 - USG-backed loan guarantees
- Strict conflict of interest rules to ensure transparency
- Flexible, informal USG interface arrangement to streamline oversight processes and increase opportunities for communication and common goal-setting with the government

Congress, as part of establishing a dedicated capability and appropriating funds, may also prescribe certain terms and conditions on the USG agencies involved, the capability itself, and industry partners. As noted, no additional statutory authority is needed in order to do so. The terms and conditions of the partnership would be defined by two agreements: a charter agreement and a memorandum of understanding.

A charter agreement is a sponsoring agreement between the USG and a private entity to operate and manage a dedicated capability. The USG sponsor could be a lead agency, such as DoD or HHS, or perhaps an interagency authority. Charter agreements are common governance instruments for government-industry partnerships: FFRDCs have such agreements with their sponsoring agencies, and innovative ventures such as In-Q-Tel have them as well with their USG partners.

A dedicated capability's charter agreement would define the terms, conditions, protections, and responsibilities that the private manager must accept and would also state the length of time the agreement would remain in effect. The USG would need to specify formal mechanisms to

⁶⁶ One possible incentive would be to award participating firms priority-review vouchers, although that would require additional legislative action.

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ensure that the managing entity protected the public's financial and production interests. These interests include a commitment to enter into fair market business transactions with biopharmaceutical companies, biotechnology firms, and investors; the avoidance of conflicts of interest; and a commitment not to abandon the initiative at a critical juncture. To the extent industry partners participating in the PPP are awarded special incentives, the need to ensure that the public interest is being promoted becomes greater.

There is flexibility, under existing authority, as to how the USG and the manager of the capability would be able to structure respective commitments. For example, the USG might insist that the private manager obtain USG approval for its joint ventures and its pooling of private and public funding above a certain threshold. The USG also could solicit competitive bids for all subcontracts over a certain dollar amount. Participating biotechnology and biopharmaceutical firms could provide an initial investment outlay to better ensure that they will not back out of the relationship at a critical juncture. The USG might also insist that the directors of the managing nonprofit have no conflicting relationships with participating for-profits. Moreover, the USG will want to include specific termination provisions for the private manager and the USG, whereby each could exit the partnership in an equitable manner. In turn, the private manager would seek to codify many assurances of discretion and flexibility.

Once a dedicated capability became operational, the USG would provide funding through contracts for the advanced development and procurement of MCMs. The USG might demand, among other things, that the private manager provide an estimated operating budget, reach particular production benchmarks, present periodic progress reports, and conduct internal audits.

Because a dedicated capability may generate profits through IP licensing agreements or sales of excess production on the private market, it also will need a memorandum of understanding (MOU) that specifies how those profits will be allocated. To the extent the manager is allowed to enter into joint ventures with for-profit partners, the MOU could require the private manager to reinvest some percentage of the income generated in furtherance of the capability's mission. Any condition included in the MOU would, of course, create conditions above and beyond the nonprofit's preexisting obligations under the federal tax code.⁶⁷ In addition, the profit-sharing MOU would state a formula for how the nonprofit manager shares profits with a for-profit partner. The MOU that governs the Central Intelligence Agency's (CIA's) technology venture—In-Q-Tel—and its share of profits for its venture capital investments may provide insight in the design of a MOU for a dedicated capability. The In-Q-Tel MOU details both the organization's relationship with the technology companies with whom In-Q-Tel works and how In-Q-Tel would benefit from any contracts the companies secure with the CIA. Figure 26 shows one model for how a PPP could be structured to bring the USG and a nonprofit capability together through a charter agreement and a MOU.

⁶⁷ See I.R.C. § 501(c)(3).

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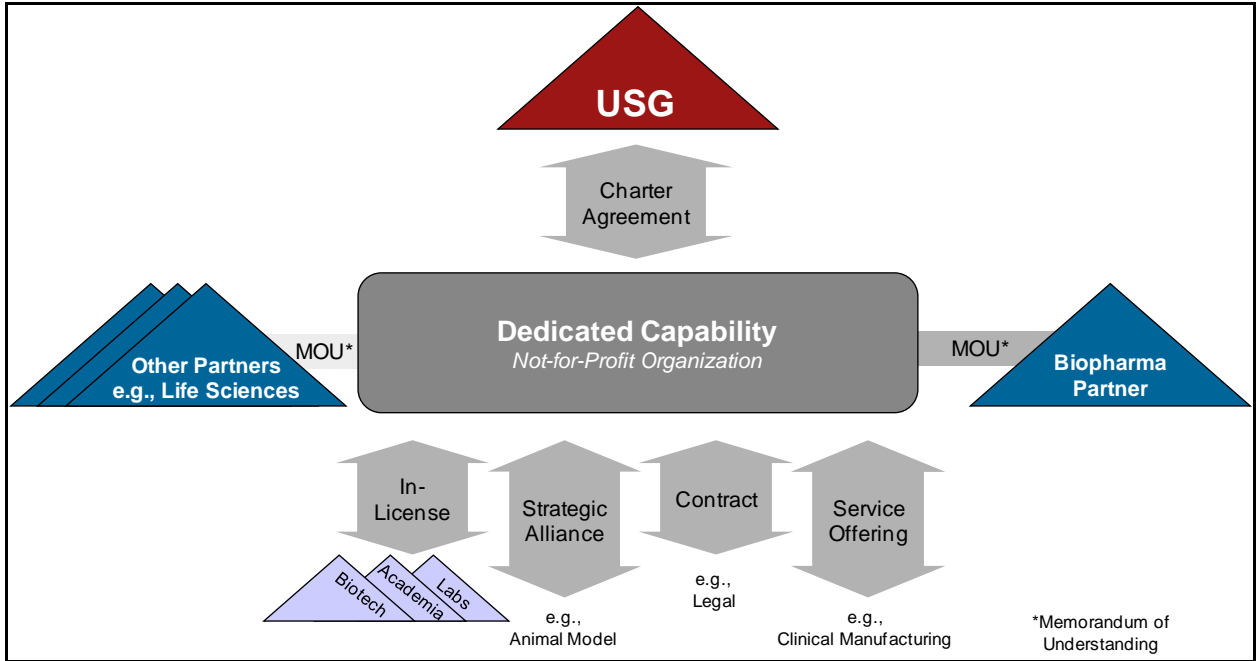


Figure 26: Public-Private Partnership Structure

In this model, the USG through a lead agency or agencies enters into a charter agreement with the not-for-profit capability manager. The charter agreement protects the interests of the USG, details terms for investment and performance, and provides termination provisions for both USG and a dedicated capability should either party decide that the facility’s usefulness has come to an end.

The not-for-profit manager of a dedicated capability separately enters into a MOU with industry partners, including a biopharmaceutical company and possibly other partners, such as an academic life sciences institution. The MOU ensures unity of command by defining each partner’s contribution, compensation, and termination provisions through which each could end participation without threatening the facility’s operations.

The not-for-profit organization managing the dedicated capability could conduct core operations of advanced development and manufacturing internally. As discussed in Section 4, it would engage in strategic alliances and contracts to outsource those components of operations which are best accomplished elsewhere.

Operations

The operations of a dedicated capability are designed to compensate partners for providing resources to the dedicated capability, as discussed in Sections 4.4 and 4.5. Figure 27 shows one model for how the facility could do so.

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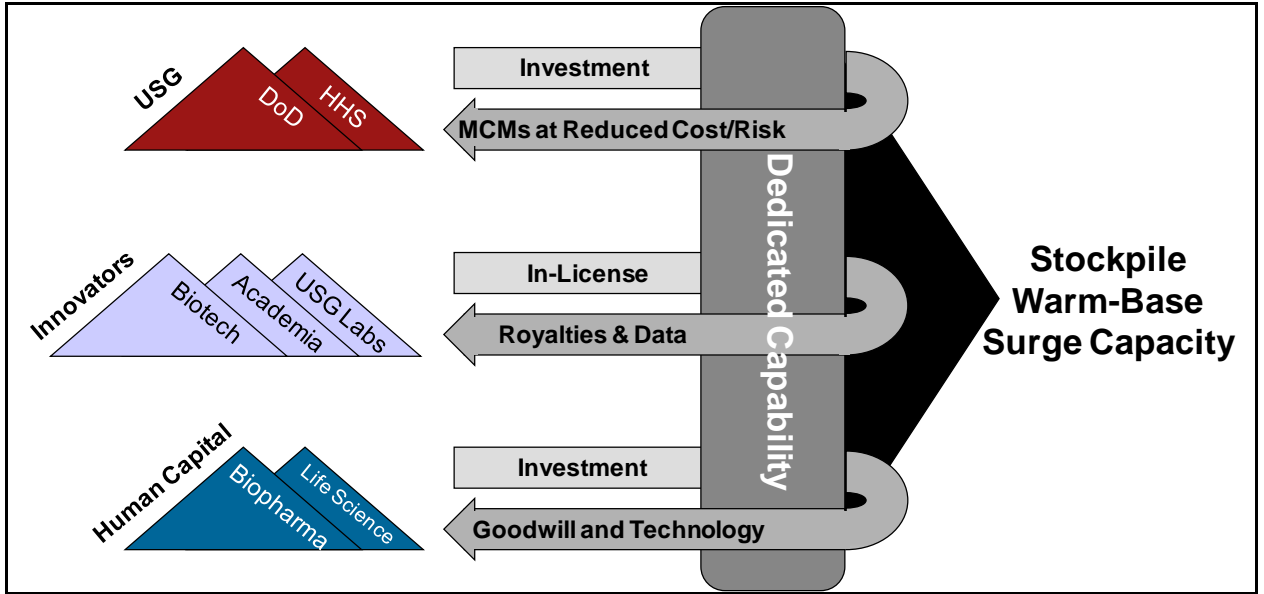


Figure 27: Operations Model

In this model, the USG invests the majority of financial capital to build the facility and procure MCMs at reduced cost and risk. Biodefense innovators in-license early-stage (Phase I complete) MCM candidates. In return, innovators could receive such incentives as milestone payments when product candidates reach advanced development milestones, data on candidates' development that can be leveraged to research other new products, and royalties on sales of successful candidates. A biopharmaceutical company or other life science partner would invest some funds, but more importantly such a partner would bring human capital to the facility. As compensation, biopharma could receive both goodwill for participating in a national security and public health initiative and early access to technology developed at the facility. The limited discussions with industry to date confirmed that biopharma considered goodwill a significant incentive for participation in a venture such as a dedicated capability.

Governance Structure

A dedicated capability should be governed by a board of directors with deep experience in industry and also expertise in working with government in national security, public health, and nonprofit management. Retired biopharma and biotech industry leaders could help ensure industry partner interests are aligned. If leaders were to come from companies other than industry partners, they would broaden the range of industry participation. Former senior government officials from DoD, HHS, or DHS would bring valuable understanding of working with government and help maintain the facility's focus on its public mission. Current USG officials would need to provide oversight through a different mechanism.

The USG sponsor for a dedicated capability should create an internal working group to interface with the capability's leadership on a regular basis. This group would ideally include stakeholders from both DoD and HHS that would procure MCMs through the facility. From the lead USG sponsor, the group should include officials experienced in contracting, R&D of MCMs, and stockpile and delivery issues.

This model for a USG working group to interface with a dedicated capability is based on a similar and successful mechanism employed by the CIA to work with its public-private venture

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In-Q-Tel. The CIA uses a working group known as the “In-Q-Tel Interface Center” to manage its relationship with In-Q-Tel. The In-Q-Tel Interface Center is a panel of CIA executives from different directorates who communicate closely and informally with In-Q-Tel management.⁶⁸ Figure 28 illustrates a sample governance structure for a dedicated capability.

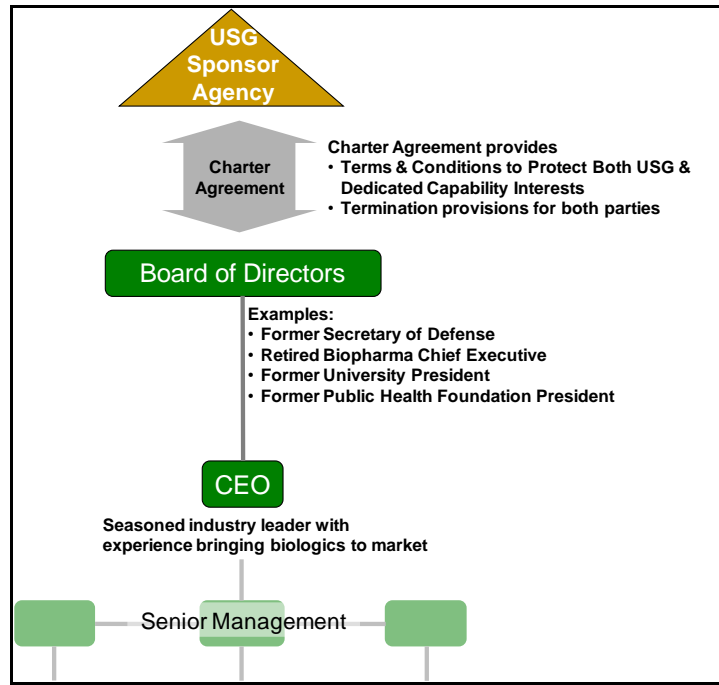


Figure 28: Illustrative Example of Governance Structure

5 Conclusions and Recommendations

Summarized below are the conclusions and recommendations of the UPMC study conducted from July 2007 to July 2008.

- The DoD has established requirements for most MCMs that are determined necessary for force protection. Although many of these MCMs are not funded currently for full development and procurement, many are underway and in Phase I/II clinical testing. The entry of HHS into the biodefense procurement space in 2001 illustrates that its systems, strategy, and organization continue evolving. It is difficult to determine the exact HHS requirements for MCMs, as most interviewees believe that these HHS requirements are significantly constrained by funding and do not reflect the actual magnitude of the threat. The lack of transparency in the requirements for MCMs is particularly noticeable in the prioritization of the national biodefense R&D portfolio, which several procurement officials have referred to as inconsistent with their priorities. Communication and articulation in regard to MCMs can help align purpose across groups from the science and technology (S&T)/R&D communities through to licensure thereby ensuring prioritization occurs and is consistent with MTDs.

⁶⁹ Report of the Independent Panel on the CIA’s In-Q-Tel Venture, June 2001.

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- New technologies played a key role in the development of the demand forecasts. Broad-spectrum products hold great hope for the reduction of the ultimate cost of developing MCMs against the current and evolving threats, but when licensure will occur making broad-spectrum products available for use is difficult to predict. All interviewees appeared to agree that a balanced S&T/R&D portfolio is necessary to achieve the best possible breadth of MCMs in the future.
- The DCA model presented herein was developed to inform the design of a new capability to deliver MCMs to DoD and HHS. From the information surveyed, it was clear that there is a convergence on a set of core technologies that will be used to make MCMs from the current portfolio of products. Although each MCM will have specific attributes, the core technologies offer opportunities for significant efficiencies in their ultimate manufacture.
- Given the complexities of the USG research pipeline, the evolving budgetary priorities of the USG funding agencies, and the dynamic nature of the threats, it will be important to re-examine the DCA model on a regular basis. Re-examinations should be done to determine both what end-state the portfolio is trending towards and how innovative technologies, such as multi-product facilities, can best meet the USG MCM demand.
- The analysis herein demonstrates that a flexible, multi-product approach makes solving production problems associated with procuring biologic MCMs required by the USG a manageable prospect. Although a wide array of products is required, the determined USG need for each product is a fairly small quantity when compared to the commercial manufacture of drugs. This paradigm of a low number of doses with a wide array of products lends itself well to a multi-product facility, which FDA approved for licensure in 1995. Furthermore, since this change in FDA guidance, a wide range of disposable technologies has come to market. These technologies greatly simplify the cleaning process between batches, making it more feasible and cost-effective to produce several different MCMs within a single production suite during a year.
- An 8-suite, flexible, multi-product facility built with the goal of using disposable technologies can accommodate the initial stockpile buildup and replenishment as well as fulfill many surge requirements. Precisely how much surge capacity the country requires is a policy decision requiring discussion. With its ability to surge production, the facility presented herein is critical to making such a conversation possible.
- To fulfill its mission, a dedicated capability must be able to perform advanced development and manufacture of MCMs to meet USG demand requirements in a reliable and cost-effective manner. The current path for USG MCM acquisition relies on industry to develop MCMs through FDA licensure, followed by USG procurement on a product-by-product basis. This strategy has resulted in limited success. A better poised strategy should involve both the public and private sectors to support advanced development and manufacturing. A successful capability would bring together the ingenuity of biodefense innovators and the development expertise of large biopharma. The USG must demonstrate a long-term commitment to MCM demand as doing so will strengthen the economic rationale for all industry partners to remain involved.
- One potential disadvantage of a single facility is a lack of resilience in the event of crisis. It is proposed that the dedicated facility described herein be a prototype facility and that

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there be eventual construction of at least one more dedicated domestic plant. It is also recommended that the USG collaborate with international allies and organizations—such as the North Atlantic Treaty Organization (NATO) and the Association of Southeast Asian Nations (ASEAN)—to discuss building a network of interlocking capabilities to ensure that the international community works to cost share and build the same level of protection for global security and public health.

- The UPMC study concludes that mixed public and private participation both reduces long-term cost and mitigates risk in terms of producing required MCMs. A PPP—defined as a not-for-profit organization that licenses early-stage MCM candidates from biodefense innovators and leverages biopharma expertise—is recommended. It is further recommended that the PPP be created with an objective of attracting and retaining an industry-competitive workforce to successfully complete product development and manufacture the resulting MCMs for USG stockpile and use.
- A flexible, multi-product facility to accomplish advanced development and production of biologic MCMs will enable numerous scientific, technological, and economic benefits over the current system. Operated as a PPP, a facility supporting both advanced development and manufacturing would be able to:
 - 1) Provide the nation with a domestic industrial base for vaccines and therapeutics;
 - 2) Streamline the effectiveness of advanced development capabilities while simultaneously reducing risk;
 - 3) Lower significantly the government’s cost of acquisition, particularly during times of fiscal constraint;
 - 4) Secure the nation’s first flexible surge capability for both CBRN and non-commercial public health threats;
 - 5) Consolidate and cultivate a domestic scientific and technical knowledge base; and
 - 6) Develop a forum to strengthen biodefense innovators

Industry Outreach: Executive Summary

The industry outreach goal was to determine the requisite factors needed to encourage industry participation in biodefense medical countermeasure (MCM) development and manufacturing for the United States Government (USG) through a Biologics Development and Manufacturing Infrastructure (BDMI). To achieve the goal, a series of stakeholder meetings with industry participants was conducted. Industry meetings included participants from large biopharma, biotechnology and biodefense innovators, and contract manufacturing organizations. Additionally, a roundtable discussion was conducted with government representatives, industry stakeholders, and subject matter experts with expertise in biologics development and manufacturing.

These outreach activities allowed stakeholders to provide their perspectives on the BDMI concept and offer guidance to the USG on potential partnership roles and an appropriate path forward in regard to options that would result in building a viable biodefense enterprise with reduced cost, high probability of success, and USG requirements' compliance.

The results of the industry outreach indicated a preference for BDMI operating models that enhance collaboration among all stakeholders, with the most support aligned behind those models that include the element of co-location of advanced development with manufacturing.

Participants identified the key factor for encouraging participation to be longer term commitments both to product acquisition and to compensation, which could be in the form of either direct payments with commercially competitive margins or indirect incentives that would bolster commercial business operations.

Outreach participants also identified critical barriers to participation that must be sufficiently resolved by providing appropriate intellectual property (IP) protection for industry partners, increasing clarity around regulatory approval pathways, and streamlining the government contracting process. Of these barriers, stakeholders were most optimistic about addressing the last two, which they felt could be overcome by a concentration of experience provided by those within the BDMI structure and by USG and regulatory authorities.

6 Introduction

The USG faces an unprecedented technological challenge over the next 25 years to meet its biodefense medical countermeasure requirements. As previously described, 17 novel biologics must be developed to meet specified Department of Defense (DoD) biodefense and Department of Health and Human Services (HHS) requirements. Meeting these needs requires the stockpiling of approximately 1.3 billion doses of vaccines and therapeutics, the majority of which are not yet licensed. To put this challenge into perspective, more novel vaccines must be developed in the next 25 years than the global pharmaceutical industry has licensed over the previous 25 years.

In recognition of this emerging biodefense challenge, analysis of the USG's biologics advanced development and manufacturing capabilities that included a demand capacity assessment, a high-level capability design, and an operating model assessment was provided in previous sections.

In summary, the first phase of the study determined that investment in a Biologics Development and Manufacturing Infrastructure (BDMI), through a mix of public and private participation, would enable the USG to meet its development and production requirements for biodefense biologics at lower cost and reduced risk. A successful capability would bring together the ingenuity of biodefense innovators, the development expertise of large biopharma, and the financial support of the USG. The current US biodefense infrastructure is not equipped to meet the numerous biodefense challenges facing the USG. The shortfalls include: (1) Biopharma's expertise and experience are not engaged; (2) Small biotech and biodefense innovators, with limited capacity and experience in advanced development and manufacturing, dominate the market; (3) A comprehensive strategy to maintain the warm-base production for biologics requirements does not exist; and (4) no surge production capacity for emergency response exists.

In recognition of these deficiencies, a comprehensive industry outreach was conducted to assess the role that industry stakeholders may play in the development of a BDMI for the USG and characterize the barriers and incentives that could impact stakeholders' degree of participation.

7 Background

7.1 Barriers to Participation

When market values fail to reflect the social benefit derived from a good or service—as is the case with developing and producing biodefense biologics—government intervention is often necessary. Accordingly, effective market incentives are needed to develop a viable BDMI in the US that will ensure the protection of US citizens and servicemen and women in the event of a public health emergency or biological weapons attack in theater or on the US homeland.

Barriers to entry into the biodefense biologics market have historically discouraged large biopharma companies from participating in biodefense biologics development and manufacturing. Significantly greater risks and obstacles posed by substantial upfront costs and high market and development risks associated with pharmaceutical markets confront players within the smaller biodefense biologics market. Very little commercial market exists for these products, and because the USG is likely to be the only purchaser, demand, which is dependent on evolving threat assessments, is ambiguous and variable. All of these factors combined make the MCM market relatively risky to enter and thinly profitable, relative to investment in commercial biopharmaceutical alternatives.

Investments in novel MCMs are also technically more challenging than commercial product investment. Using standard clinical trials to assess the efficacy and safety of many biodefense biologics is difficult as they are relatively novel products and the agents they are made to defend against may not occur naturally very often in humans. Compounding this is that the Food and Drug Administration's (FDA) Animal Efficacy Rule⁶⁹ has yet to be fully developed and has only been used for a few licensures of products that were developed decades ago.

Investments of time, human capital, and intellectual property into BDMI partnership may distract from industry's core business efforts. The opportunity cost of the required investment—spanning at least 10 to 15 years—would be significant.

Finally, degrees of uncertainty that include project financing and policy support are associated with long-term USG projects. Whereas large biopharma typically views investments in terms of 10- to 20-year time horizons, the USG budget is drafted on a year-by-year basis. Thus, even long-term funding authorizations are subject to amendment, as authorized funds may not be appropriated in a given year. Further hampering long-term commitment is that the political will for the USG to continue such effort may change substantially depending on evolving policy priorities.⁷⁰

While barriers exist that discourage industry's participation in the BDMI effort, benefits of participation also exist and can provide significant sources of value for industry partners. While participating in the USG-funded effort, industry may develop new intellectual property that can be transferred to commercial efforts. Additionally, product pipelines can be expanded and diversified. Most importantly, however, is that industry would be providing a tremendous service to the public. Participating in such a venture would help strengthen the USG's public

⁶⁹ The FDA "Animal Rule" (finalized May 2002) applies to development/testing of drugs/ biologicals to reduce or prevent serious/life-threatening conditions caused by exposure to lethal /permanently disabling toxic agent (chemical, biological, radiological, or nuclear substances), where human efficacy trials are not feasible or ethical, accessed 16 February 2009.

⁷⁰ PRTM, "Incentives to Achieve U.S. Pandemic Influenza Vaccine Production Capacity: A Portfolio Approach," May 2005.

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health infrastructure, protect civilians and military personnel, and strengthen overall US national security.

7.2 *USG Efforts to Incent Participation*

The USG has actively sought industry participation in the advanced development of critical national security MCMs through various government programs and initiatives. While these efforts have enabled greater participation from commercial entities, they have not been sufficient to attract the companies most experienced in advanced development and manufacturing of novel vaccines and therapeutics to biodefense. Summaries of some of the programs and the barriers they aim to address are listed in Table 8.

Table 8. Examples of USG Programs and Incentives for Biologics Advanced Development

| Relevant Government Act/Program | Program/Act Incentives | Implementation Examples | Barriers Addressed |
|---|---|--|---|
| Orphan Products Program | 50% tax credit for clinical research; seven-year market exclusivity | Over 1800 products, including treatments for anthrax, smallpox, encephalitis, various forms of cancer, organ transplant rejection, and HIV | Profitability |
| Priority Review Voucher (PRV) Program for tropical diseases | Tradable voucher for a six-month timeline for FDA review | N/A ⁷¹ | Profitability |
| Research and Development (R&D) Tax Credit | 20% tax credit on qualified expenditures | | Profitability |
| National Institute of Allergy and Infectious Diseases (NIAID) R&D grant program | ~\$1.7 B/year in research grants | HIV vaccine development collaboration with Merck | Profitability |
| Project Bioshield Act | Authorized \$5.6 billion through FY13 for MCM development, manufacturing, and procurement | Funding used for smallpox, anthrax, botulinum toxin, and other treatments | Investment commitment – partially addressed |
| Support Anti-terrorism by Fostering Effective Technologies Act (SAFETY Act) | Predetermined liability limits; government contractor defense | X-ray systems; Preferred Traveler technology; baggage-check technology coverage (2008) | Liability |
| Public Readiness and Emergency Preparedness Act (PREP Act) | Individual, manufacturer, distributor, and program planner immunity | Pandemic influenza immunity (2007) | Liability |

⁷¹ Novartis may be eligible for the PRV program if Coartem[®] for malaria treatment is approved by the FDA.

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| Relevant Government Act/Program | Program/Act Incentives | Implementation Examples | Barriers Addressed |
|---|--|---|--------------------|
| Pandemic and All-Hazards Preparedness Act (PAHPA) | Established the Biomedical Advanced Research and Development Authority (BARDA) | Provides guidance on USG MCM policies, procurement and budget; oversees Project Bioshield | Governance |

7.3 The Economics of the BDMI Concept

Currently, the USG provides grants for early research and development, mainly through the National Institutes of Health’s (NIH) NIAID. NIAID provides approximately \$1.7B in grants per year.⁷² Advanced research, development, and manufacturing are typically funded through USG-sponsored cost-plus or acquisition contracts. The Project Bioshield Act of 2004 authorized \$5.6B in funding through FY2013 for the advanced development, manufacture, and procurement of biodefense medical countermeasures.^{73,74} BARDA—established by the Pandemic All-Hazard and Preparedness Act (PAHPA) of 2006—provides guidance on USG biodefense medical countermeasure policies and oversees Project Bioshield.

This current operating model has resulted in both a high failure rate for the development of biodefense MCM products and high costs for those attempting to win government biodefense contracts. Reasons that include limited returns on investment (due to high development costs and lack of commercial markets) deter many large biopharma companies from participating in MCM development. The market is dominated by smaller biotechnology firms and biodefense contractors, whose limited expertise and longevity only increase product development risk from both timeline and cost perspectives. The high risk inherent in the attempts by these innovators increases the required market return for investors, thereby increasing capital costs. In instances of funding development or product procurement, these high costs are passed along to the USG.

Capital costs are also a significant contributor to overall costs related to developing and manufacturing a product. A BioProcess Technology Consultants, Inc. study analyzed the manufacturing costs associated with a monoclonal antibody (mAB) process. According to that study, capital costs were the single largest contributor to manufacturing costs, ranging from 29% to 40% of the total cost dependent on the scale of production.⁷⁵ Under the BDMI concept, the infrastructure would be USG-funded; therefore, the capital costs for property and plant investment would be substantially lower than in the current model.

Although advanced development and manufacturing contracts would continue to exist, the decrease in the overall cost of capital achieved by implementing the BDMI concept would result in a decrease in the overall cost of USG procurement. This dynamic is illustrated in Figure 29. The BDMI framework also yields additional efficiency gains because it centralizes advanced development and manufacturing.

⁷² Jason Matheny and others, “Incentives for biodefense countermeasure development,” *Biosecurity and Bioterrorism* 5, no.3 (September 2007): 228-238.

⁷³ Matheny, “Incentives for biodefense countermeasure development,” 232.

⁷⁴ As of July 2007, obligations totaled \$1.5B. The amount remaining for FY 04-08 is \$1.9B; the amount remaining for FY 09-13 is \$2.2B. (Project BioShield: Annual Report to Congress, August 2006-July 2007)

⁷⁵ Eric S. Langer and Joel Ranck, “The ROI case: economic justification for disposables in biopharmaceutical manufacturing,” *Disposable Economics*, (October 2005), 48.

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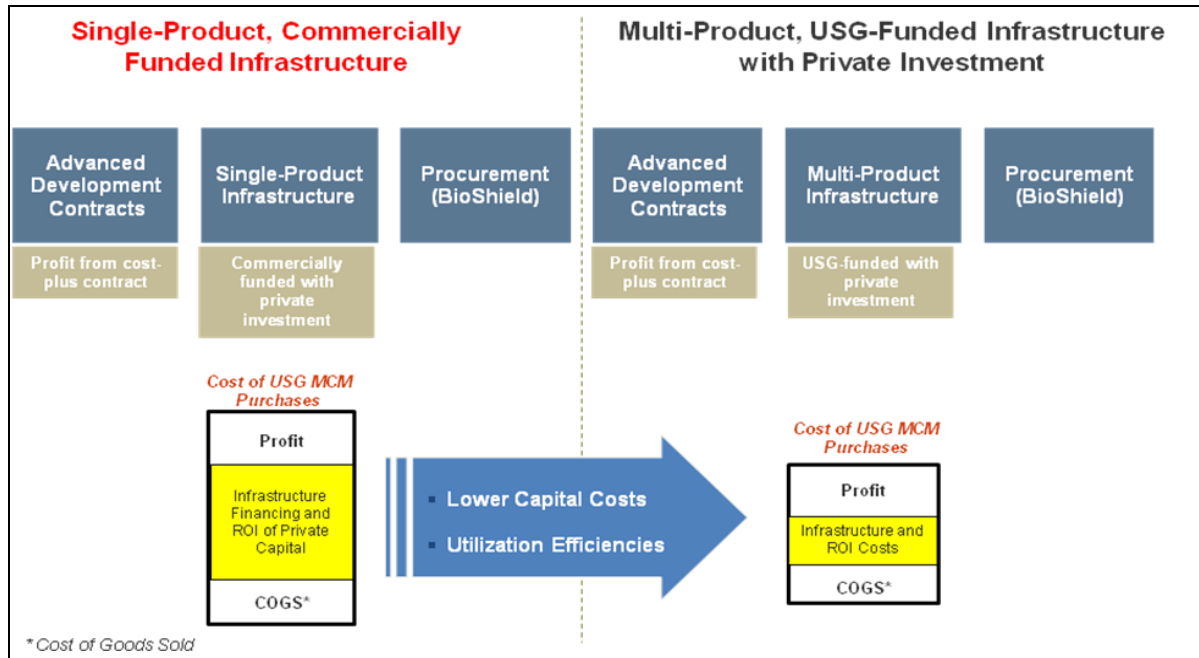


Figure 29. Potential Impact on the Cost of USG MCM Purchases by Implementing the BDMI Concept

A salient feature of the BDMI concept is the use of a multi-product facility that implements disposable bioprocessing technology versus dedicated, single-product facilities that predominately use traditional stainless steel equipment. Phase I of the 2008 study determined that a multi-product approach to the development and manufacture of biologics has significant long-term benefits in fulfilling requirements compared to the current single-product path (independent development and manufacturing of each biologic).

Significant findings of Phase I included:

- ~80% average annual manufacturing savings would result from implementation of the proposed multi-product facility
- Overall savings of ~\$30B in pre-clinical and clinical development, manufacture, fill-finish, licensure, and stockpiling would accrue over 25 years
- Overall cost reductions would result from high utilization of the facility and inherent efficiencies would be achieved through multi-product manufacturing, industry-leading technical expertise, and the lower cost per dose related to the lower cost of capital for a USG-funded facility

7.4 Operating Models

Several options exist in regard to operating models to produce USG biodefense requirements. Figure 30 illustrates four potential operating models: the current model of single firm research, development, and manufacturing (Single Product Model); the 2008 study-recommended BDMI model described earlier (Alternative 1); the contract manufacturing

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organization (CMO) model (Alternative 2); and the Shared Development Center model (Alternative 3).

Under the CMO model, the biotechnology innovator who discovers the biologic takes it through early research and development as well as clinical studies and holds the biologics license application (BLA). The biologic technology is transferred to a CMO, which provides assistance with formulation, process development, and warm-base production. Under the Shared Development Center model, individual innovators who discovered a biologic would transfer their technology to a shared development center and conduct clinical development studies and process development in coordination with the center operator. Scale-up and manufacturing—including warm-base and surge production if needed—would be controlled and coordinated by the center operator. Either the center or the original innovator could hold the BLA.

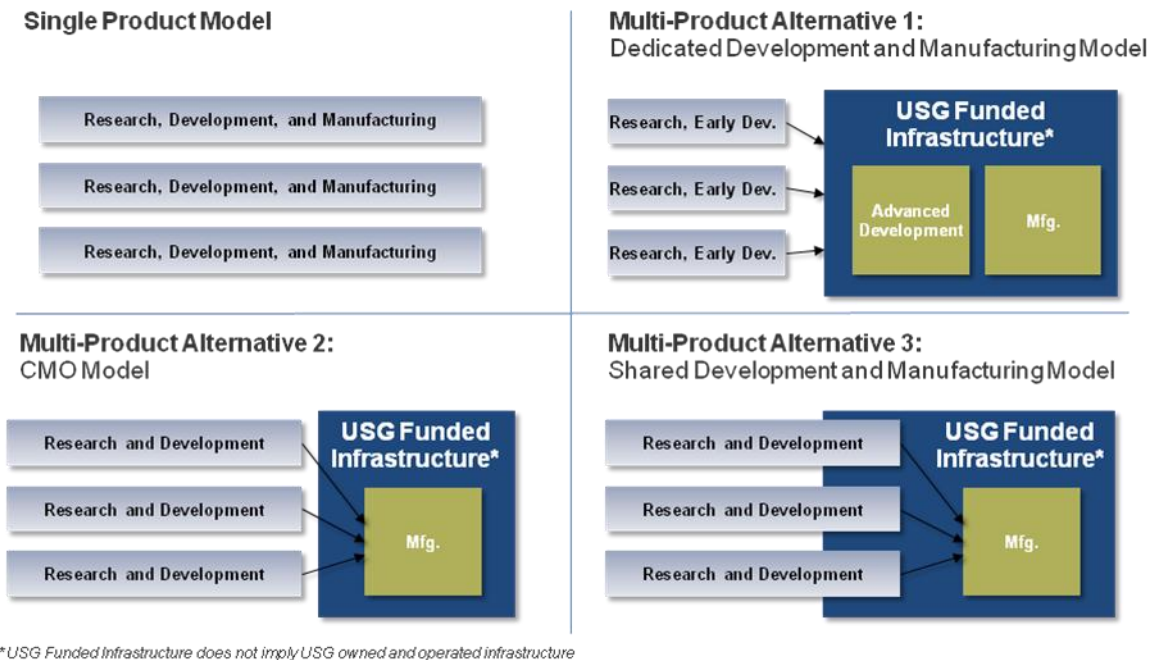


Figure 30. Proposed Operating Models for Production of USG Biodefense Requirements

These four models were presented as the initial framework for discussion during the industry interviews and the roundtable discussion. Industry participants provided substantive commentary on these operating models and described additional models that are discussed in subsequent sections of this report.

7.5 Options for Participation

Once incented to participate, industry can play various roles in developing a sustainable BDMI for the USG. A successful, dedicated capability will require the alignment of various stakeholders’ interests and resources, including those of the USG, biotechnology innovators, biodefense contractors, and large biopharma. Phase I of the 2008 study provided a paradigm for such partnerships as shown in Figure 31.

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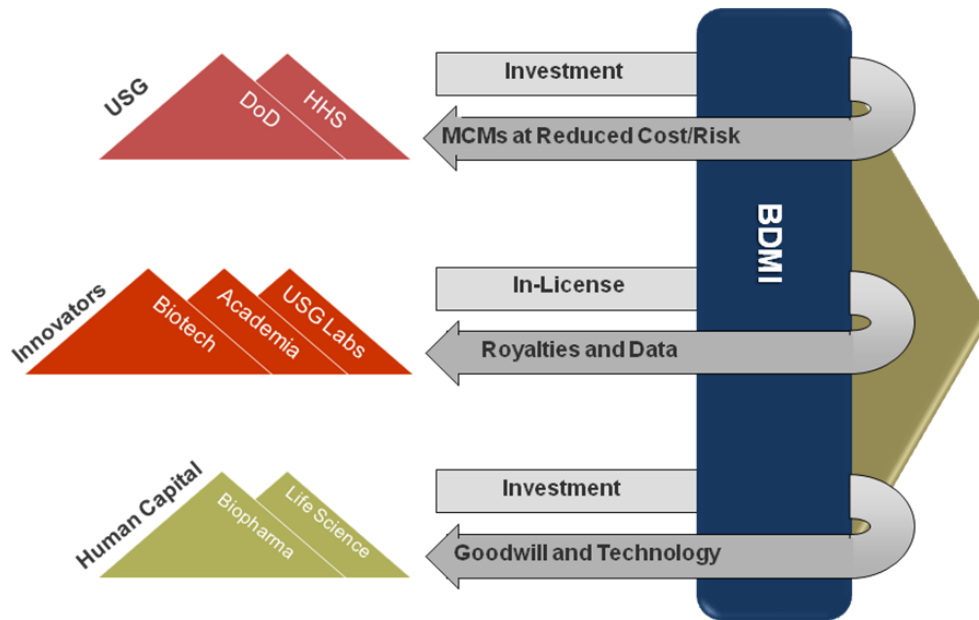


Figure 31. Framework for the Development of a Stable BDMI for the USG

Under this recommended framework, the USG would provide funding to design and build the infrastructure. The BDMI would acquire biological candidates from biotechnology innovators (including small biotech companies as well as academic and government labs), develop the candidates through licensure, and oversee post-licensure operations, warm-base production, and surge production, if needed. Large biopharma would assist in reducing development cost and risk by playing a significant role in providing process development, formulation and manufacturing expertise, and human capital to support the advanced development of biodefense biologics. Within such a model framework, substantial roles exist also for biotechnology innovators, biodefense contractors, and contract manufacturing organizations in terms of providing novel candidates, IP, and general know-how.

Although this paradigm is recommended, it is not the only viable option for developing the BDMI. Several alternative degrees of participation from industry partners are possible and would allow industry to offer a range of expertise, human capital, and IP assistance.

Industry partners may provide various levels of personnel commitment, including (1) an advisory group/steering committee, (2) a leadership team to oversee operations, (3) rotational staff appointments to BDMI facilities or (4) full-time management personnel and subject-matter experts in biologics development and manufacturing, with the latter being the recommended commitment level. Industry partners may also offer degrees of IP assistance to include (1) guidelines and manuals on best business processes (BBPs) and standard operating procedures (SOPs) for advanced biologic development and manufacturing, (2) workshops, seminars, and training courses for BDMI facilities' personnel on BBPs and SOPs, or (3) the recommended level or commitment: case-by-case development of processes in regard to each biologic candidate. While varying levels of participation from industry are possible, it will be the extent of that participation that will most impact the overall successes associated with launching and sustaining the BDMI.

7.6 *Enabling Industry Participation*

Building a sustainable and cost-effective BDMI requires significant participation from industry partners. To encourage this participation, the USG must remove the barriers that limit the degree of industry engagement and provide sufficient incentives to attract key industry players. Effort will be required both to align diverse partner interests and to create a sustainable and cost-effective infrastructure. The 2008 study's industry outreach took under consideration what barriers had to be removed and what incentives had to be provided in order to enable value-added engagement from industry.

8 *Methodology*

To determine the factors needed to incent industry participation in the development of a BDMI, a series of stakeholder meetings were held with industry—including representatives from biopharma, biotechnology, biodefense, and contract manufacturing industries—culminating in a roundtable discussion between government and industry stakeholders with expertise in biologics development and manufacturing. These outreach activities were designed to: (1) inform stakeholders of the biodefense challenges facing the USG, (2) brief stakeholders on the objectives of the study, (3) provide a high-level overview of key findings to date, (4) solicit feedback on the role stakeholders might play in the development of a BDMI, and (5) determine the barriers and incentives that would impact the degree of participation.

Individual industry interviews allowed stakeholders to provide their perspectives on the BDMI concept without concurrent engagement with other key industry stakeholders. The roundtable discussion complemented the industry interview phase of the study. It served as a forum for stakeholders to engage with each other in regard to the BDMI concept as well as to provide guidance to the USG in regard to potential partnership roles and the most appropriate path to take forward in order to build a viable biodefense enterprise meeting USG requirements.

8.1 *Individual Interviews*

Over 15 companies—including large biopharma companies, various biodefense contractors, biotechnology innovators, and contract manufacturing organizations—were interviewed. The majority of interviews were face-to-face; others were conducted via teleconference. A detailed list of participants is provided in Appendix A.

A background package that overviewed the biodefense challenge, goals of the study, and BDMI concept was presented to participants. Following review of the background material, feedback was solicited on: (1) various operating models designed to meet biodefense biologic requirements; (2) the degree of potential industry participation required for successful implementation of the paradigm model; and (3) the critical factors that would impact participation on the part of biotech and biopharma partners. These conversations provided a base from which operating model alternatives were refined and one additional operating model alternative was added for discussion during the roundtable.

8.2 *Roundtable Discussion*

The roundtable discussion was held on January 15th, 2009 and consisted of 12 participants from industry, government, and nonprofit sectors including executives from major pharmaceutical

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companies and biodefense-focused biotechnology companies, and additional experts in the fields of biosecurity and biomanufacturing. Representatives from the USG included senior policy and program officials from the DoD and HHS. All comments provided by the attendees were on-the-record but non-attributable. A list of participants and the roundtable discussion questions are included in Appendix B. Building on the insight gained during the outreach meetings, three key topics focused the roundtable discussion: (1) Integrated Advanced Development and Multi-Product Manufacturing, (2) Advanced Development and Multi-Product Manufacturing Operating Models, and (3) Keys to Success: Addressing Barriers and Incentives.

9 Results: Outreach Meetings

Four operating models were discussed during the industry interviews, and industry representatives were asked to comment on the feasibility, advantages, and disadvantages of the models. Alternative model concepts were also requested from the participants themselves. Additionally, participants were asked to discuss the barriers and incentives that would impact their decision as to whether or not participation seemed possible.

9.1 *Operating Model*

Most industry representatives overwhelmingly agreed that in theory the integrated advanced development and manufacturing concept is advantageous. Co-locating advanced development and centralized manufacturing would enable continuity in product development activities from process and analytical development through clinical trials and manufacturing, thereby streamlining the technology transfer process. Potential hurdles in formulation, validation, and consistency associated with the scale-up process could be obviated as R&D scientists and process developers would begin working with one another and sharing knowledge earlier in the product development process..

However, industry participants indicated that operating a multi-product facility with co-located advanced development and centralized manufacturing—as illustrated in the Shared Development and Manufacturing model and the Dedicated Development model—would create challenges that would need to be addressed:

- **IP protection.** Stakeholders (small innovators, biodefense contractors, and large biopharma) expressed concerns with protecting IP, including trade secrets and other proprietary information, in a multi-product facility. Innovators' IP was described as one of their greatest assets. Compromising such information could be detrimental to a company. Large biopharma indicated that not only preventing the disclosure of IP but also preventing inadvertent transfer of IP from one party to another was important. Unauthorized use of another's IP, whether intentional or not, could lead to lawsuits and collusion claims.
- **Management.** Many stakeholders indicated that a multi-product facility, particularly if a Shared Development and Manufacturing model, would be difficult to manage because of the need to balance interests among all participants. Innovators and biodefense contractors would want to manage the timeline of their products' development and

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production to assure the products' success and timely compensation, either through royalties or product procurement. Facility operators and owners would face challenges in terms of prioritizing access to the facilities and meeting stakeholders' demands.

- **Licensure.** According to industry, the degree of participation from various industry players would be dependent on ownership rights of the BLA for products in the facility. Biotech/biodefense innovators emphasized the importance of maintaining the BLA to control development of the product and capture the higher margins associated with procurement contracts. Such BLA ownership, however, would limit the facility owner's ability to dictate processes and procedures for product development, thus diminishing process standardization efficiencies and complicating management further.
- **Multi-product operations.** Some stakeholders expressed concern with operation of a multi-product facility because of the perceived risk of cross-contamination. Other stakeholders did express the opinion that using disposable technology could mitigate this risk.

Stakeholders who commented on the four operating models presented did not overwhelmingly prefer either the Shared Development and Manufacturing model or the Dedicated Development and Manufacturing model.

Although a consensus was not expressed on the most effective and efficient model, trends among stakeholders were evident. In general, CMOs (i.e., "Alternative 2" in Figure 30) believed in their capabilities to effectively provide advanced development and manufacturing assistance to meet the USG's requirements using existing infrastructure; however, the surge issue could not be addressed. Some innovators and current biodefense contractors expressed interest in the Shared Development and Manufacturing model (i.e., "Alternative 3" in Figure 30) because it would enable greater control for the innovator throughout the product development process. It would also create a better learning environment in which innovators would be able to learn from manufacturing outcomes, thus encouraging higher levels of innovation. On the other hand, large biopharma indicated that the Shared Development and Manufacturing model would be very challenging to manage whereas the Dedicated Development and Manufacturing model (i.e., "Alternative 1" in Figure 30) would be more operationally efficient. However, the Dedicated Development and Manufacturing model would require the innovator to transfer control of the product very early on in phase 1 or 2 of clinical development.

9.2 *Alternative Operating Models*

9.2.1 Using Existing Capacity

Notably, some stakeholders believe that sufficient production capacity is available in existing facilities and building additional capacity is not cost-effective, particularly for the production of mAB-based products.⁷⁶ This scenario would mean that pharmaceutical companies or CMOs could use their excess capacity to undertake USG warm-base production and

⁷⁶ A subsequent phase of this study addresses the potential of using existing mAB production capacity to satisfy USG requirements.

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stockpiling to biodefense biologics requirements when such undertakings are compatible with the technology platforms used in their facilities. Fill and finish could be contracted out to a CMO or completed by the USG. Under this model using existing facilities, surge requirements (not yet specified for all products) would be stockpiled at higher levels leading to higher steady-state costs, thus USG policy considerations in terms of procurement and stockpile levels would be necessary. Figure 32 provides an illustration of this model, referred to as the *Cluster model*.

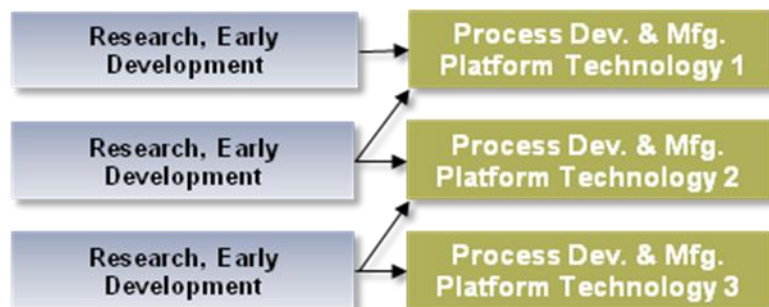


Figure 32. The Cluster Model

As a variation to the Cluster model, the USG could build a biologics biodefense enterprise that developed products only requiring basic technologies while contracting and paying a premium for private sector biologic development services when innovative technologies were required.

9.3 **Barriers**

Stakeholders expressed concerns over the economics of biodefense projects, regulatory ambiguity for the development and licensing of biodefense MCMs, and the arduousness of the USG contracting process. Barriers expressed included:

- **Low economic returns.** As publicly traded companies, stakeholders expressed the need to meet shareholders' expectations by earning "reasonable" pharmaceutical industry margins on projects. Currently, biodefense projects are not as lucrative as commercial projects. Higher margins than the standard 20% for procurement contracts and the standard 5% for research and development contracts are needed. The current returns on biodefense projects were viewed by many stakeholders as a minimum threshold to secure participation.
- **Evolving guidance on the animal rule.** Bids are often requested for products that will require use of the animal rule for licensure, yet the FDA does not provide clear guidance upfront on the requirements. To date only two products, neither of which were biological in nature, have been approved using the animal rule. The FDA guidance continues to evolve although it is hampered by FDA inexperience in applying the animal rule and the wide breadth of biologic product platforms to which the animal rule may be applied. Until animal rule requirements are clearly decided, determining the cost to execute a

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contract is extremely difficult. As a result, contracts may yield lower margins than anticipated, possibly becoming unprofitable.

- **Lack of contract adaptability.** Request for proposals (RFPs) do not reflect an understanding of pharmaceutical/biotechnology business operations. The government uses a one-size-fits-all approach to contracting even though the business models of all the key players can vary substantially. The economics of academic institutions, biotechnology firms, biodefense contractors, and biopharma differ. The structure/economics of contracts should vary depending on the intended industry or academic recipient.
- **Substantial administrative burden.** Completing RFPs for the USG constitutes a huge administrative burden. Commercial bids—typically more lucrative—and non-government organization (NGO) public health bids are less arduous, making them more attractive pathways for applying limited corporate resources. Further, some industry participants indicated that both cost accounting and federal acquisition rules (FARs) are a hindrance.
- **Ambiguous demand.** Ambiguity exists in regard to the amount of therapeutic or vaccine the government wishes to procure.
- **Contract length.** Industry would like longer term USG commitments than provided by the year-to-year contract renewal process. Longer commitments would reduce pressure on the required return on investment (ROI) because of the steady year-to-year cash flow. Stakeholders expressed the opinion that commitments of at least 10 years or longer would meaningfully reduce this barrier.

9.4 Incentives

Providing effective incentives to industry to overcome the stated barriers is imperative to encourage participation in any form of a USG-funded biodefense biologics enterprise. The incentives that industry representatives expressed can be categorized: as direct (monetary compensation) and indirect (provisions to financially benefit commercial efforts). Notably, biotechnology innovators and biodefense contractors prefer receiving direct incentives, whereas large biopharma companies prefer indirect incentives.

9.4.1 Direct Incentives

Innovators would consider participation if guaranteed payment for their products, including indirect payments through royalties or milestone and direct payments through procurement contracts. Biodefense contractors would consider participation if provided steady revenue commensurate with shareholder expectations. This would include margins closer to commercial industry standards—such as cost plus 20% contracts—and longer-term contracts on the order of a 10-year commitment.

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9.4.2 Indirect Incentives

The appropriate profile of incentives would strengthen and drive, without disrupting their ongoing commercial business operations was the consensus expressed by large biopharma participants.

There are two basic justifications for this logic: (1) A sustainable company would not make sufficient returns from biodefense products because commercial products garner significantly higher margins than successful biodefense products; (2) Given point one, biodefense products would be only a small segment of a company's portfolio and would become a distraction/nuisance if not counteracted by incentives to help the more substantive commercial product line.

Incentives that meet the aforementioned criteria include the following:

- Utilizing excess capacity of BDMI facility to produce commercial products, potentially for use in developing countries;
- Receiving rights to sell the products in commercial markets and to other governments;
- Extending patent protection;
- Receiving “preferred status” with the FDA, enabling faster review of BLA amendments across all products and faster evaluation of new facilities.

Note: Many stakeholders were skeptical regarding the real value of Priority Review Vouchers (PRVs), indicating that a PRV may not expedite the approval process because of the FDA's workload. Stakeholders believe the FDA is understaffed and would not be able to meet a six-month review deadline under current staffing conditions.

10 Results: Roundtable Discussion

As previously described, a roundtable discussion was held in order to build on the insights provided during the outreach meetings. Three key topics were discussed during the roundtable: (1) Integrated Advanced Development and Multi-Product Manufacturing, (2) Advanced Development and Multi-Product Manufacturing Operating Models, and (3) Keys to Success: Addressing Barriers and Incentives. Roundtable participants represented industry, government, and nonprofit sectors.

10.1 *Topic 1: Integrated Advanced Development and Multi-Product Manufacturing*

A key theme that emerged during the discussion of topic 1 was that information sharing among BDMI stakeholders was imperative. Participants identified that transferring information during the early stages of MCM development, post-Phase 1, is a more efficient and effective approach to developing biodefense requirements. Currently, transfers occur later in the process. It was also suggested that forming advanced development teams of both industry and regulatory experts to address common development inefficiencies experienced during complex analytical development, formulation, and animal study design activities would contribute to successful information sharing.

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There was general agreement among participants that the overarching objective of MCM development is licensing safe and efficacious products in a timely fashion to save lives. To successfully achieve this objective requires substantial expertise and experience, especially in late-stage drug development. Such expertise presently is distributed throughout industry with much know-how residing with large biopharma. Large biopharma does not currently participate in the biodefense space but, nonetheless, possess the requisite knowledge in process development and manufacturing to produce novel biologic products. To meet the USG's ambitious MCM development objectives, such expertise must coalesce.

During discussion, participants suggested various strategies to efficiently transfer technology between early-stage development experts (innovators) and late-stage development experts:

- Front-load information sharing between innovators and advanced development and manufacturing teams during the early stages of development. For example, scientists and engineers representing advanced development and manufacturing would begin providing assistance with formulations during the pre-clinical stage; and
- Contract for services when expertise is not available in the current USG biodefense enterprise.

Regardless of the strategy employed, participants indicated that effective technology transfer should be a continuous process that includes lessons learned from past development failures as well as successes. The process should also be sensitive to IP concerns. The following qualifications for developing an appropriate technology transfer process were expressed:

- Information sharing should be fluid, flowing forward and backward in the development process among innovators, regulators, and process engineers;
- Understanding the reasons for failure in research and early development is valuable. Information on past failures shared between government and industry could enable developers to avoid previous mistakes, thereby saving time, money, and, potentially, lives. Sharing information on failures is not standard practice, however, as many industry participants consider it part of their IP;
- Protecting and safeguarding IP when transferring technology is a concern.

10.2 Topic 2: Choosing the appropriate operating model

Four operating models were discussed for advanced development and manufacturing of MCMs and included the addition of the *Cluster model* (Alternative 4 in Figure 33), which was based on feedback expressed during the industry outreach interviews. These models were highlighted in the memo sent out prior to the roundtable and are represented below.

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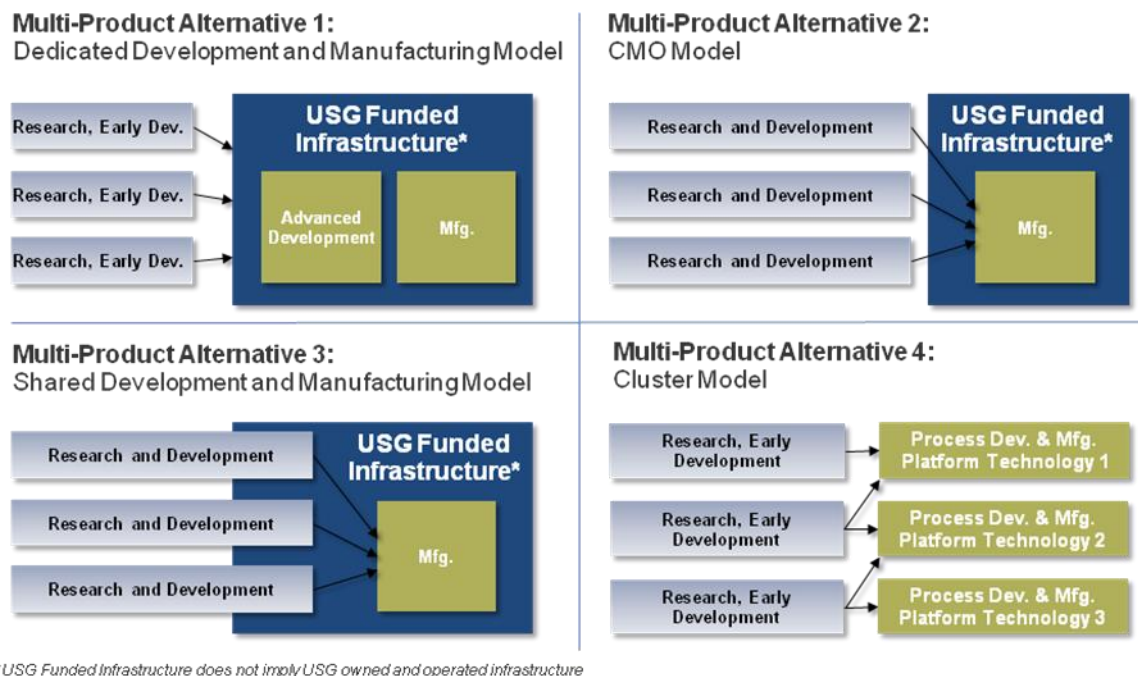


Figure 33. Multi-product alternative operating models

When reviewing the benefits and risks of the proposed operating models for a potential government investment in infrastructure, participants identified the following characteristics to be the most important in terms of benefit:

- Access to expert advanced development teams
- Ability to apply best practices to adapt to new regulatory pathways
- Ability to rapidly and consistently adapt to evolving standards
- Capability of being a sustainable enterprise
- Capability for surge production
- Ability to foster learning across products

The following were identified as the most significant risks:

- Limited regulatory and process development learning across the biodefense enterprise
- Production capability investment that does not cover all products
- Reliance on less experienced organizations for late-stage development
- Inability to meet surge requirements
- Late technology transfer
- Management of competing timelines across products
- Integration and maintenance of facility across all platform technologies

Using the aforementioned criteria, participants viewed *Dedicated Development and Manufacturing Model* as the most favorable model, followed by *Shared Development and Manufacturing Model*. Both operating models provide many key benefits and minimize risks

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associated with an MCM production facility. The *CMO Model* was viewed less favorably as it possessed a relatively equal number of benefits and risks.

Notably, when the *Cluster Model* was considered based on the aforementioned criteria, participants were not receptive. The *Cluster Model*, participants indicated, would not yield the operational efficiencies generated from sharing knowledge, including regulatory knowledge, across technologies. Some participants suggested that the *Cluster Model* would enable more innovation in selection of platform technologies than the other models. Concern was raised that some MCM products might be forced to fit a particular development path, which could stifle innovation, if based on specific platform technologies.

10.3 **Topic 3: Barriers Discouraging Industry Participation**

Roundtable participants generally agreed that the barriers as highlighted by industry during the interview stage of the industry outreach study were areas of concern. Mechanisms that could alleviate the most significant of those barriers were determined to include:

- **The Animal Rule.** Regulation in regard to the animal rule is evolving. Presently, there is not enough information available to formulate a well-defined approval pathway; therefore, the current process is iterative, requiring significant redundancy. Some participants expressed optimism that as more experience is gained, this fledgling regulatory area would improve over time. In the interim, participants suggested that regulators work closely with development teams to share information more quickly and streamline the process.
- **Government Contracting.** Participants acknowledged that the USG contracting process is arduous; however, they indicated that the process is not likely to improve in the near term due to the lack of contract and acquisition specialists in the USG. Integrating contract and acquisition specialists with experience in utilizing “other transactions” authority (OTA)^{77,78} into the development/manufacturing operating models was suggested as a method to improve the contracting process.
- **Innovation Encouragement.** Ideas were suggested for how—within a shared infrastructure—innovation could be encouraged while also enabling advanced development. Specifically, the concept of giving innovators a choice at the point of transitioning the product to the advanced development unit of either taking an immediate one-time award for their product or taking a milestone/license/royalty fee for the product was discussed as a potentially attractive alternative for supporting the diverse interests and goals of innovators of novel MCMs.

⁷⁷ 10 U.S.C. 2371(a) (2000); see Participant Views of Advanced Research Projects Agency “Other Transactions,” available at www.darpa.mil/body/d1791.

⁷⁸ 42 U.S.C.A. § 247d-7e(c)(4)(B)(iv).

11 Conclusions and Recommendations

Summarized below are the conclusions and recommendations of the industry outreach conducted from September 2008 to March 2009.

- Information sharing and communication were identified by participants as critical to ensuring success in addressing the USG's MCM development and manufacturing challenges. Three key interfaces were identified where good communication was essential:
 - At the transfer point between innovators and advanced development participants to improve the probability of success for development of effective MCMs;
 - When a technology transfer occurs across the advanced development and manufacturing interconnection point; and
 - Between the MCM developers and regulatory authorities to ensure that developments in regulatory approval pathways and the application of the animal rule are streamlined.
- Two operating models were identified by roundtable participants as being the most appropriate: (1) *Dedicated Development and Manufacturing* and (2) *Shared Development and Manufacturing*. Of these two models *Dedicated Development and Manufacturing* was the favored choice. The key feature making these models preferable to the other alternatives was the co-location of advanced development activities with manufacturing. It is believed that co-location would improve both information sharing and communication by concentrating expertise in the following areas:
 - Advanced process and analytical development
 - Regulatory approval pathways
 - Government contracting

Both the *Cluster model* and the *CMO model* were not as well received by outreach participants as they did not provide the co-location benefits while presenting additional challenges:

- That the BDMI—regardless of the operating model structure—should not be government-owned or government-operated was the consensus from industry participants. Participants expressed concern that government ownership or operation would impose significant limitations on the ability of the BDMI to attract required talent and would reduce flexibility in infrastructure management.
- Attracting talent with the required background and experience level was confirmed by industry participants to be a significant hurdle in staffing the BDMI. Suggestions to diminish the challenge of attracting talent included:
 - Locating the facility close to an existing talent pool; and

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- Making a sustained effort to offer incentives (e.g., the types of incentives used to develop life sciences clusters) that would attract talent to an area that does not have an existing talent pool.
- Addressing barriers to participation in a creative manner was termed essential to ensuring success. From an internal perspective, all industry stakeholders (both innovators and biopharma) were most concerned about the impact of participation on the protection and safeguarding of their IP. Concerns were raised with regard to preventing both the disclosure of IP to other stakeholders as well as the unauthorized use of another's IP.
- Additional barriers to participation were identified with respect to the USG:
 - The current regulatory ambiguity that exists in regard to the animal rule results in an iterative biologics licensing approval process that requires significant redundancy. Participants agreed that not enough information is available currently to formulate a well-defined approval pathway, and some expressed optimism that this emerging regulatory area would improve in time as additional experience is acquired. In the interim, participants suggested that close collaboration/sharing of information between regulators and development teams would streamline the process.
 - A lack of contract and acquisition specialists in the USG with the appropriate experience to manage the complexities involved with development and procurement of MCMs results in the existing arduous USG contracting process. This non-technical barrier to participation can be addressed by the USG through hiring of personnel with appropriate background and experience.

Stakeholders expressed optimism that closer collaboration with the USG would create concentrations of both industry and government expertise from which these issues could be addressed.

- Stakeholders identified that compensation remained the essential incentive for participation, although the type required varied among the stakeholders. Compensation is often grouped into two categories: (1) direct, which includes guaranteed payment for products through royalties or milestone payments and through procurement contracts and (2) indirect, which could include a set of incentives aimed to bolster, without interrupting, the ongoing commercial business operations of industry partners.

Typically, smaller innovators and most current biodefense contractors focused on direct compensation as their primary incentive for participation. Innovators were most interested in flexibility around IP licensing, and existing biodefense contractors had significant interest in procurement contracts. Biopharma stakeholders were more concerned with forms of significant indirect compensation that would bolster the earning potential of their commercial portfolios.

In addition, to make the compensation incentive more attractive to stakeholders, the USG would need to demonstrate a longer term commitment to developing and maintaining the MCM stockpile by setting longer timeframes for procurement contracts.

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10 years was the most often mentioned minimum threshold for contract duration that would make participation attractive for industry stakeholders.

11.1 Elements for Enabling Industry Participation

Based on the industry opinions expressed during both the outreach interviews and the industry roundtable, the following table summarizes the barriers that mitigate against and the incentives that can be used to encourage industry participation in biodefense BDMI for MCM production:

Table 9. Minimum Requirements for BDMI Participation by Various Potential Stakeholders

| Participation Requirements | Innovators | Current Adv.Dev.and Manufacturing Biodefense Contractors | Biopharma |
|--|-------------------|---|------------------|
| BDMI not government-owned or -operated | ✓ | ✓ | ✓ |
| IP protection | ✓ | ✓ | ✓ |
| Prevention of unauthorized use of another’s IP | | | ✓ |
| Creative licensing | ✓ | | |
| Direct incentives providing good economic returns | ✓ | ✓ | |
| Longer-term commitment (>10 years) | | ✓ | |
| Availability of “indirect” incentives applicable to other products | | | ✓ |

Clearly any incentive structure developed to encourage participation must be flexible enough to attract all the required stakeholders and must include consideration of both direct and indirect compensations. The direct link that has been identified between the type of incentive offered and the willingness of a stakeholder to participate can be used as an effective tool in the development of the BDMI operating structure.

Monoclonal Antibody Manufacturing Options: Executive Summary

This section determines the feasibility of utilizing existing domestic commercial production capacity for the purpose of manufacturing monoclonal antibody (mAB)-based biodefense MCMs. Feedback gathered from the Comprehensive Industry Outreach indicated that excess capacity exists domestically and that utilizing that capacity may be a cost-effective approach to achieving USG biodefense requirements.⁷⁹

This section is divided into three parts. Part one evaluates both domestic capacity and the factors driving an excess of that capacity. Part two is a cost analysis determining the impact of excluding mAB production from the dedicated BDMI. Part three explores additional considerations regarding the appropriate manufacturing strategy for mAB-based MCM products.

In part one, analysis of domestic mAB production capacity indicates that excess capacity currently exists. However, a set of competing factors (technological advancements, infrastructure investment, and increasing commercial demand for mAB-based products) may serve to reduce this excess as early as 2013. In part two, a cost analysis suggests that outsourcing mAB production to a contract manufacturer may save 15% to 20% in manufacturing costs at the baseline process efficiency of 333 doses per liter (d/L). However, lower d/L process efficiencies may reduce or reverse these savings, making mAB production in the BDMI the more cost-effective option. For the purpose of this report, CMO capacity is considered to include both contract manufacturing organizations as well as existing excess capacity at biopharma companies. In part three, evaluation of other factors affecting the outsourcing decision indicate that the exclusion of all mAB products from the BDMI will significantly increase the risk related to production of mAB-based MCMs by limiting the ability of the USG to respond rapidly to surge requirements and likely contributing to delays in time to licensure.

Overall, excluding all mAB production from the dedicated capability is a viable option, but it introduces additional risks for a moderate economic benefit. In deciding to outsource mAB production, all stakeholders should account for risks associated with outsourcing and incorporate risk-mitigation strategies in selecting the chosen production method.

⁷⁹ Industry Outreach report, Section 4.2.1, 19.

12 Introduction

The purpose of this section is to explore the feasibility of utilizing existing domestic mAB production capacity for the production of mAB-based biodefense products required by the USG. The objectives of this study are to:

- Evaluate current commercial mAB production capacity to determine if an excess exists that could be utilized by the USG for the purpose of mAB-based MCM production.
- Assess the facility and operating cost implications across a range of possible production efficiencies for producing mAB MCMs with a contract manufacturer versus within a dedicated MPMU capability
- Explore factors affecting the decision to outsource mAB production to a contract manufacturer and the extent to which this should be done

This study was conducted in response to feedback gathered during the Comprehensive Industry Outreach⁸⁰, which indicated that in recent years excess manufacturing capacity for mABs has been created in the US due to significant advances in high-yield mAB technologies. Industry outreach participants speculated that utilizing this excess domestic production capacity could be a cost-effective approach to meeting USG biodefense requirements, specifically for the mAB-based biodefense product candidates currently in development (e.g., therapeutic products for anthrax and botulinum threats as well as broad spectrum therapeutic products).

12.1 Methodology

12.1.1 mAB Production Capacity

Domestic mAB production capacity was evaluated through a review of publicly available documents, including commercial and academic literature, and verified through interviews with industry experts. The evaluation also used information gathered from the webinar “Flexible Manufacturing - The New Driver in Monoclonal Antibody Process Economics.”⁸¹

12.1.2 Cost Implications of mAB Outsourcing

The modeling tools used to develop the High Level Capability Design for the first section of this study⁸² were also used to evaluate the cost implications of mAB outsourcing.

This section assessed the facility and operating cost implications of producing mAB MCMs using a contract manufacturer versus within the proposed dedicated capability. Analysis included the baseline mAB production efficiency assumptions used in the initial HLCD (333 d/L) as well as two additional sets of mAB production efficiency assumptions, labeled “conservative” and

⁸⁰ *Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government*. DARPA Cooperative Agreement HR0011-07-2-000. Industry Outreach, Section 9.2.1, pg. 80.

⁸¹ Günter Jagschies, "Flexible manufacturing - the new driver in monoclonal antibody process economics," General Electric Healthcare Life Sciences Webinar, 24 Feb. 2009.

⁸² *Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government*. DARPA Cooperative Agreement HR0011-07-2-000. Industry Outreach, Section 6, pg. 69.

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“aggressive.” The conservative assumptions present the worst-case scenario of extremely low yields and high-dose requirements (low efficiency) and the aggressive assumptions present the best-case scenario of extremely high yields and low-dose requirements (high efficiency). .

12.1.3 Additional Considerations Regarding Outsourcing of mAB Production

A series of interviews were conducted with industry experts to gain a deeper understanding of the factors that must be accounted for when considering outsourcing mAB production. Relevant publicly available documents, including commercial and academic literature, were also reviewed.

13 Evaluation of mAB Production Capacity

For this report, production capacity is considered across the entire manufacturing process from upstream processing through to finished bulk mAB products. “Excess capacity” is defined as the difference between available domestic mAB production capacity and demand for mAB-based products.

13.1 *Overview of mAB Manufacturing*

mAB manufacturing consists of three major phases that are part of all mAB-derived drug development platforms: upstream production, clarification and concentration, and downstream processing,. Each is described below, with special attention paid to its respective degree of standardization as this has a direct effect on the ease of transferring or augmenting production.

13.1.1 Upstream Production

Upstream production refers to the large-scale production of antibodies from a chosen cell line. In this phase, working cell banks are expanded through the use of a series of small bioreactors into the full-scale production train. At the end of the batch cycle, reactor contents move to the clarification and concentration phase.

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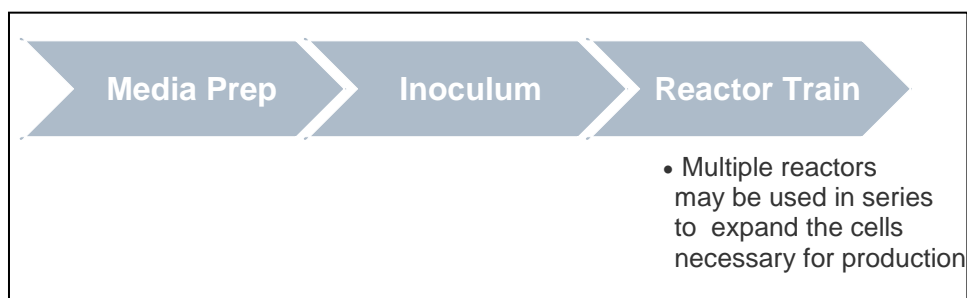


Figure 34. Upstream process flow.

Research indicates that development of the master and working cell lines to produce the target mAB has become relatively standardized. Industry has almost universally adopted the use of either Chinese hamster ovary cells (CHO) or PER. C6 cells for mAB production.⁸⁵ The generally accepted procedure for hybridoma production is a murine myeloma fusion with antibody-producing cells. Additionally, the DNA sequencing steps and transfection steps use standard biomolecular procedures with little variation.⁸⁶

13.1.2 Clarification and Concentration

The clarification and concentration phase, consisting primarily of a series of consecutive or concurrent filtration or centrifugation steps⁸⁷, focuses on extraction of the desired antibodies from the solution produced in the bioreactor.⁸⁸ Techniques for clarification and concentration include tangential flow filtration, high-speed centrifugation, depth filtration, concentration and diafiltration.

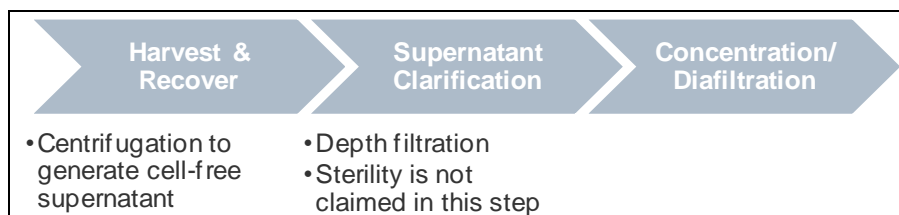


Figure 35. Clarification and concentration process flow.

While standardized procedures for clarification and concentration exist, sequencing these procedures varies from product to product based upon each manufacturer's respective optimization criterion and models.⁸⁹

13.1.3 Downstream Processing

The final phase of mAB production is downstream processing, which refers to the purification of the target mAB to achieve final bulk drug product. This phase, when successful,

⁸⁵ Interviewee, Antibody Production Company, Telephone Interview, 3 February 2009.

⁸⁶ Interviewee, Antibody Production Company, Telephone Interview, 3 February 2009.

⁸⁷ Joe X. Zhou and others, "Implementation of advanced technologies in commercial monoclonal antibody production," *Biotechnology Journal* 3, no. 9-10 (2008):1189-1192.

⁸⁸ Manager, Precision Antibody, A&G Pharmaceutical, Telephone Interview, 3 February 2009.

⁸⁹ Susan S. Farid, "Established antibody bioprocesses as a basis for future planning," *Advances in Biochemical Engineering/Biotechnology* 101 (2006): 16-18.

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isolates the desired antibody from byproducts from the upstream bioreactor phase.⁹⁰ Downstream processing typically involves a series of chromatographic and filtration unit operations, with product recovery estimated to be 60% to 80%.^{91,92}

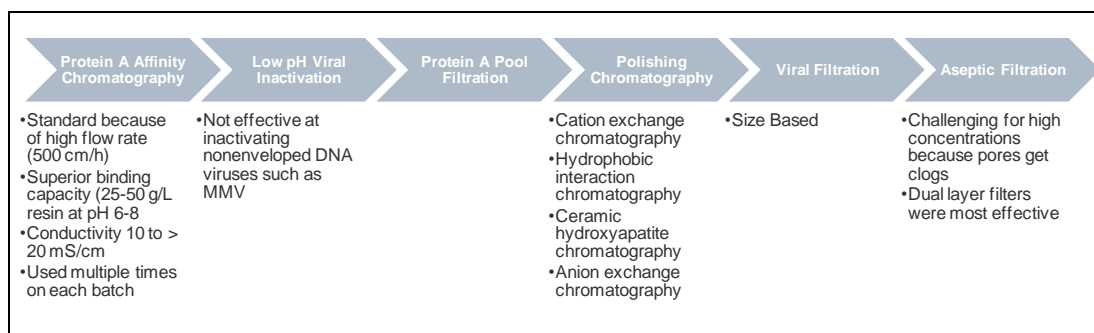


Figure 36. Downstream process flow.

As shown in Figure 36, protein A chromatography is a commonly used downstream processing technology in mAB production. Protein A, one of the most expensive raw materials used in downstream processing, is used to selectively bind the mAB away from other process contaminants. There are two strategies to optimize the use of a protein A affinity chromatography step (see Figure 36 above).⁹³ This step is used to. One strategy emphasizes efficiency in material usage (minimal cost of resin) and the other emphasizes efficiency in change-over time (maximum throughput of product through facility).

Material efficiency is achieved through the reuse of protein A resin. While this method reduces cost in terms of purchasing resin, it increases change-over times due to required cleaning and validation activities between products.⁹⁴ On the other hand, change-over times can be reduced if the protein A resin is treated as a single-use component and disposed of between products. However, the high cost of protein A resin makes this a costly option for increasing downstream capacity. Developers generally weigh both options and attempt to optimize their system based on their priority and focus.

13.2 Evaluation of Factors Affecting mAB Production Capacity

Three major factors affecting domestic mAB production capacity were identified:

- Technology improvements are driving production efficiency for existing infrastructure
- Companies are investing in new biomanufacturing infrastructure
- Demand for mAB-based products is increasing

The first two factors have a positive impact on available excess capacity, while the third has a negative effect. Each of these three factors is discussed in more detail below.

⁹⁰ Zhou, "Implementation of advanced technologies in commercial monoclonal antibody production," 1189-1192.

⁹¹ John R. Birch and Andrew J. Racher, "Antibody production," *Advanced Drug Delivery Reviews* 58 (2006): 671-85.

⁹² Brian Kelly, "Very large scale monoclonal antibody purification: the case for conventional unit operations," *Biotechnology Progress* 23, no.5 (2008 online): 1000.

⁹³ Zhou, "Implementation of advanced technologies in commercial monoclonal antibody production," 1189.

⁹⁴ Zhou, "Implementation of advanced technologies in commercial monoclonal antibody production," 1190.

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13.2.1 Technology Improvements

Improvements in technology involve adopting new procedures that may expedite certain processes or increase the return on each step of a process. The development of cell lines through transcription of antibody genes using appropriate expression vectors, the use of cell lines capable of translating antibody mRNA, and the use of cell lines with sufficient secretory capacity⁹⁵ are examples of improvements where the industry has adapted fairly uniform technologies and procedures. As described earlier, procedures in mAB processing have become, to varying degrees, more standardized and optimized as technology has matured.

Technology improvements have also produced higher yields throughout the mAB production process, translating into lower requirements for production capacity. As final yield is impacted by bioreactor titer, clarification and concentration efficiency, and downstream purification efficiency, improvements in technology associated with any processing step may result in a reduction in required upstream capacity and a lower cost product.

13.2.2 Upstream Production Improvements

The most common bioreactor sizes for commercial mAB production are 10,000L and 20,000L. Such large-scale production is possible because of improved understanding of low-shear mixing and better controllability of gas transfer.⁹⁶ The availability of these large-volume bioreactors has enabled the modern large multi-product facility. Companies such as Amgen, Biogen, Boehringer Ingelheim, Genentech, ImClone, and Lonza now have facilities up to 500,000 square feet with a total bioreactor capacity of 200,000L, accomplished by using multiple 25,000L bioreactors.⁹⁷

In addition, advances in mAB expression vectors have resulted in a multiple fold increase in mAB titer over the last 25 years, from less than 0.5 grams/liter to 5 grams/liter or greater. This reflects the pace of development, as titers in 1995 were measured in milligrams, not grams (see Table 10 below). As of 2005, 5g/L was the best reported titer in mAB production,⁹⁸ with titers up to 10g/L considered technically feasible.^{99,100}

Table 10. Advances in mAB expression expressed as bioreactor titer (mg/L).¹⁰¹

| mAB Expression | 1985-1995 | 1995-Current |
|-----------------------|---------------|----------------|
| | Titer (mg/L) | Titer (mg/L) |
| Hybridoma | 150 to 500 | Not Available |
| Myeloma | 500 | Not Available |
| CHO | 90 to 550 | 5,500 to 6,100 |
| EBV-transformed human | 90 | Not Available |
| NSO | Not Available | 5,100 |

⁹⁵ Birch and Racher, "Antibody production," 673.

⁹⁶ Zhou, "Implementation of advanced technologies in commercial monoclonal antibody production," 1188.

⁹⁷ Susan S. Farid, "Process economics of industrial monoclonal antibody manufacture," *Journal of Chromatography B* 848 (2007): 9.

⁹⁸ Michael Butler, "Animal cell cultures: recent achievements and perspectives in the production of biopharmaceuticals," *Applied Microbiology & Technology* 68 (2005): 283.

⁹⁹ Kelly, "Very large scale monoclonal antibody purification: the case for conventional unit operations," 995.

¹⁰⁰ Farid, "Established antibody bioprocesses as a basis for future planning," 10.

¹⁰¹ Farid, "Established antibody bioprocesses as a basis for future planning," 10

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Larger bioreactors and increased titers have positively affected the efficiency of upstream operations in mAB production and have had a positive impact on the availability of production capacity.

13.2.3 Downstream Production Improvements

Advances in fermentation titer and bioreactor technologies have allowed upstream production of mABs to outpace advances in downstream purification processes.¹⁰² As a result, downstream processing has become the bottleneck in high-yield mAB production.^{103,104} When fermentation titers increase, downstream operations typically increase capacity using additional and/or larger chromatography columns, which, because of their size, can be unwieldy and difficult to manage. Cost analysis supports this assertion; with greater upstream production efficiency, the ratio of upstream cost to downstream cost is 1:4, whereas in balanced production the ratio is closer to 1:1.¹⁰⁵

Industry is aware of the limiting constraints of the downstream processing stage and various R&D units are currently seeking to improve this phase of the mAB production process. For example, Millipore recently developed a protein A resin with an antibody binding capacity (which is a primary driver of downstream production capacity) of up to 50mg/mL, an increase from the more typical binding capacity of 40mg/mL.¹⁰⁶ This imbalance in production capability between upstream and downstream is creating a bottleneck in mAB production at the downstream processing phase, negating the efficiency gains resulting from improvements in fermentation titers. New infrastructure investment will only be able to take advantage of the improvements in fermentation titer if downstream processing unit operations are designed at an appropriate scale.¹⁰⁷

13.2.4 Investment in Infrastructure

Biopharma companies are building more capacity for production of mABs, increasing the availability of product supply. The following table is a sampling of recent domestic construction and expansion by major biopharma companies:

¹⁰² Jagschies, General Electric Healthcare Life Sciences Webinar, 24 Feb. 2009.

¹⁰³ Birch and Racher, "Antibody production," 673.

¹⁰⁴ Interviewee, Steering Team, Telephone Interview, 17 February 2009.

¹⁰⁵ Farid, "Process economics of industrial monoclonal antibody manufacture," 13.

¹⁰⁶ Gail Dutton, "Downstream bottlenecks: are they myth or reality?" *Genetic Engineering & Biotechnology News* 28, no. 8 (15 April 2008 online).

¹⁰⁷ Jagschies, General Electric Healthcare Life Sciences Webinar, 24 Feb. 2009.

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Table 11. Examples of recent domestic investment in bioreactor capacity.¹⁰⁸

| Company | Location | Facility Complete | Capital Investment (US \$M) | Area (sq ft) | Production Bioreactor Capacity | | |
|---------------------|-----------------------------|-------------------|-----------------------------|--------------|--------------------------------|----------|-----------|
| | | | | | Number | Size (L) | Total (L) |
| Genentech | Vacaville, CA | 2000 | 250 | 310,000 | 8 | 12,000 | 96,000 |
| ImClone | Branchburg, NJ | 2001 | 53 | 80,000 | 3 | 10,000 | 30,000 |
| Biogen | Research Triangle Park , NC | 2001 | 175 | 245,000 | 6 | 15,000 | 90,000 |
| Lonza Expansion | Portsmouth, NH | 2004 | 207 | 270,000 | 3 | 20,000 | 60,000 |
| Amgen | West Greenwich, RI | 2005 | 500 | 500,000 | 9 | 20,000 | 180,000 |
| Genentech | Oceanside, CA | 2005 | 380 | 470,000 | 6 | 15,000 | 90,000 |
| ImClone | Branchburg, NJ | 2005 | 260 | 250,000 | 9 | 11,000 | 99,000 |
| Genentech expansion | Vacaville, CA | 2009 | 600 | 380,000 | 8 | 25,000 | 200,000 |

The increasing success of mABs as treatment options is driving this supply expansion.¹⁰⁹ The large number of mAB products under development has resulted in an increase in the construction of mAB production facilities. Because of the long lead time for facility construction and validation, the investment in infrastructure typically occurs several years before product approval is expected. . In terms of capacity, each facility has multiple bioreactors with capacities ranging from 10,000L to 25,000L per bioreactor. Construction on this scale represents a significant expansion of US supply, as the major projects completed since 2000, listed in the table above, represent ~70% of domestic capacity.

Further expansion of supply is expected, due to budding research in mAB production using other expression systems including the use of transgenic plants and animals. This line of research has grown in intensity in response to the realization of potential market demand for such products, which could reach several hundreds of kilograms annually.¹¹⁰ That said, new areas of research may put downward pressure on traditional mAB production supply.

¹⁰⁸ Farid, "Process economics of industrial monoclonal antibody manufacture," 10.

¹⁰⁹ Farid, "Established antibody bioprocesses as a basis for future planning," 28.

¹¹⁰ Farid, "Established antibody bioprocesses as a basis for future planning," 29.

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13.2.5 Trends in Market Demand for mAB-based Products

Increases in supply are occurring in response to anticipated demand increases. The demand for mAB-based products was increasing for many years, recently demand has slowed. However, the heavy focus of mAB technology in R&D of biologics, indicates demand may rise again in the coming years.

Market penetration of approved mAB-based products had been increasing through 2006.^{111,112} As seen in Table 12 below, sales of the top mAB products were increasing at an average year-on-year rate of ~60%, far higher than the rate of the disease population.

Table 12. Sales for bestselling mAB drugs, 2004-2006.¹¹³

| Generic Name Target | Brand FDA Approval | Company | Indication | Sales \$ billion | | |
|------------------------------|-----------------------|---------|---------------------------------|------------------|------|------|
| | | | | 2004 | 2005 | 2006 |
| Rituximab c CD20 | Rituxan 1997 | Roche | Leukemia, Lymphoma, RA | 2.8 | 3.2 | 4.7 |
| Infliximab cTNF α | Remicade 1998 | J&J | CD, UC, AS, RA, Ps, PsA | 2.1 | 3.5 | 4.2 |
| Trastuzumab hz HER2 | Herceptin 1998 | Roche | Breast Cancer | 1.3 | 1.64 | 3.14 |
| Bevacizumab VEGF hz | Avastin 2004 | Roche | Colon Cancer, Lung Cancer | 0.55 | 1.3 | 2.4 |
| Adalimumab h TNF α | Humira 2002 | Abbot | RA, PsA, AS, CD | 0.83 | 1.4 | 2.04 |

According to BioProcess Technology Consultants, "Most of the products approved in the last two to three years have either been for small-volume indications or have had relatively slow market penetration."¹¹⁴ More recent trends from 2008 suggest a downturn in the mAB market growth rate.¹¹⁵

Current R&D in biologics is highly focused on mABs, with mAB-based products making up 85%-90% of the pipeline.¹¹⁶ Not only are mAB products being considered for additional uses within disease indications already treated by mABs, but the range of conditions continues to grow in scope and is beginning to include many common chronic diseases (e.g., inflammatory diseases treated by Humira and rheumatoid arthritis treated by Remicade).^{117,118}

13.1 Supply vs. Demand in Determining Excess Capacity

Capacity for mAB production was built in expectation of an upward acceleration in demand, but that trend has slowed significantly. This circumstance has created an excess in

¹¹¹ Farid, "Established antibody bioprocesses as a basis for future planning," 28, 16 August 2006

¹¹² "Research and Markets: Xolair is set to dominate the respiratory monoclonal antibody market through to 2010 with a \$1 billion market potential by 2015." [The Free Library Farlex](#).

¹¹³ Krishan Maggon, "Monoclonal antibody 'gold rush,'" *Current Medicinal Chemistry* 14, no. 18 (2007): 1000.

¹¹⁴ Jim Miller, "Biomanufacturing Pendulum Swings Toward Overcapacity," *BioPharm*, 01 May 2008.

¹¹⁵ Miller, "Biomanufacturing Pendulum Swings Toward Overcapacity."

¹¹⁶ Howard L. Levine, "Challenges and solutions for biopharmaceutical manufacturing," BioProcess Technology Consultants, Inc., Cambridge HealthTech PepTalk Conference, San Diego, CA, 15 January 2009.

¹¹⁷ Farid, "Established antibody bioprocesses as a basis for future planning," 28, 16 August 2006

¹¹⁸ Farid, "Established antibody bioprocesses as a basis for future planning," 28, 16 August 2006

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supply, as manufacturers may have chosen to err on the side of oversupply. As recently as 2009 Genentech—cited as having too much capacity—responded, “A six-month delay in having capacity ready for a product can mean a loss of \$1 billion a year, whereas having too much capacity costs about \$50 to \$150 million a year – so the natural tendency is to build more.”^{119,120}

Determining the level of excess domestic mAB production capacity is a dynamic exercise due to the constant flux of supply and demand for mAB-based products. As discussed in section 13.2, several factors indicate that excess capacity may exist. Improvements in upstream processing technology, investment in new infrastructure, and underutilization of existing infrastructure are all factors that increase the availability of capacity; however, they are counter-balanced by factors that decrease excess capacity (e.g., fewer improvements in downstream purification and increasing demand for mAB-based products).

To determine the potential level of excess domestic capacity, theoretical annual domestic production capacity was compared with an estimate of annual mAB demand. To conduct this analysis, three estimates of domestic mAB production capacity were calculated based on varying assumptions of production efficiency. Production capacity was calculated as the product of bioreactor volume, fermentation titer, purification yield, and bioreactor turns. Current domestic bioreactor volume was estimated using a summation of publicly available information on domestic commercial capacity.

The three bioreactor efficiency scenarios (high, moderate, low) used for this comparison—based on average titers of *currently manufactured products*—are outlined in Table 13:

Table 13. Bioreactor production efficiency scenarios for estimates of domestic mAB production capacity

| Scenario | Domestic Bioreactor Volume (L) | Bioreactor Titer (g/L) ¹²¹ | Purification Yield (%) ^{122, 123, 124} | Bioreactor Turns/Yr | Estimated Domestic Supply (kg) |
|---------------------|--------------------------------|---------------------------------------|---|---------------------|--------------------------------|
| Low Efficiency | 1,200,000 | 0.5 | 60 % | 7 | 2,520 |
| Moderate Efficiency | 1,200,000 | 1.0 | 70 % | 12 | 10,080 |
| High Efficiency | 1,200,000 | 1.5 | 75 % | 20 | 27,000 |

Global mAB demands for the years 2009 and 2013 were based on published estimates of 5,800kg and 11,800kg, respectively.¹²⁵ Current US demand for mAB therapeutics was estimated at 1,150kg, based on average annual US demand per mAB drug (46kg)¹²⁶ and the current number of FDA-approved mAB drugs (25).¹²⁷ US demand in 2013 for mAB drugs was assumed to

¹¹⁹ Gregory Cancelada, “Wyeth to close Berkeley MO manufacturing plant,” *St. Louis Post-Dispatch Knight Ridder / Tribune Business News*, 19 December 2003.

¹²⁰ Laura Bush, “Capacity planning challenges even Genentech,” *BioPharm*, 11 February 2009.

¹²¹ Aforementioned industry best is 5 g/L, but many current production processes utilize dated but proven methods that result in lower titers.

¹²² Kelly, “Very large scale monoclonal antibody purification: the case for conventional unit operations,” 997.

¹²³ Butler, “Animal cell cultures: recent achievements and perspectives in the production of biopharmaceuticals,” 283.

¹²⁴ Birch and Racher, “Antibody production,” 683.

¹²⁵ Levine, “Challenges and solutions for biopharmaceutical manufacturing,” 21.

¹²⁶ Farid, “Established antibody bioprocesses as a basis for future planning,” 18.

¹²⁷ UPMC Scientist, In-Person Interview, 16 February 2009.

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increase at the same rate as that of global demand – giving a US demand estimate for 2013 of 2,339kg.

Determination of excess capacity or under-capacity was made based on calculation of the difference between estimated demand and estimated supply. A summary of the calculation results for each of the production efficiency scenarios is provided in Table 14, where a negative number indicates under-capacity and a positive number indicates excess capacity. Additional details regarding the modeling methodology and assumptions are found in Appendix C.

Table 14. Estimate of excess domestic mAB production capacity vs. global and US demand.

| Level of Efficiency | Domestic Supply (kg/year) | Global Supply-Demand Gap ¹²⁸ (kg) | | US Supply-Demand Gap (kg) | |
|---------------------|---------------------------|--|-------------------------|---------------------------|------------------------|
| | | 2009 (5,800 kg demand) | 2013 (11,800 kg demand) | 2009 (1,150 kg demand) | 2013 (2,339 kg demand) |
| Low Efficiency | 2,520 | -3,280 | -9,280 | 1,370 | 181 |
| Moderate Efficiency | 10,080 | 4,280 | -1,720 | 8,930 | 7,741 |
| High Efficiency | 27,000 | 21,200 | 15,200 | 25,850 | 24,661 |

Table 14 indicates that in the moderate and high efficiency scenarios, at current domestic capacity levels, excess domestic capacity for mAB production exists.

In order to determine if the estimated level of excess capacity was sufficient to support production of mAB-based MCM products, an estimate of peak annual demand for building and maintaining the stockpile of these products was required. Peak annual demand was estimated as the product of the peak number of annual doses required (750,000 doses¹²⁹) and dose strength. Three scenarios for dose strength—based on the range for mABs as noted in published references (Lucentis for macular degeneration is 0.5mg, Cleveland BioLabs’ radiation therapeutic is 3mg, DARPA Accelerated Manufacturing of Pharmaceuticals (AMP) program references a dose as high as 400mg, Synagis is 1000mg)—were evaluated. The scenario assumptions are detailed in Table 15 below:

Table 15. Peak annual mAB-based MCM requirement scenarios.

| Scenario | Dose Strength (mg/dose) | Peak Annual mAB Requirement (kg) |
|---------------------|-------------------------|----------------------------------|
| Conservative | 800 | 600 |
| Baseline/Aggressive | 3 | 2.25 |

Based on this analysis, it appears that currently there is sufficient domestic production capacity to accommodate the outsourcing of mAB-based MCM production and that further feasibility and cost analysis is warranted.

¹²⁸ Levine, “Challenges and solutions for biopharmaceutical manufacturing,” 21.

¹²⁹ Established in the HLCD.

14 Cost Implications of mAB Outsourcing

The assessment of domestic mAB production capacity indicates that there may be excess capacity that could potentially be used for the production of MCMs. In order to determine if it is economical to use this capacity as an alternative to producing the respective MCMs within the dedicated capability, the cost and facility-sizing implications of leveraging CMO capacity to manufacture those MCMs was assessed.

The following analyses assess the facility and operating cost implications across a range of possible production efficiencies of producing mAB MCMs, either within the proposed dedicated capability or using a contract manufacturer. Given the necessary uncertainties in estimating the efficiency of mAB production technology, the full range of possibilities in terms of facility sizing and costs resulting from variations in those efficiencies was articulated. (Please note that the final calculated costs reflect direct facility and manufacturing cost only and do not include profit margins, capital cost, development, technology transfer or fill/finish costs.)

14.1 Assumptions

Six scenarios were evaluated, characterized by production efficiencies as well as inclusion/exclusion of the respective mAB-based MCMs in the dedicated capability. With regard to production efficiencies, the “baseline” scenarios were constructed using the moderate yield and dose requirement assumptions that were first used in the HLCD analysis of the first phase of the study.¹³⁰ Two additional sets of scenarios—labeled “conservative” and “aggressive”—have been included in this analysis, with the conservative estimates presenting the worst-case scenario of extremely low yields and high-dose requirements (low efficiency) and the aggressive estimates presenting the best-case scenario of extremely high yields and low-dose requirements (high efficiency). For each of these sets of assumptions, costs and facility sizes were estimated in terms of both the inclusion and the exclusion of mAB production from the dedicated capability. The six resulting scenarios are summarized in Table 16 below.

Table 16. Cost modeling scenario definitions.

| Scenarios | Include mABs | Exclude mABs |
|------------------------------------|--------------|--------------|
| Conservative: Low Yield, High Dose | Scenario A | Scenario D |
| Baseline | Scenario B | Scenario E |
| Aggressive: High Yield, Low Dose | Scenario C | Scenario F |

In defining production efficiency assumptions, the absolute minimum and maximum levels of efficiency were explored in order to understand the full range of possible cost and facility-sizing implications. For yields, the major cell lines used for production currently are CHO, NSO, BHK and C127 with documented yields between 1 g/L and 14 g/L.¹³¹ The range of dose requirement assumptions has been based on the dosing ranges for mABs found in published references (Lucentis - 0.5mg for macular degeneration, Cleveland Biolabs’ - 3mg radiation therapeutic, DARPA’s AMP program - with 400mg as the highest dose, and Synagis - with

¹³⁰ *Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government: A Summary of Key Findings and Conclusions*. DARPA Cooperative Agreement HR0011-07-2-000. Section 3, 20.

¹³¹ John Birch, Upstream mammalian cell processing – challenges and prospects, BioProcess International, Berlin, April 11-14, 2005.

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1000mg highest dose.) Table 17 below details these assumptions, complete with constant estimates for chromatography efficiency, bioreactor size, and cycle time.

Table 17. Production efficiency assumption details.

| Efficiency | Titer (mg/Liter) | Downstream Processing Recovery Rate | Dose (mg) | Yield (d/L) | Bioreactor Size (L) | Cycle Time (wks) |
|---------------|------------------|-------------------------------------|-----------|-------------|---------------------|------------------|
| Conservative* | 1,000 | 70% | 800 | 0.9 | 2000 | 4 |
| Baseline | 1,425 | 70% | 3 | 333 | 400 | 4 |
| Aggressive | 10,000 | 70% | 3 | 2,333 | 400 | 4 |

*Conservative scenario evaluated with 2,000L bioreactor due to the extraordinary workload generated by the low efficiencies.

14.2 Results

Initial analysis indicates that for the baseline and aggressive scenarios, outsourcing production of mAB MCMs to CMOs varies by efficiency level and may be more economical at higher efficiencies and less economical at lower efficiencies. In any case, costs do not vary by more than 20% over the given time horizon.

Table 18. Total estimated direct costs over 25 years*

| Estimated Direct Costs | Include mABs (M) | Exclude mABs from BDMI and Outsource to CMO (M) |
|------------------------------------|------------------|---|
| Conservative: Low Yield, High Dose | \$8,700 | \$9,700 |
| Baseline | \$5,000 | \$4,100 |
| Aggressive: High Yield, Low Dose | \$5,000 | \$4,100 |

*Calculated by 21 years of production, plus the allocated cost of the facility amortized and recapitalized over 10 years; in 2007 US dollars.

The results of scenarios A-C, in which the mAB MCMs are included in the dedicated capability, reveal that any greater efficiency, beyond the baseline assumptions, will not reduce costs or facility size. This is because—even with the baseline assumptions—each requirement for each MCM or MCM component is produced in a single batch already. Lower efficiencies (scenario A), which are very unlikely, would require a larger facility and could increase costs significantly.

Table 19. Direct costs of production of all MCMs within dedicated capability

| Direct Costs | Suites | Facility Cost (M)* | CMO Operating Cost (M) | BDMI Operating Cost (M) | Total Operating Cost (M/yr) | 25-Year TOTAL COST (M) |
|-----------------|--------|--------------------|------------------------|-------------------------|-----------------------------|------------------------|
| A. Conservative | 15 | \$993 | \$0 | \$313 | \$313 | \$8,700 |
| B. Baseline | 8 | \$731 | \$0 | \$167 | \$167 | \$5,000 |
| C. Aggressive | 8 | \$731 | \$0 | \$167 | \$167 | \$5,000 |

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The results of scenarios D-F, in which mAB MCMs were excluded from the dedicated capability, reveal that the facility could be reduced to six suites, saving ~\$170M in facility costs and ~\$40M in operating costs per year. These savings would, of course, be offset by the cost of manufacturing those MCMs with a CMO (estimated here at \$1.25M per batch, based on industry benchmarks).

Table 20. Direct costs of production of all MCMs, with mAB MCMs outsourced to CMO

| Direct Costs | Suites | Facility Cost (M)* | CMO Operating Cost (M) | BDMI Operating Cost (M) | Total Operating Cost (M/yr) | 25-Year TOTAL COST (M) |
|-----------------|--------|--------------------|------------------------|-------------------------|-----------------------------|------------------------|
| D. Conservative | 6 | \$562 | \$278 | \$126 | \$404 | \$9,700 |
| E. Baseline | 6 | \$562 | \$12 | \$126 | \$138 | \$4,100 |
| F. Aggressive | 6 | \$562 | \$12 | \$126 | \$138 | \$4,100 |

* The cost savings of eliminating two suites is far greater than the cost of adding two suites because in scenarios A-C only the scale is increasing, while in D-E entire MCMs and production platforms are being eliminated.

15 Considerations Regarding Outsourcing of mAB Production

Developing an appropriate manufacturing strategy for biologic MCMs requires optimizing the competing benefits and risks that each strategic option provides with respect to achieving the biodefense mission of the USG. Previous sections of the study¹³² identified that the current “single-product approach” to MCM development and manufacturing is high-risk and high-cost. The study recommended the consideration of a public-private partnership as a more efficient and cost-effective approach to advanced development and manufacturing of biologic MCMs.

Within the current MCM development portfolio, mAB-based products are unique in that excess domestic manufacturing capacity may already exist, as discussed in earlier sections of this report. Given the potential for excess capacity within the U.S., the decision to build mAB production capacity in the dedicated BDMI versus outsourcing of mAB production, (taking advantage of existing commercial capacity), merits further consideration.

15.1 Considerations in the Outsourcing Decision

In discussions with industry experts regarding the outsourcing of mAB-based MCM production to existing commercial capacity, several key considerations were highlighted:

- Access to Capacity:** Lead times for scheduling bioreactor capacity with CMOs are typically long. This is not a significant issue in cases where production requirements are known (such for MCM stockpile building and warm-base manufacturing) as production can be scheduled well in advance. However, in a surge situation with little advance notice, access to commercial production capacity may be limited or require pre-negotiated “surge scenario” agreements as it is extremely difficult to break into commercial production schedules.

¹³² Industry Outreach report, Section 6, 29.

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- **Production Schedule Control:** Although securing production slots for known requirements can be done in advance, any delays in production start-up (such as late supply of a critical ingredient) may result in the loss of a scheduled production slot. While holding production slots is possible, doing so is also extremely expensive as CMOs have to balance the competing priorities of their customers.
- **Warm-base Manufacturing:** Regardless of where the mAB product is initially produced, maintaining a warm-base manufacturing capability for each product is essential to retaining FDA approvals, sustaining the strategic national stockpile, and providing surge capacity. This approach requires manufacturing at least one batch per year to maintain production capability. For products manufactured at multiple sites, there should be a primary manufacturing location that produces batches annually, though secondary locations could reduce production to every two to three years. Given the maturity of mAB technology, the requirement for annual production may be relaxed.
- **Development Capability:** Due to standardization of mAB-based manufacturing technologies, advanced development does not need to take place at the same physical location as commercial-scale production. This circumstance allows for conducting product development activities at one location and executing a technology transfer to move production to another location.
- **Infrastructure and Operating Cost:** Preliminary analysis indicates that outsourcing versus building internally capacity for mAB-based MCMs may have some economic benefit, but is coupled with some additional risk. Feedback from interviews with industry experts indicates that building internal capacity is preferred to subsidizing a reserved capacity through (or “with”) a contractor. This strategy ensures secure manufacturing capacity when it is needed.¹³³

15.2 *mAB Manufacturing Options*

From a high-level perspective, there are several options available for the production of the mAB-based MCM products:

- **100% In-house Capability:** All mAB manufacturing is conducted internally.
- **100% Outsource with a 10 year + Commitment and Surge Capacity Guarantee:** All mAB manufacturing is outsourced to a third party under a contract that guarantees the CMO’s capacity to USG for warm base operations. Additionally, the agreement would be structured so as to prioritize USG needs in a surge situation.
- **100% Outsource According to Market Availability:** All mAB manufacturing is outsourced to a third party. The CMO is chosen based on available capacity at the time of need. This is not an advisable strategy as it introduces the most risk. Table 21

¹³³ Interviewee, Steering Team, Telephone Interview, 17 February 2009.

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compares each mAB manufacturing option in terms of the five considerations identified in section 16.1.

Table 21. Evaluation of mAB production outsourcing scenarios.

| USG Needs | 100% In-house Capability | 100% Outsource (w/10yr+ Commitment and surge capacity guarantee) |
|------------------------------------|--|---|
| Access to capacity | Capacity is available when required. Surge access is not an issue. | Capacity is available when required per agreement. Partner maintains facility in case of surge scenario per agreement. |
| Production schedule control | Production scheduling is done internally. High flexibility in adjustments to production schedules. | MCM has priority in production scheduling. |
| Warm-base manufacturing | Annual production required. Smaller batch sizes may reduce annual production costs. | Annual production required. Larger batch sizes to ensure surge capacity may increase costs. |
| Development capability | No post-approval tech transfer required. | Tech transfer required post-approval. |
| Infrastructure and operating costs | Potentially higher infrastructure and operating costs based on lower productivity | Possibly lower overall cost. However, a premium may be necessary to pay to the company for facility maintenance and priority scheduling. Flexibility in production scheduling may result in cost decreases. |

Any final decision regarding the optimum appropriate operating model for production of mAB-based MCM products must clearly weigh several competing criteria. Alternative models to consider may include manufacturing some mAB products in-house and outsourcing others.

16 Conclusions and Recommendations

In support of USG objectives, the following conclusions and recommendations regarding mAB production were made:

- Preliminary analysis comparing current global mAB demand to current domestic production capacity indicates that excess capacity exists that could be utilized to satisfy mAB-based MCM production biodefense requirements. The availability of future excess capacity is difficult to forecast as there are several competing factors in play:
 - Technical advancements are increasing bioreactor production efficiency; however, these efficiency gains are not currently balanced with downstream processing efficiency. Research into downstream processing improvements or investment in downstream processing capacity will improve overall production efficiency and result in an increase of domestic capacity.
 - Projected increases in industry investment in mAB production infrastructure will also serve to add domestic capacity.
 - Approvals of successful, new, commercial, mAB-based products will close the demand-supply gap for mAB production capacity and serve to reduce excess capacity. Projections for utilization of mAB production capacity by 2013 range between 60% and 90% of available supply— based primarily on the success rate for approvals of the top five high-volume driving products in the current global pipeline.¹³⁴

A cost analysis of the impact of excluding mAB production from the dedicated BDMI capability indicates that the decision to outsource this capacity may provide modest cost savings under the right assumptions. The economics are driven by overall production efficiency measured in d/L of bioreactor capacity. From a cost perspective, outsourcing is slightly favored as the more efficient production process.

Excluding all mAB production from the dedicated capability is a viable option, but it introduces additional risks for a moderate economic benefit. However, these risks can be overcome with relative ease, if the proper risk mitigation strategies are implemented to ensure production capacity and capability. This may be done, for example, by assuring a contracted CMO a higher level of USG stockpile manufacturing in exchange for a long-term CMO capacity commitment.

¹³⁴ Levine, “Challenges and solutions for biopharmaceutical manufacturing,” 12.

Validation of Single-Use Technologies: Executive Summary

Biologics companies continuously seek ways to cut costs and improve process efficiencies. One method for addressing such challenges is the adoption of single-use bioprocessing equipment. Single-use equipment—often referred to as “disposable”—is typically defined as equipment that is used once and then discarded.

Many large and small biopharma companies currently utilize single-use bioprocessing equipment in manufacturing facilities, and the adoption of this trend will continue. For example, companies such as Bavarian Nordic, Baxter, and ImClone have adopted single-use equipment in manufacturing licensed biologics. Other companies have likely adopted single-use technologies for manufacturing biologics as well, and the list of licensed products utilizing this technology will continue to grow. To identify the trends in implementing single-use equipment, interviews were conducted with single-use equipment developers and manufacturers, single-use equipment adopters, and pharmaceutical facilities’ engineering consultants. Additional information was obtained from attending conferences as well as from the public domain. Some of the key trends identified were:

- Advancements in single-use technology continue to expand;
- Industry is increasingly implementing single-use equipment in process development and manufacturing. Biopharma and CMOs are looking for “lean” processes that improve efficiencies and reduce costs and are adopting single-use equipment to achieve these goals;
- Supply chain risk management is a common concern for single-use equipment adopters, especially since single-use equipment is a relatively new technology, and standardization across products is lacking. Among the issues are multiple-sourcing, equipment handling, and inventory management. Although traditional facilities implement some inherently single-use equipment (e.g., filters), the single-use developers, manufacturers and adopters agree that these supply chain risks must be mitigated.
- Concerns regarding extractables/leachables are prevalent and are being addressed by both single-use equipment adopters and developers and manufacturers.

Although more companies are increasingly adopting single-use technology, interviewees cautioned that single-use technology may not necessarily be advantageous for everyone. The degree of risks in adopting single-use equipment must be weighed against the degree of benefits (Figure 37). For example, if a potential single-use equipment adopter performed a cost analysis and determined that switching over to single-use equipment would not provide any cost advantages, then the single-use adopter may choose not to implement such equipment. Interviewees concurred that each risk/benefit analysis is unique to an individual manufacturing facility/process, and thus a standardized cost analysis would not reflect accurately BDMI’s estimated costs for adopting single-use equipment. Additionally, whether implementing from the beginning or retro-fitting a facility, the quality of the MCMs must not be sacrificed; stringent quality systems need to be implemented.

The use of single-use equipment results in many positive business outcomes including flexible manufacturing infrastructure, reduced capital and operating costs, and increased

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manufacturing efficiencies. Single-use equipment developers and manufacturers are expanding their product lines and services to address current technology gaps where single-use equipment is not presently available. While the FDA does have concerns with single-use equipment for biologics manufacture, overall the agency seems favorable towards the idea of adopting single-use technologies due to reduced cleaning and validation procedures.

Due to the low volume requirements for biologics MCMs and the benefits just described, single-use equipment is both a practical and cost-effective option for use in the BDMI facility.

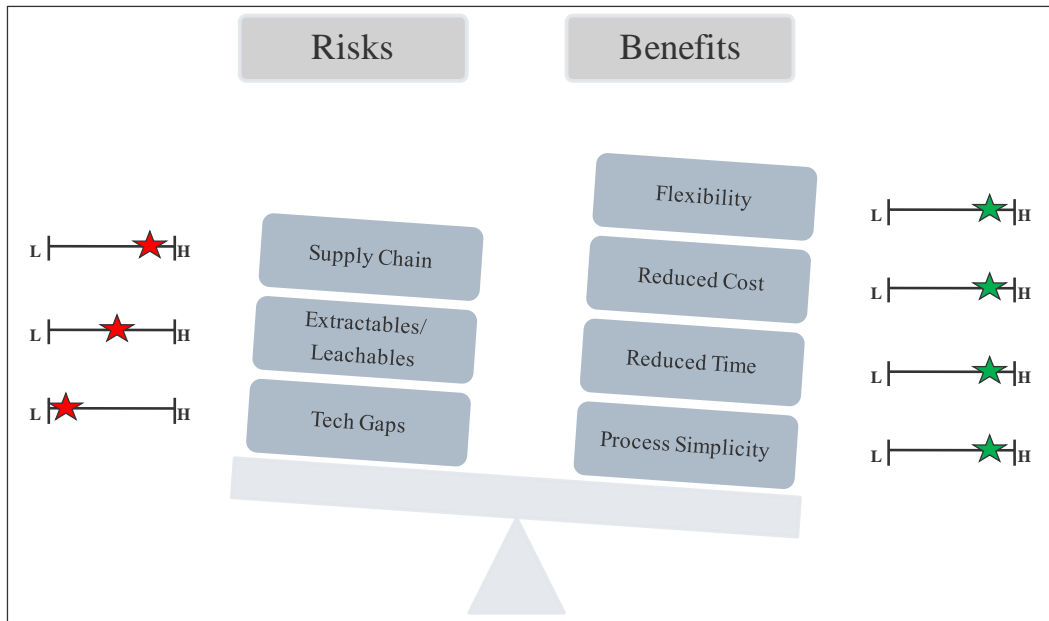


Figure 37: Weighing the risks vs. benefits of adopting single-use equipment

17 Introduction

The impetus for the recent emergence of single-use bioprocessing equipment was FDA's 1995 guidance that allowed pilot scale manufacturing facilities to be licensed to manufacture products.¹³⁵ Single-use equipment developers and manufacturers quickly took advantage of this regulatory change and introduced a new array of single-use technologies that enabled smaller scale, flexible manufacturing.

Prior to the mid-1990s, biologics were manufactured in traditional stainless steel equipment that required extensive and laborious cleaning and validation procedures. However, with the introduction of the WAVE bioreactor in 1998, a paradigm shift commenced within biologics manufacturing. The WAVE bioreactor is a single-use bioreactor for cell culture that substitutes for the bulky stainless steel bioreactor. WAVE single-use bioreactors allowed biologics manufacturers to simply discard the plastic bags after producing their products without any loss in yields compared to those achieved using a stainless steel bioreactor. This provided significant time and cost reductions due to the greatly reduced and simplified cleaning validations. In 2002, Xcellerex, Inc. introduced fully disposable manufacturing modules. Xcellerex's FlexFactory™ is a bioprocess manufacturing platform that is built using single-use technology almost exclusively and with production trains that are modular and configurable to meet a broad range of production needs, from cell culture through bulk drug substance.¹³⁶ Each unit operation within the FlexFactory™ module is self-contained in an encapsulated, controlled environment throughout the entire bioprocessing stages, thereby eliminating the need for expensive clean-room facilities.

In addition, many of the companies that were manufacturing and developing typical laboratory research products began to invest in their R&D programs in order to develop and produce their own single-use equipment products.

As more biopharma companies began to realize the benefits of using single-use equipment, the demand for such equipment proportionally increased. To keep pace with the demands, single-use manufacturers and suppliers began to invest heavily in R&D, and a number of new companies entered the market. Today, companies such as Millipore, Sartorius-Stedim, Pall, GE, ATMI, Hyclone and Xcellerex continue to develop single-use technologies to support the activities involved across the bioprocessing spectrum (Figure 38).

¹³⁵ FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products, July 11, 1995, Federal Register, Vol. 60, 35750.

¹³⁶ Xcellerex, FLEXFACTORY SCOPE, SCALE & APPLICATION, accessed 13 February 2009.

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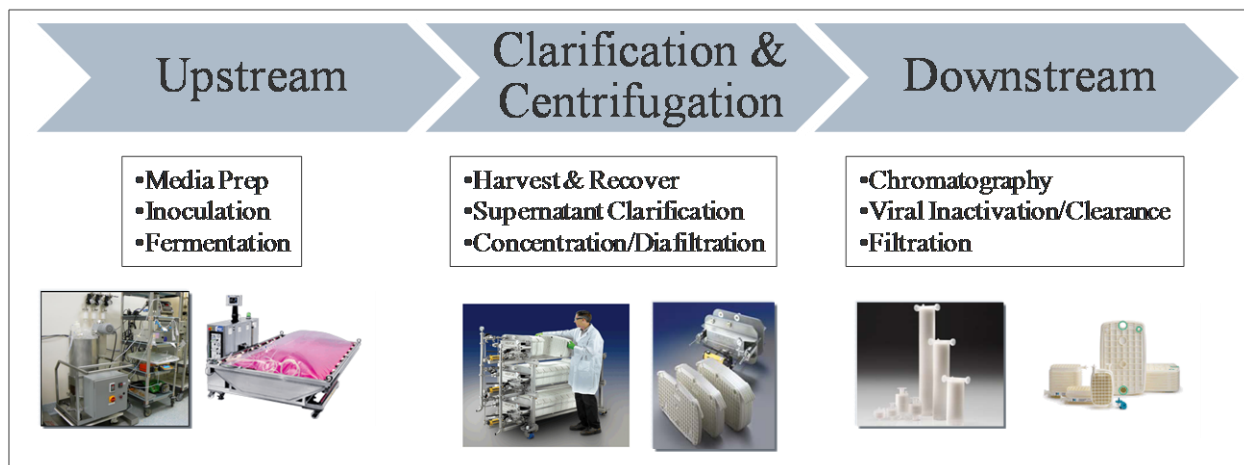


Figure 38: Overview of the bioprocessing process

With FDA's 1995 guidance, an increasing number of companies began to adopt single-use technology in their process development stages. As this technology expanded, the biopharmaceutical companies began to realize the cost-efficiencies and process flexibilities that single-use equipment provides. Today, many of the large biopharma companies (e.g., Merck, Baxter, Novartis), as well as the smaller companies (e.g., Novavax, Genentech, Biogen Idec), have adopted single-use technology (Figure 39). Bavarian Nordic and ImClone are examples of companies that have implemented single-use equipment for the manufacture of their licensed products, IMAVUNE® and Erbitux®, respectively. The list of companies adopting single-use equipment is expected to grow, and more licensed products will be manufactured with single-use equipment.

Identifying the current trends in single-use bioprocessing equipment and validating the concept of incorporating single-use bioprocessing equipment in a multi-product facility are the foci of this section.

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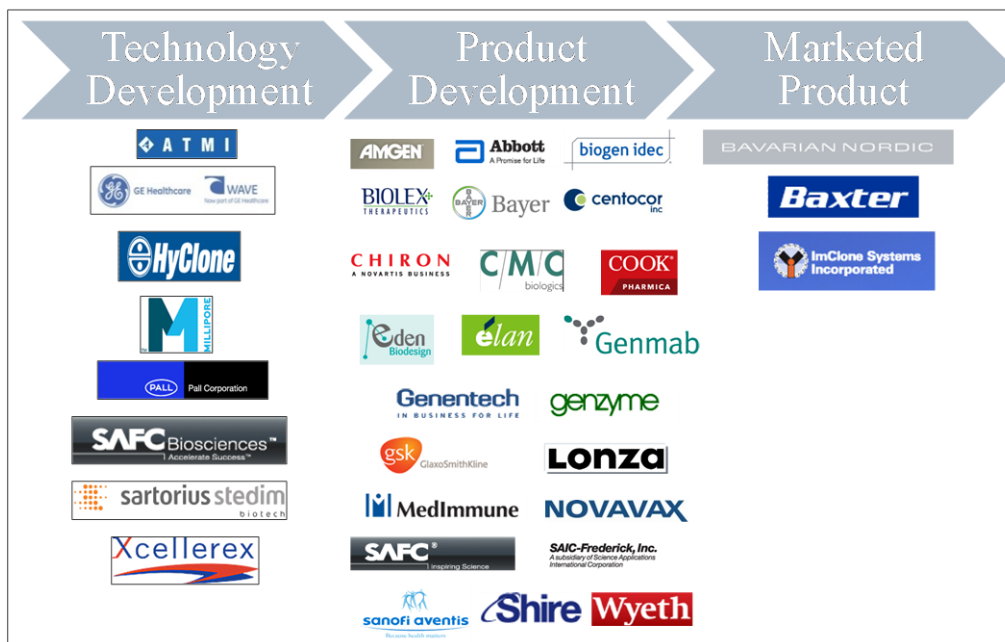


Figure 39: Companies adopting single-use equipment

18 Methodology

A total of eight interviews were conducted with single-use equipment developers and manufacturers, single-use equipment adopters, and pharmaceutical facilities engineering consultants (Appendix E) to discuss the trends; identify the technology gaps that currently exist; gauge perceptions and adoption of single-use equipment, and characterize concerns associated with single-use equipment). An interview guide (Appendix F) was provided to the interviewees prior to the discussions. In addition, valuable information was gathered from attending the following conferences:

1. International Business Communications 4th International Biopharmaceutical Manufacturing & Development Summit, Dec. 8-9, 2008. This conference was attended by single-use equipment manufacturers as well as companies who have adopted single-use equipment in their bioprocessing operations.
2. 7th Annual Phacilitate Vaccine Forum, January 26-28, 2009.

As noted, data also was gathered from publicly available documents.

19 Analysis

19.1 *Benefits of Adopting Single-Use Bioprocessing Equipment*

During interviews, the interviewees highlighted many benefits, including:

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- **Cleaning validation is not required**

One of the most commonly cited advantages of adopting single-use equipment is that they are disposable after use, therefore significantly reducing the number of cleaning validation studies and time-consuming cleaning and changeover procedures. Traditional stainless steel equipment requires labor-intensive cleaning validation studies prior to initial use and for each different product to ensure no cross-contamination of future production lots. Validating the equipment and processes associated with cleaning activities for each batch accounts for 15 to 25% of the total bioprocessing costs.¹³⁷ On the other hand, single-use equipment is immediately discarded after use, eliminating the need for the additional equipment and process validation and reducing the overall time and costs to manufacture the MCMs.

- **Reduction of Liquid Waste**

Facilities with single-use equipment are able to reduce the large volumes of liquid waste that would be typically required from clean-in-place (CIP) and steam-in-place (SIP) processes for traditional stainless steel equipment. Approximately 50 to 90% of the total water used in bioprocessing is allocated for CIP/SIP.¹³⁸ Therefore, significant reduction of water waste is obtained when adopting single-use equipment. Finally, at large volumes (some processes can require more than 20,000 gallons/yr), the cost for water-for-injection (WFI) can become significant. Thus, minimizing the total water used in a facility results in further reduced costs.

- **Reduction in Equipment Complexity and Associated Process Failure Risks**

Since single-use equipment is pre-sterilized by the vendors and disposed of following initial use, sterilizing and cleaning steps are eliminated. This process circumvents risk of sterilization failures, which can compromise the integrity of the bioprocess batches produced in traditional stainless steel equipment. In addition, since disposable equipment is pre-assembled with respect to gaskets and seals, the risk of assembly errors are eliminated. In traditional manufacturing using stainless steel equipment, improper assembly of the vessel and associated components may result in improper sealing of the vessel and ultimately, contamination of the batch. Although inherent risks do exist when purchasing single-use equipment from developers and manufacturers, process failure rates are mainly due to operator errors (9% for stainless-steel equipment compared with 6% for single-use equipment).¹³⁹ Additionally, adopting single-use equipment mitigates risks of cross-contamination between in-process bulk and

¹³⁷ “[Biodisposables Utility and Technological Advances](#)” Drug & Market Development Publications, Report # 9215, June, 2006.

¹³⁸ Disposable Bioprocessing: State of the Industry, Economics and a Novel Manufacturing Platform Case Study, North Carolina Biotechnology Center, BPD Conference, Geoffrey Hodge, VP Technology, Xcellerex, 18-Nov-04

¹³⁹ Interviewee, Bioprocessing, November 18 2008.

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final products. Overall, disposable technologies simplify the manufacturing process, reducing the opportunities for process errors and equipment failures.

- **Decrease in Full-Time Equivalent (FTE)**

As described, adopting single-use equipment reduces the need for CIP/SIP and for subsequent validations. CIP/SIP accounts for 15 to 33% of the total bioprocessing labor. Therefore, less human capital is needed when implementing single-use bioprocessing equipment, resulting in less required FTEs to run the manufacturing processes. No additional, extensive training is involved to set-up the single-use equipment, and in some cases the vendors offer to set-up the equipment on-site. In fact, one single-use equipment manufacturer and supplier provides demonstrations and training sessions on implementing the equipment for the adopters.

- **Increased Ergonomics**

With advances in manufacturing technologies, process yields have improved, allowing for dose needs to be met using smaller sized vessels. Installing smaller, less bulky disposable bioreactors reduces the equipment footprint, providing operators with additional space in which to work. In terms of construction, a new facility adopting disposable equipment requires less square footage and reduces/eliminates the extensive CIP/SIP piping commonly found in a traditional stainless steel equipped facility. Ultimately, the smaller facility footprint means that less energy is required for operations and additional cost savings are provided the manufacturer.

- **Speed and Flexibility for Clinical and Commercial Manufacturing**

Implementing single-use equipment provides a more efficient and flexible multi-product capability than does a multi-product facility with traditional stainless steel equipment. To efficiently develop and manufacture multiple MCMs within a single facility requires quick product change-over procedures. Since implementing disposable technologies eliminates costly and time-consuming cleaning validations and changeover protocols, the BDMI would be able to efficiently manufacture multiple MCMs simultaneously. Reducing the cycle time between MCMs results in a shorter period in which to manufacture multiple products (Figure 40). In contrast, a facility exclusively implementing traditional stainless steel equipment would be able only to produce multiple MCMs following the completion of cleaning procedures after each MCM manufactured (Figure 40). Installing multiple trains of traditional stainless steel equipment would increase efficiency by allowing for the simultaneous manufacture of multiple MCMs. This configuration, however, would require significant infrastructure and incur higher costs, ultimately resulting in less efficient manufacturing processes.

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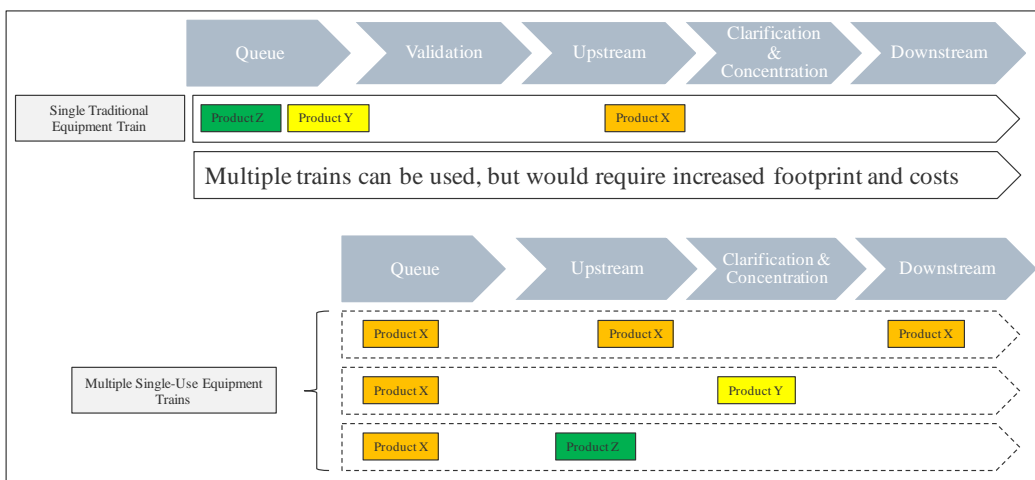


Figure 40: Single-use equipment provides flexibility and speed between change-overs

19.2 Risks of Adopting Single-Use Bioprocessing Equipment

The interviewees cautioned that adopting single-use equipment is not without risks. The following concerns were voiced:

- **Technology Gaps**

Significant strides have been made in technological advancements in single-use equipment since the WAVE bioreactor was first introduced in 1998, and industry experts expect this trend to continue; however, technological gaps remain (Figure 41).

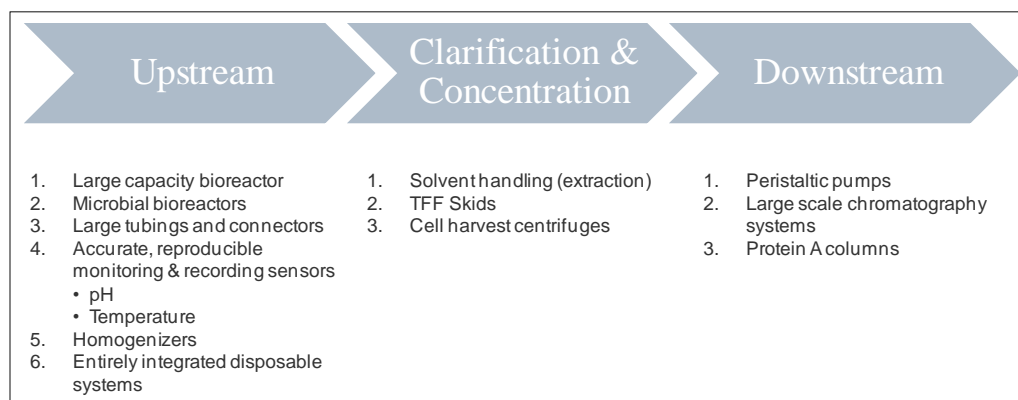


Figure 41: Technology gaps associated with single-use equipment

Arguably the most glaring gap involves upstream processing equipment as two commonly used capacities are lacking: single-use large-capacity bioreactors and microbial fermentors. In 2008, Xcellerex introduced what is currently the largest single-use bioreactor (2000L capacity) for mammalian cells on the market. For microbial single-use bioreactors, limited options currently exist at scales suitable for large-scale manufacturing purposes as vendors have found it challenging to meet the oxygen demands associated with high-density microbial fermentations. Other significant

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technology gaps include disposable tangential flow filtration (TFF) skids, high-speed centrifugation units, and large-scale chromatography systems.

Although these technology gaps in single-use equipment exist, the interviewees were confident that advancements would be made in technology that ultimately would fill these voids. For example, more options for larger scale (500L and 1000L, working volume) single-use microbial stirred tank bioreactors are expected to become available by the end of 2009.

- **Supply Chain Management**

Increased reliance on single-use equipment developers and manufacturers could become problematic for several reasons:

- The reliable availability of the single-use equipment was a common concern voiced by single-use adopters. For example, Baxter has a significant market share in single-use bioprocessing bag production. A limited number of suppliers of raw materials for bags means that single sourcing of components may become problematic due to vendor shortages, back-order situations or shipping delays. The lack of standardization of single-use equipment further complicates supply-chain management by restricting the adopters from multiple sourcing. In addition, the single-use adopters must rely on the vendors for equipment qualification and validation.
- Handling single-use equipment, in particular single-use bags, is a concern, and care must be taken during unpacking or assembly. Although single-use bioreactor bags are not easily damaged, punctures and tears to the bags can occur. Furthermore, bulk drug shipping in disposable bags is a concern. Issues voiced by adopters included bag integrity and film embrittlement (especially at low temperatures), air bubbles introduced during bag filling, and bag cuts caused by sharp frozen bulk drug product.
- Other issues included equipment shelf-life and inventory. One concern was that expensive single-use equipment would sit idle until expiring. While most disposable bags have a shelf-life that exceeds one year, adopters are very mindful of the large purchase costs of disposable bags. Another concern was that as new single-use equipment becomes available, adequate validation (e.g., sterility) of such equipment may not be performed by the single-use manufacturers and suppliers due to increased costs. If this occurs, the result would be conservative shelf-life estimates for many products that otherwise might be perfectly usable over longer durations. It is conceivable that additional costs would be incurred through either the adopters performing the equipment validations themselves or having to re-stock their inventory more frequently. Also, additional time and

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resources are may be needed, as implementing single-use equipment leads to more components that must be inventoried.

Failure to mitigate these supply chain risks could lead to inefficient and more costly manufacturing processes, causing critical delays in production. Ensuring an adequate supply of single-use equipment is critical to the BDMI's success in meeting surge production demands.

- **Leachables and Extractables**

Perhaps the greatest concern in regard to using single-use equipment is the risk posed by extractables and leachables. Extractables are defined as:

“Chemical compounds that migrate from any product contact material, including elastomeric, plastic, glass, stainless steel or coating components when exposed to an appropriate solvent under exaggerated conditions of time and temperature.”¹⁴⁰

Extractables include known additives, impurities in additives and polymers, and reaction products of material with extraction solvents. Leachables are defined as:

“Chemical compounds, typically a subset of extractables, that migrate into the drug formulation from any product contact material, including elastomeric, plastic, glass, stainless steel or coating components as a result of direct contact with the drug formulation under normal process conditions or accelerated storage conditions and are found in the final drug product.”¹⁴¹

Leachables include known extractables as well as those that are chemically modified by drug formulations.

Rejected lots of MCMs that do not meet pre-determined quality specifications and ultimately reduced acceptance of disposable technologies overall would result if vendors failed to address the following two risks:

- Increased levels of extractables/leachables from plastic materials vs. traditional stainless steel equipment
- Unknown and uncharacterized extractables/leachables from solvents

The Bio-Process Systems Alliance (BPSA), an organization that advocates the use of single-use equipment, recommends that adopters of single-use equipment develop a plan for mitigating the risks of extractables/leachables migrating into the final drug product. This extensive, yet necessary, process includes creating lists of product contact

¹⁴⁰ Jerold Martin, Bio-Process Systems Alliance (BPSA) Technical Guides for Application of Single-Use Disposable in Bio-Pharmaceutical Manufacturing.

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components and measuring the levels of extractables/leachables throughout all bioprocessing stages. Furthermore, the BPSA suggests collaboration between the suppliers and end-users to correlate data regarding leachables with extractables and pre-leachables.¹⁴¹

- **Initial Costs and ROI**

The initial costs incurred present one barrier to implementing single-use equipment. For example, the single-use bioreactor bags tend to be costly, and companies are hesitant to invest heavily in them or other expensive single-use equipment. Larger companies that have already invested in traditional stainless steel equipment in their manufacturing facilities are initially reluctant to switch to single-use equipment. If hardware (e.g., piping for CIP/SIP) has been installed already, using disposables may not be economically advantageous. However, some companies are retro-fitting facilities with disposable equipment and thus, implementing a hybrid system that incorporates both traditional and single-use equipment. Still, companies that build entirely new manufacturing facilities tend to implement more disposables than those companies that operate already existing facilities.

As costs for large single-use equipment are significant, they must be weighed against adoption risks and benefits. Each company must perform its own cost/benefit analysis to determine whether adopting single-use equipment is economically advantageous for its facilities.

- **Waste Removal**

While liquid waste may be reduced when single-use equipment is adopted, solid waste generation is increased. Some of the concerns associated with the waste disposal of single-use equipment include the following:

- Volume of solid waste
- Inability to recycle the complex materials
- Costs associated with transporting waste from a facility
- Disposal frequency
- Physical and chemical properties of waste
- Cost-ineffectiveness associated with state/local regulations

Several options for waste disposal exist, and each has its own advantages and disadvantages (Figure 42). For example, although recycling is the most environmentally friendly method for disposing of plastics, one of the concerns with single-use bags is that most are composed of 5 to 7 layers of polymers that are extremely difficult to separate for recycling. Facilities may not necessarily be able to implement the most cost-effective disposal method, thus incurring attendant expenses. However, waste removal issues

¹⁴¹ Jeff Craig, "Single-use technologies for acceleration of biopharmaceutical manufacturing: LevTech-NewMix & Nucleo," DARPA AMP Review Program, 7 November 2008.

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although voiced by the single-use equipment adopters are not likely to deter companies from switching over to single-use equipment.

| Disposal Method | Sub-type | Advantages | Disadvantages |
|-----------------|-----------------------------------|--|--|
| Recycling | Reprocessing of Recycled Material | 1. Reduced carbon footprint | 1. Limited to single polymer components—most disposable bags are composed of 5-7 layers of different polymers 2. Presence of contaminating or hazardous substances 3. High costs |
| | Pyrolysis | 1. Improved environmental benefits over both incineration and landfill options 2. Conversion to fuel | 1. Large capital investments |
| Incineration | With Energy Recovery | 1. Available in many locations 2. Moderately low operating costs 3. Eliminates/reduces toxicity of hazardous waste | 1. Potential release of particulate and gaseous pollutants 2. Risk of toxic emissions 3. High carbon dioxide emissions |
| | Without Energy Recovery | 4. Reduction of volume of waste 5. Can provide energy recovery by cogeneration | 4. High investment costs for new facilities to meet latest emission controls and regulations |
| Landfills | Non-hazardous Waste | 1. Low operating costs 2. Available in most locations 3. Suitable for most solid wastes | 1. Shortage of landfill sites 2. High bulk volumes of untreated wastes |
| | Hazardous Waste | 4. Reduction in volume 5. Conversion to energy (from methane use) | 3. Local opposition based on their noise, odors, and appearance |
| | Methane Use | | 4. Financial levies and/or legislative restrictions on landfill |

Figure 42: Options for Solid Waste Management¹⁴²

19.3 Cost Analysis

To obtain a better understanding of the costs involved in adopting single-use equipment, cost analyses were obtained from interviewees, conferences, and publically available presentations. The variability among analyses was noted by interviewees, who cautioned against relying on any particular analysis. Instead, they recommended using the available analyses simply as points of reference or as tools to conduct internal analysis. The various cost analyses presented represent some of single-use equipment capital costs, operating costs, and facility build-up costs.

1. Advanced Technology Materials (ATMI)

ATMI is the market leader in the semiconductor industry for specialty chemicals, chemical delivery, and ultra-clean packaging. Headquartered in Danbury, CT, ATMI is a publicly traded company, with approximately 800 employees worldwide, and annual revenues of ~\$400M.¹⁴³ The company has an aggressively growing presence in the life science market for single-use bioprocessing equipment and ultra-clean packaging. Some of ATMI's products include single-use bioreactors, mixing units, and bioprocessing bags.

¹⁴² Hélène Pora and Bruce Rawlings, "Managing solid waste from single-use systems in biopharmaceutical manufacturing," *BioProcess International* 7, no. 1 (2009): 18-25.

¹⁴³ Jeff Craig, "Single-use technologies for acceleration of biopharmaceutical manufacturing: LevTech-NewMix & Nucleo," DARPA AMP Review Program, 7 November 2008.

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ATMI performed a cost analysis comparing its single-use WandMixer™ attached bioprocessing container with a traditional stainless steel mixer. The analysis, which included capital equipment and facility costs, showed an approximately 88% reduction in operating costs (3).¹⁴⁴ A significant contributor to the 88% reduction was the decrease of CIP/SIP quality assurance operation costs.¹⁴⁴ As the number of performed mixes increases, the variable costs in CIP/SIP quality assurance operations increase as well.

| Comparison of Operating Costs | | |
|---|-----------------|------------|
| | Stainless Steel | Wand Mixer |
| <u>Amortization of Capital Equipment Expenses</u> | | |
| 50L Stainless Steel Tank with Fittings | \$6,000 | |
| CIP/SIP Equipment & Lines | \$7,000 | |
| RWM Drive Unit, 50L Tank & Accessories | | \$1,200 |
| Total Capital Equipment Amortization | \$13,000 | \$1,200 |
| <u>Amortization of Facilities Expenses</u> | | |
| Construction (\$175/ft) | \$15,750 | \$1,750 |
| Validation of Facility (15% of Construction) | \$2,363 | \$263 |
| Total Facilities Amortization | \$18,113 | \$2,013 |
| <u>Maintenance of Facility (\$50/ft)</u> | \$1,500 | \$500 |
| <u>Variable Costs</u> # Mix/Yr. = 240 | | |
| CIP SIP QA Operations | \$576,000 | \$2,400 |
| Contamination Write-Off (\$5,000 per run) | \$120,000 | \$12,000 |
| Disposable Bags & Impellers | | \$72,000 |
| System Maintenance | \$750 | \$20 |
| Waste Disposable Costs | \$3,600 | \$480 |
| Subtotal Variable Costs | \$696,750 | \$86,420 |
| Total Mixing Costs per Year | \$732,963 | \$90,613 |
| RATIO = 8.1 X | | |

Figure 43: Operating cost comparison of bioprocessing containers

2. Baxter, Inc.

Baxter, Inc. is an international pharmaceutical company with nearly 50,000 employees worldwide and annual revenue of approximately \$10B.¹⁴⁵ In 2007, Baxter provided a presentation summarizing the installation of their manufacturing suites in their Hayward facility, which is used for Phase I/II CMO services as well as for internal biologics production. Baxter had initially installed multiple suites with traditional stainless steel equipment in their Hayward manufacturing facility. Subsequently, they also installed a suite implementing single-use equipment. Baxter's presentation included a comparison of costs, bioreactor capacity, area footprint, and time to install and validate the suites. The installation of their single-use bioreactor (SUB) suite resulted in

¹⁴⁴ Jeff Craig, "Single-use technologies for acceleration of biopharmaceutical manufacturing: LevTech-NewMix & Nucleo," DARPA AMP Review Program, 7 November 2008.

¹⁴⁵ Fauad Hasan, "Installation of a bioreactor suite, single-use bioreactor suite," 2nd Facilities Planning and Design for Pharmaceuticals, Philadelphia, PA, December 2007.

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reductions of facility footprint, costs, and time to build and validate, as well as capacity increases (Figure 44).¹⁴⁶

| Project | Project Description | Area | Capacity | Est. Cost | Project Duration |
|---------------------------|--|------------|----------|-----------|------------------|
| Installation of Suite A | <ol style="list-style-type: none"> 1. Acquiring existing 300L microbial fermentor and converting it into a cell culture bioreactor. 2. Modifying clean room into bioreactor suite. 3. Suite Preparation Installation (Equipment, piping) 4. Utilities configuration for the new suite, including CIP and SIP. 5. Bioreactor installation, Commissioning (SAT) and Validation (IQ, OQ) | N/A | 300L | \$1M | 213 days |
| Expansion of Suite A | <ol style="list-style-type: none"> 1. Modification to Suite A to install a 1200L bioreactor 2. Utilities upgrade to meet the requirement of additional bioreactor. 3. Design, procurement and installation of 1200L bioreactor with local controls 4. Commissioning (SAT) and Validation (IQ, OQ) | 644 sq. ft | 1500L | \$1.7M | 255 days |
| Installation of Suite B | <ol style="list-style-type: none"> 1. Feasibility Study (Architectural, Electrical) 2. Conversion of multiple suites into one Large Scale Manufacturing Suite. 3. Utilities configuration for the new suite, including connecting to existing CIP and SIP. 4. Procurement and Installation of 400L and 1600L Bioreactors 5. Commissioning (SAT), Validation (IQ, OQ) | 755 sq. ft | 2000L | \$2M | 395 days |
| Installation of SUB Suite | <ol style="list-style-type: none"> 1. Conversion of an existing unused suite into one Single-use Manufacturing Suite. 2. Electrical modification (new outlets, backup power - UPS). 3. Customized Controller Design. 4. Procurement of Bioreactors and support equipment 5. Installation, commissioning, and validation. | 377 sq. ft | 2500L | \$400K | 120 days |

Figure 44: Comparisons - installing traditional and single-use bioreactor suites¹⁴⁷

3. Biogen Idec

Biogen Idec, Cambridge, MA, is a global leader in the discovery, development, manufacturing, and commercialization of innovative therapies, employing more than 4,200 people worldwide.¹⁴⁸ Biogen Idec's products address diseases such as lymphoma, multiple sclerosis, and rheumatoid arthritis.¹⁴⁹ In 2007, Biogen Idec's total revenues grew 18 percent over its 2006 revenues to almost \$3.2B.¹⁵⁰

Biogen Idec has adopted single-use bioreactors for its process development steps and conducted a cost analysis comparing operating costs of a 1,000L single-use bioreactor vs. 4x200L traditional stainless steel bioreactors. Its studies demonstrated an approximately 40% reduction in operating costs using single-use bioreactors compared to traditional stainless steel bioreactors.¹⁵¹ Capital investments were not included in this analysis, and the calculations assumed that the operations were performed in a non-good manufacturing procedure (GMP) facility with no formal product changeover required.

¹⁴⁶ Hasan, "Installation of a bioreactor suite, single-use bioreactor suite."

¹⁴⁷ Hasan, "Installation of a bioreactor suite, single-use bioreactor suite."

¹⁴⁸ Biogen Idec, accessed 13 February 2009.

¹⁴⁹ [Biogen Idec, accessed 13 February 2009.](#)

¹⁵⁰ [Biogen Idec, accessed 13 February 2009.](#)

¹⁵¹ Kelly R. Wiltberger, "Update: 1,000L disposable bioreactor system evaluation and performance," IBC 4th International Biopharmaceutical Manufacturing and Development Summit, Durham, NC, 8-9, December, 2008.

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| Seed-train Application | | |
|------------------------|------------------------|-----------|
| 250L SUB | 200L Stainless Steel | |
| \$3,313 | \$2,293 | Cost/run* |
| Process Development | | |
| 250L SUB | 200L Stainless Steel | |
| \$4,681 | \$4,300 | Cost/run* |
| 1000L SUB | 4x200L Stainless Steel | |
| \$7,407 | \$12,077 | Cost/run* |

Figure 45: Biogen Idec’s Cost Analysis for Single-Use Bioreactors

4. Jacobs Engineering Group

Jacobs Engineering Group, Pasadena, CA, is one of the world’s largest and most diverse providers of professional technical services. With annual revenues exceeding \$11B, Jacobs Engineering offers full-spectrum support services, including scientific and specialty consulting as well as all aspects of engineering and construction and operations and maintenance to industrial, commercial, and government clients across multiple markets.¹⁵² Typical projects for clients in the pharmaceutical and biotechnology industry include laboratories, R&D facilities, pilot plants, bulk active pharmaceutical ingredient production facilities, full-scale biotechnology production facilities, and secondary manufacturing facilities.

Jacobs conducted an analysis comparing the capital costs for stainless steel buffer hold/preparation containers vs. single-use bag holders and demonstrated an approximately 95% reduction in costs when adopting the single-use bag holders.¹⁵³ In addition, Jacobs determined that adopting single-use bags would reduce the annual heating, ventilation, and air conditioning (HVAC) costs by approximately 15%, as bags could be stored in a controlled non-classified (CNC) area rather than an [international organization for standardization \(ISO\) 9](#) area.¹⁵⁴

5. Xcellerex

Xcellerex develops biomanufacturing systems, including single-use bioreactors and mixers as well as turnkey modular single-use production plants (FlexFactory™). In addition, Xcellerex provides CMO services. Two investigational new drugs have been filed for products developed and manufactured using the FlexFactory™.

¹⁵²Jacobs Engineering, Overview, accessed 13 February 2009.

¹⁵³ Bob Bader (Jacobs Engineering), “Single use life cycle cost analysis,” Vaccines Europe: Workshop Z.

¹⁵⁴ Bader, “Single use life cycle cost analysis,” Vaccines Europe: Workshop Z.

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At a recent conference, Xcellerex presented a comparison between its FlexFactory™ and a traditional stainless steel bioreactor.¹⁵⁵ The analysis indicated the following advantages:

- 50% reduction in capital cost
- 70% reduction in time to build and start GMP mfg.
- 25% reduced operating costs
- 70% reduction in water consumption
- 70% reduction in waste water generation
- 20% reduction in utility consumption

Xcellerex's study demonstrates the significant cost savings that can be realized in adopting single-use equipment. Furthermore, Xcellerex's FlexFactory™ modular system provides a model for implementation of single-use equipment for each of the proposed eight suites in the BDML. Theoretically, each of these FlexFactory™ modular systems could be transported in and out of each suite, and thus the Xcellerex analysis provides a good reflection of the estimated costs.

20 Case Study: Novavax

Novavax, Inc., headquartered in Rockville, MD, has adopted a 100% single-use equipment bioprocessing facility for the development of their influenza virus-like particle vaccine. Novavax has implemented WAVE single-use bioreactor technology with enhanced aeration and process control for the production of clinical material in support of its ongoing Phase II clinical studies.¹⁵⁶

High production yields allowed Novavax to consider adopting single-use equipment. Otherwise, implementing a 100% single-use equipment bioprocessing system may not have been possible.¹⁵⁷ The high yields make the ongoing costs of operating a facility with 100% single-use equipment feasible (i.e. lower up-front costs are traded off with higher ongoing costs balanced against higher product yields from platform technologies). By utilizing only single-use equipment, Novavax has been able to significantly reduce the amount of process and support equipment required compared to that necessitated by traditional egg-based manufacturing (Figure 46). The implementation of single-use technology is capable of achieving similar reductions in CIP/SIP equipment and process validation against systems utilizing traditional stainless steel equipment (Figure 46). In addition, single-use equipment tends to be smaller sized, thus providing increased flexibility in floor space as well as ease of equipment handling and manipulating. Novavax also noted the simplicity of their process compared to traditional approaches.¹⁵⁸ For example, the upstream process implements one type of equipment (the single-use bioreactors) whereas the egg-based process involved with the development of most influenza vaccines necessitates four unique equipment types (Figure 46). Similar process simplicities would be evident if Novavax's single-use equipment process was compared to a cell-based traditional stainless steel process.

¹⁵⁵ Parrish Galliher, "Turnkey, modular disposable vaccine production plants," IABS International Scientific Workshop, New Cells for New Vaccines III: From Lab Bench to Clinical Trials, Wilmington, DE, 28 September – 1 October 2008.

¹⁵⁶ Interviewee, Novavax, Inc., 5 January 2009.

¹⁵⁷ Interviewee, Novavax, Inc., 5 January 2009.

¹⁵⁸ Interviewee, Novavax, Inc., 5 January 2009.

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| Equipment for Bioprocessing | | | Equipment for Support | | |
|-----------------------------|-------------------------------|----------------------------|--------------------------|--------------------------------|--------------------------------|
| Process | Traditional | Single-Use | Support | Traditional | Single-Use |
| Upstream | Custom Inoculators | Single-Use Bioreactors | Process | Large WFI System | Small WFI System |
| | Large Incubators | | | CIP Skids (Multiple) | N/A |
| | Candling Stations | | | Clean Steam/SIP Systems | N/A |
| | Custom Harvestors | | | Egg Disposal System | N/A |
| Purification | Large Fixed Tanks | Single-Use Bags | | Autoclaves | N/A |
| | Low Speed Centrifuges | Single-Use Ultrafiltration | | Parts Washers | N/A |
| | Filtration | | | Decon Autoclave | Decon Autoclave |
| | Ultrafiltration Skids | Single-Use Ultrafiltration | | Large Liquid Waste Kill System | Small Liquid Waste Kill System |
| | Ultra-Centrifuges | | | BL2+ Facility Design | GLSP Facility Design |
| | Chromatography | Chromatography | | Class B HVAC Systems | Class C HVAC Systems |
| | Buffer Prep | Single-Use Buffer Prep | | | |
| | Buffer Storage | Buffer Bags | | | |
| Sub-micron Filtration | Single-Use Sub-micron Filters | | | | |
| Equipment Used: 13 vs. 8 | | | Equipment Used: 10 vs. 5 | | |

Figure 46: Novavax reduced total equipment number by adopting single-use equipment

Because Novavax implemented single-use equipment, less infrastructure was required and the time to build and validate its manufacturing facility was nearly two years less than that of a facility implementing traditional stainless steel equipment. When implementing single-use equipment versus traditional stainless steel equipment, similar time and cost savings for facility construction and validation can be expected (Figure 47).¹⁵⁹

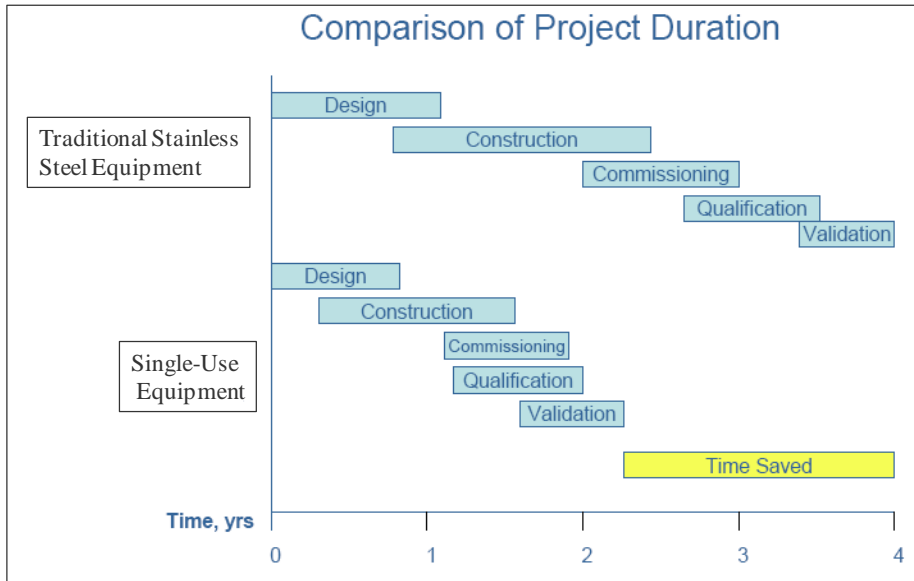


Figure 47: Adopting single-use equipment reduces time to build and validate new facility¹⁶⁰

By adopting a 100% single-use equipment bioprocessing scheme for the manufacture of vaccines, Novavax reduced its time to build and validate its manufacturing facility. Also,

¹⁵⁹ Novavax, Inc., Interview, 5 January 2009.

¹⁶⁰ Novavax, Inc., Interview, 5 January 2009.

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its overall manufacturing process was simplified by not implementing traditional stainless steel equipment. Novavax demonstrated not only the feasibility of building a completely single-use equipment manufacturing infrastructure but also the benefits of adopting single-use equipment. With advances in bioprocessing technology, especially in single-use equipment, more companies will be able to develop vaccines at lower costs and with less infrastructure.

21 Conclusion

Advancements in single-use equipment technology have made great strides in the past five years, and the interviewees expect this trend to continue. An increasing number of biopharma companies are implementing single-use equipment, especially companies that manufacture low-volume biologics. For example, single-use equipment is an attractive option for companies that manufacture orphan drugs.¹⁶¹ These manufacturers do not likely need a 20,000L stainless steel bioreactor, since the market demand for orphan drugs is considerably less than for that of a “blockbuster” therapeutic. Single-use equipment allows for scaling down productions. In addition, academic institutions could benefit from the use of single-use equipment since less footprint area is required and most are manufacturing biologics on a pilot scale. In fact, an academic institution has applied for a USG grant that implements single-use equipment for the current GMP manufacture of an antibody that reduces *Staphylococcus aureus* infections from blast-induced wounds and allows for the reduction of wound-related infections in theater.¹⁶²

Unfortunately, whether BLAs have been filed on biologics that were manufactured completely with single-use equipment (e.g., bioreactors and bags) was not unequivocally confirmed. However, Bavarian Nordic, ImClone, and Baxter have adopted single-use components within their bioprocessing steps. Single-use bioprocessing equipment is gaining traction, and it is only a matter of time until the pharmaceutical production field utilizes a fully disposable production system for biologics. While the FDA does have concerns with single-use equipment for biologics manufacture, overall the agency seems favorable towards the idea of adopting single-use technologies.

Although single-use equipment is gaining popularity, not all companies may benefit. Biopharma companies that have already invested large amounts of resources into building manufacturing facilities with large stainless steel bioreactors may not benefit by switching completely to single-use equipment. Each company must perform an independent analysis unique to that company, rather than blindly instituting single-use technology.

Implementing single-use equipment is highly advantageous in a facility that proposes to develop multiple products using various manufacturing technology platforms (e.g., monoclonal antibodies (mABs), nucleic acids, live viruses). Many manufacturers are hesitant—or even refuse—for fear of cross-contamination, to manufacture live viruses in a facility that previously manufactured only recombinant proteins. However, adopting single-use equipment mitigates such risks, as disposable equipment is considered a “closed” system, and the equipment is discarded after use.

¹⁶¹ A drug that treats a “rare disease or condition” [which] (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.” The Orphan Drug Act, online, accessed 18 February 2009.

¹⁶² Interviewee. December 5 2008

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The manufacturing cycle time between MCMs is long when using traditional stainless steel equipment. Cleaning and sterilizing the equipment as well as validating the process are time-consuming, ultimately delaying the manufacture of other MCMs in the queue. However, with a single-use equipment process train, the components are simply discarded, eliminating equipment cleaning and reducing changeover times. Therefore, a multi-product facility with flexible single-use modules for each manufacturing suite would be more practical and cost-effective than a facility with rigid, permanent infrastructure. Lastly, each manufacturing suite with single-use modules would be able to rapidly transition from one MCM manufacturing process to another in order to meet necessary surge requirements.

Formulation, Fill, Finish Technologies: Executive Summary

This section examines form/fill/finish (FFF) capacity with bulk manufacturing as it relates to the dedicated BDMI for the advanced development and manufacturing of biologic MCMs for USG. Having evaluated commercially available technologies, estimated BDMI requirements and explored strategic considerations, the recommendation is that the dedicated capability should include some internal form/fill/finish capacity while simultaneously maintaining a network of CMOs to conduct high-volume filling. This strategy would provide the BDMI direct access to the vital form/fill/finish function while ensuring surge capacity availability when required.

This section is divided into three parts. The first part describes several commercially available form/fill/finish technologies, including a discussion of emerging product dose formats. The second part suggests that a single clinical-scale filling line is capable of providing adequate capacity to support form/fill/finish operations for most BDMI production scenarios. Since final product format plays a significant role in determining the required filling capacity, thus, for large-scale production, multi-dose product formats should be considered. The third part evaluates factors affecting the outsourcing strategy. Balancing of internal and outsourced operations is critical to reducing the challenge of finding external capacity capable of supporting the filling of small scale and complex products (e.g. formulation development, clinical production, and live agent products) while also creating supply sources for reduction of overall production risk, especially in surge production scenario.

22 Introduction

Previous stages of analysis for this study identified that integration of bulk manufacturing with FFF capabilities is critical to successfully delivering MCMs to the stockpile and distributing them to the field. In recognition of the critical nature of FFF capabilities, this section augments the HLCD and examines the FFF capacity as it relates to the BDMI. The objectives of this section are to:

- Benchmark commercially available form/fill/finish options
- Estimate required FFF infrastructure capacity required.
- Explore the factors that affect whether and to what extent form/fill/finish functions should be performed internally, as opposed to being contracted out or fulfilled through a partnership with another organization

23 Methodology

- **Benchmarking Commercially Available Form/Fill/Finish Options**
 - Evaluation of available form/fill/finish options consisted of a review of publicly available documents (commercial publications and academic literature) to benchmark commercially available FFF options and verification through interviews with industry experts.
- **Estimating the Required Form/Fill/Finish Infrastructure**
 - A model was developed in order to estimate the number of fill lines required for the BDMI form/fill/finish infrastructure. Key inputs to the model were finished dose production requirements expressed as the number of doses produced within a specified timeframe. Dose numbers and timeframes were bounded by the stockpile production requirements and surge requirements as defined in the HLCD analysis. Infrastructure cost and size were extrapolated from publicly available information on construction of aseptic filling facilities.
- **Form/Fill/Finish Outsourcing Decision-Making Considerations**
 - Additionally, for FFF outsourcing decision-making considerations, a series of interviews with industry experts was used as the primary source for determining the considerations involved with outsourcing form/fill/finish operations. As noted, supporting material was drawn from a review of publicly available documents.

24 Benchmarking Commercially Available Form/Fill/Finish Options

24.1 Process Overview

The form/fill/finish process consists of a series of standardized steps run on a set of standard equipment; therefore, the process is generally not drug-specific. A single form/fill/finish resource is usually sufficient for multiple drugs and multiple delivery formats, although equipment configuration must be adjusted when switching from one drug delivery format to another (e.g., vial to pre-filled syringe) or when adding additional processing operations (e.g., lyophilization). Figure 48 is a generic representation of the form/fill/finish process:

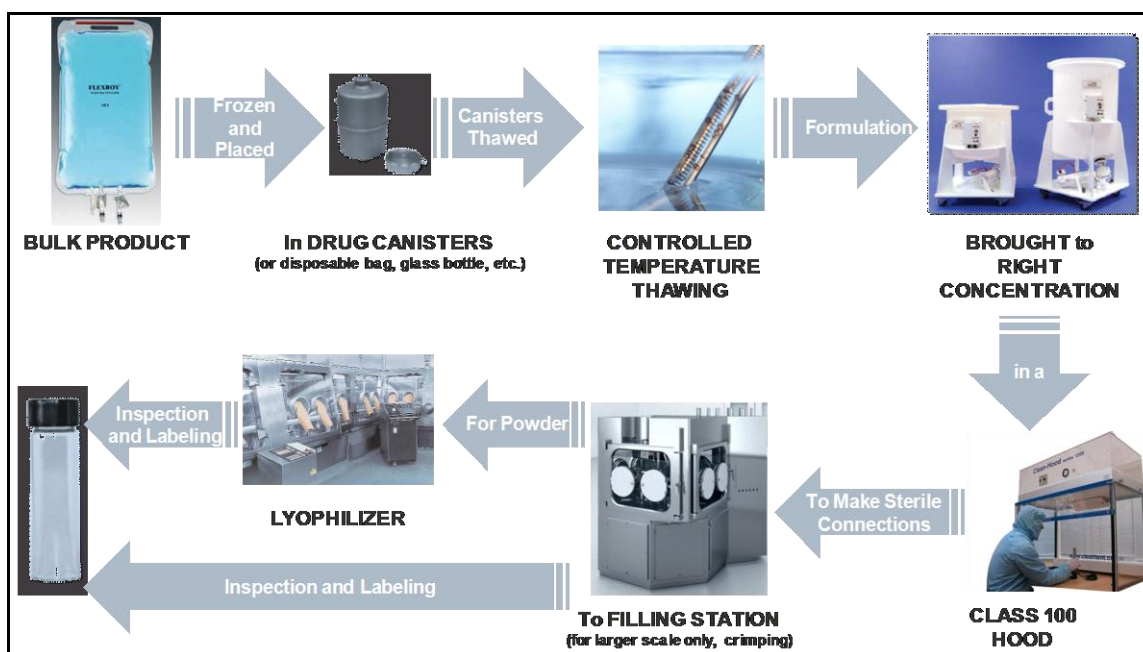


Figure 48. Form/Fill/Finish process overview

Formulation begins with bulk product that is typically stored in containers such as disposable bags, glass bottles and aluminum tubes. If frozen, bulk product is thawed and then formulated in order to be brought to the right concentration for filling. The entire process is performed under sterile conditions.

Prior to filling, the fill apparatus will be cleaned, and calibrated to deliver the required amounts of product. Since most vaccines are delivered by injection, filling of vials or pre-filled syringes are the typical product formats. Product container selection is influenced by variables such as size, type, number of needle punctures, water vapor transmission rate, ability to retain bound water, gas transmission, and the stoppering equipment of the filling line.

The selection and setup of specific filling equipment (e.g. tubing, pumps, etc.) are influenced by various factors including solution volume, fill tolerance, production throughput, drug viscosity, drug foaming, gas blanketing, drug temperature, potent compounds, drug stability, and reactivity.

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Once line setup and formulation are complete, product filling takes place. Containers are aseptically filled with the required amount of and stoppered upon completion. In the case of liquid formulations, the next step is container sealing, which occurs immediately after the stoppering. However, if the drug requires a solid formulation, the stopper is only partially seated on the vial, and the vial is placed in a lyophilizer to remove water prior to sealing.

A portion of the final, filled product vials are submitted for quality control analysis where they are analyzed for bacterial or viral contamination as well as key product attributes. As a visual inspection is only about 85% effective in detecting compromised vials, even when performed by trained and tested inspectors, many companies have implemented double inspection or included an automated process for vision standards as part of a fill line.¹⁶³

24.1 Fill Line Systems

Three major systems are used in the filling process: traditional, isolator, and restricted access barrier system (RABS).

The traditional system is suitable for small-scale production (less than 2,000 vials) but impractical for larger volumes. It consists of gowned operators performing all tasks by hand under a Class 100 hood as just described in the previous section. Due to this method's heavy interaction between operators and bulk material, contamination risk is the highest.¹⁶⁴

Another system for fill/finish is the isolator system. The isolator system uses high-efficiency particulate air (HEPA) filters and a glove box like structure to minimize human intervention and provide increased control of contamination risks. Isolators are self-contained systems that are easily sanitized by vaporized hydrogen peroxide. The isolator system does, however, have its drawbacks. In addition to requiring an expensive capital investment, it is far more complex to install, qualify, and operate than the traditional system. The isolator system also offers less flexibility in changeover to different fill sizes and products. However, it is the ideal method for high-volume dedicated drug production.¹⁶⁵

The RABS is similar to the isolator system but with a few modifications. It has the same glove ports features as the isolator system and other similar sterile operator features, yet it is different in that it utilizes conventional cleanroom gowning and aseptic techniques. Its primary advantages are reduced capital investment and quicker validations and operational startup (with the latter leading to a reduced lot-to-lot turnaround time). Also, the RABS is easier to clean, making it useful for the production of viral, bacterial, and live agent drugs.¹⁶⁶

24.2 Single-use Equipment in Form/Fill/Finish

24.2.1 Single-use Equipment in Filling

Single-use technologies have come to play a significant role in the filling process. . Fill stations now feature single-use bags, single-use aseptic filters, disposable tubing sets for

¹⁶³ Douglas Stockdale, "Overview of aseptic fill/finish manufacturing," *American Pharmaceutical Review*, September/October 2004.

¹⁶⁴ Stockdale, "Overview of aseptic fill/finish manufacturing."

¹⁶⁵ Stockdale, "Overview of aseptic fill/finish manufacturing."

¹⁶⁶ Stockdale, "Overview of aseptic fill/finish manufacturing."

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peristaltic pumps, disposable liners, disposable needles, etc. – all of which have been validated to meet regulatory standards and can be used to fill a variety of molecule types, including small molecules, proteins, peptides, and monoclonal antibodies.

Single-use technologies provide many advantages over their non-disposable counterparts; hence, their use is becoming preferred throughout the form/fill/finish process. Single-use bag systems are now fulfilling the role once entrusted to traditional stainless steel vessels.¹⁶⁷ With the advent of disposable peristaltic pumps, the need for costly cleaning validations has been eliminated. Disposable pumps provide precision filling for challenging media types, e.g., slurries, viscous solutions, and shear-sensitive fluids as well as conventional liquid products.¹⁶⁸ Finally, new technologies such as monobloc filling lines enable rapid product changeover through the efficient integration of disposable components (e.g. rinser, filler, capper, etc.). Similar advances have been made in incorporating disposable, as well as time- and cost-saving technologies, in the lyophilization process.¹⁶⁹

The Bosch Prevas Disposable Dosing System is an example of a flexible disposables-compatible fill station. The system—a pre-assembled, pre-sterilized, and pre-validated filling station—takes in product from a bulk bag and channels it through a disposable positive displacement-rolling diaphragm pump, disposable tubing, and disposable filling needles. The product is completely contained within the system, reducing operator exposure. The system is also highly flexible, capable of running at low speeds for syringe filling as well as at high speeds for vials. Another benefit is the ease of scale-up, as expansion only requires the addition of more disposable components. The Bosch system has demonstrated fill accuracies equivalent to traditional stainless steel pump systems. It is an example of disposable technology playing a significant role in flexible filling – as it processes powder, tablets, pellets, liquids, and even combination formats.¹⁷⁰

24.2.2 Single-use Technology in Finished Product Format

Several single-use technology advances also have been made in the finish phase. Drug delivery has traditionally presented challenges with companies attempting to simultaneously cut costs through more efficient packaging (e.g., multi-dose vials), maintain product stability and sterility, and minimize product waste. New innovations in disposable, single-use delivery methods have increased the range of finish options for fill/finish operations.

For example, the Biojector is a versatile needle-free injection system that forces liquid medications through a tiny orifice when positioned against the skin (see Figure 49). The device creates a very fine, high-pressure stream of medication that penetrates the skin and deposits the medication in the tissue beneath. While the Biojector is disposable, it is not entirely a single-use apparatus. The system has three components: a durable injection device, a needle-free syringe, and a carbon dioxide cartridge. The needle-free syringe is the disposable component of the device; the durable injection device and the carbon dioxide cartridge have been tested and are rated to deliver over 100,000 injections. A cost-saving benefit associated with the needle-free system is that a sharps container is no longer needed since the syringe uses pressure to deliver injections.

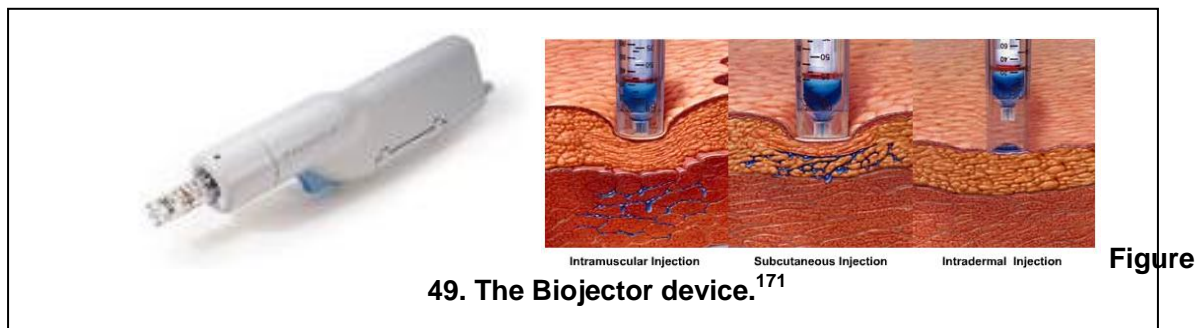
¹⁶⁷ Patheon, “Disposable Technologies,” online, 04 Feb. 2009.

¹⁶⁸ Patheon, “Disposable Technologies.”

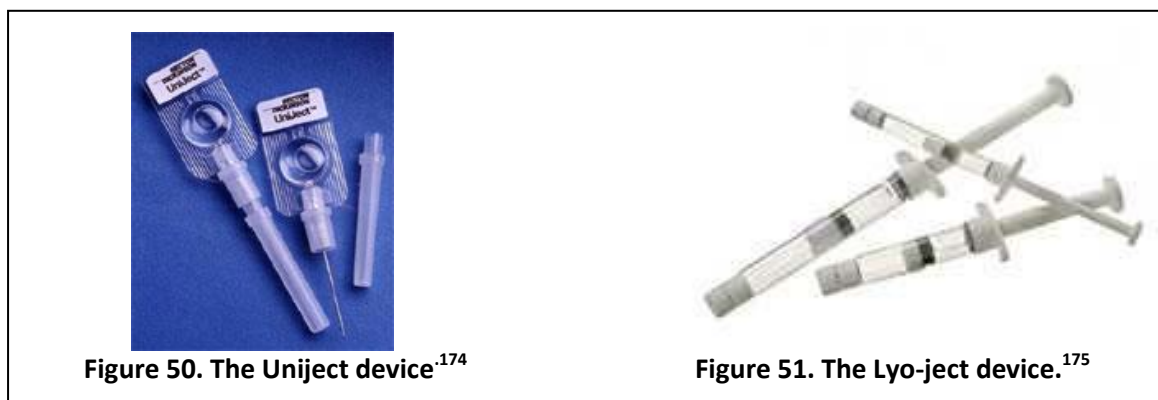
¹⁶⁹ Patheon, “Disposable Technologies.”

¹⁷⁰ Phil Taylor, “Bosch makes liquid filling a disposable option,” in-Pharma Technologist, 03 April 2008.

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Uniject™ is another disposable single-use injection system, consisting of a single-dose auto-disabling device whose ease of use permits drug administration by non-health professionals. Uniject™ eliminates the need for overfilling, thus reducing cost and vaccine waste.¹⁷² The efficiency of the system has been validated by research that has confirmed Uniject's financial justification.¹⁷³



Finally, the Vetter Lyo-Ject® is a disposable single-use syringe capable of packaging and delivering a lyophilized drug with its diluents. The apparatus has two chambers, both of which are pre-filled (one with lyophilized powder and the other with diluents). The drug can be reconstituted within the syringe. The self-contained system eliminates overfill wastage, and its single-use nature eliminates potential disease transmission. The syringe works with any lyophilized drug and can be calibrated to reconstitute the drug at the desired speed.¹⁷⁶

25 Estimating the Required Form/Fill/Finish Infrastructure

25.1 *Fill Line Capacity Requirements*

¹⁷¹ Biojector Website, <http://www.bioject.com/biojector2000.html>, 30 Mar. 09.

¹⁷² PATH, "The radically simple Uniject™ device: rethinking the needle to improve immunization," 30 Mar. 09.

¹⁷³ M. Arantxa Colchero and others, "Cost effectiveness of Uniject versus the traditional syringe and vial method in vaccination campaigns," 28 April 2009.

¹⁷⁴ PATH, "The radically simple Uniject™ device: rethinking the needle to improve immunization," 30 Mar. 2009.

¹⁷⁵ Vetter Lyoject, http://www.vetter-pharma.com/services/solutions/doppelkammertech/index_html, 30 Mar. 2009.

¹⁷⁶ Annie Lubinsky, "Syringes Reinvented to Address Safety Issues," *Pharmaceutical & Medical Packaging News*, November 1999, 19 Feb. 2009.

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The size of the form/fill/finish infrastructure required for the BDMI is determined both by finished dose demand and fill line capacity. Comparison of these two factors provides an estimated range of the number of fill lines required to fulfill MCM requirements.

25.1.1 Estimating Demand

Finished dose demand was estimated based on the demand requirements as outlined in the DCA section of this study. The range of possible filling requirements (expressed as doses filled per month) was estimated based on the following four assumptions:

- MCM stockpile requirements would need to be filled within 12 months
- Surge production would need to be filled within one month of bulk batch completion
- Surge filling could take place in parallel with bulk manufacturing
- In a surge scenario five bulk batches would be manufactured to meet the six-month surge production capacity timeline specified by DARPA Program Managers

Based on these four assumptions, Table 22 outlines the monthly filling capacity requirements for both stockpile and surge filling.

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Table 22. Estimated range for fill capacity demand requirements.

| Product | Dose Requirements (doses) | | Fill Requirement (doses/month) | |
|---|---------------------------|---|--------------------------------|----------------------|
| | Stockpile ¹⁷⁷ | Six-month Surge Capacity ¹⁷⁸ | Stockpile ¹⁷⁹ | Surge ¹⁸⁰ |
| Tularemia Vaccine | 7,800,000 | 160,000,000 | 650,000 | 32,000,000 |
| SEB Vaccine | 7,800,000 | 160,000,000 | 650,000 | 32,000,000 |
| Ricin Vaccine | 7,800,000 | 160,000,000 | 650,000 | 32,000,000 |
| Plague Vaccine | 7,800,000 | 160,000,000 | 650,000 | 32,000,000 |
| Brucellosis Vaccine | 7,800,000 | 160,000,000 | 650,000 | 32,000,000 |
| Botulism Vaccine | 7,800,000 | 160,000,000 | 650,000 | 32,000,000 |
| Anthrax Vaccine | 75,090,000 | 160,000,000 | 6,257,500 | 32,000,000 |
| Smallpox Vaccine (special population) | 20,000,000 | 80,000,000 | 1,666,667 | 16,000,000 |
| Smallpox Vaccine | 300,000,000 | 80,000,000 | 25,000,000 | 16,000,000 |
| Ebola/Marburg Vaccine A | 3,600,000 | 24,000,000 | 300,000 | 4,800,000 |
| Eastern Equine Encephalitis (EEE) Vaccine | 5,200,000 | 16,000,000 | 433,334 | 3,200,000 |
| Ebola/Marburg Vaccine B | 3,600,000 | 16,000,000 | 300,000 | 3,200,000 |
| Smallpox Therapeutic | 100,000 | 5,328,000 | 8,334 | 1,065,600 |
| Broad Spectrum Viral Inhibitor | 200,000 | 5,328,000 | 16,667 | 1,065,600 |
| Botulism Therapeutic | 200,000 | 5,328,000 | 16,667 | 1,065,600 |
| Anthrax Therapeutic | 20,000 | 5,328,000 | 1,667 | 1,065,600 |
| Radiation Therapeutic | 600,000 | 5,280,000 | 50,000 | 1,056,000 |
| Nerve Agent Therapeutic | 180,000 | 1,770,667 | 15,000 | 354,134 |

As Table 22 illustrates, a wide range of fill capacity requirements is necessary to support MCM production. Fill capacity ranges from 1,667 doses per month to 32,000,000 doses per month with the median requirement being 1,065,600 doses per month. It should

¹⁷⁷ The “Stockpile” column indicates the number of doses required for stockpile purposes.

¹⁷⁸ The “6-month surge capacity” column indicates the number of doses that could be produced at the BMDI within six months if the entire facility was setup for production of a single product. It is assumed that five “batches” of product could be produced within the 6-month surge period.

¹⁷⁹ The “Stockpile” fill requirement column indicates the number of doses that must be filled per month in order to fill the entire stockpile quantity in 12 months.

¹⁸⁰ The “Surge” fill requirement column indicates the number of doses that must be filled per month in order to fill a single “batch” of product produced under surge conditions (i.e. one fifth of the total surge capacity).

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also be noted that approximately two-thirds of the demand scenarios require a filling capacity of approximately 1,000,000 doses per month or smaller.

25.1.2 Fill Line Capacity

Since the specific finished format for each product has not yet been defined, liquid-filled vials (currently the most common product format) were used to provide estimated fill line capacity. The range of scenarios used as model inputs for liquid-filled vials is broad enough to encompass likely fill capacities for other product formats such as pre-filled syringes. Three primary variables drive fill line capacity:

- The number of doses filled in each vial (doses per vial)
- The filling rate of the fill machine (vials per eight-hour shift)
- The shift schedule (number of eight-hour shifts per day)

Based on these three variables, Table 23 outlines an evaluation of four fill line scenarios that bound the range of potential capacities:

Table 23. Fill line scenarios

| Scenario | Doses per Vial | Fill Rate (vials/shift) | Shift Schedule (shifts/day) |
|---|----------------|-------------------------|-----------------------------|
| A. Clinical-scale, low utilization | 1 | 25,000 | 1 |
| B. Clinical-scale, maximum utilization | 10 | 25,000 | 3 |
| C. High-speed commercial, low utilization | 1 | 200,000 | 1 |
| D. High-speed commercial, maximum utilization | 10 | 200,000 | 3 |

Monthly filling capacity is calculated as the product of the three primary variables as well as the number of monthly running days (uptime). The number of running days in a month used for the capacity calculation was 26, which assumes approximately 85% uptime.

Table 24. Monthly filling capacity

| Scenario | Monthly Filling Capacity (doses/month) |
|---|--|
| A. Clinical-scale, low utilization | 650,000 |
| B. Clinical-scale, maximum utilization | 19,500,000 |
| C. High-speed commercial, low utilization | 5,200,000 |
| D. High-speed commercial, maximum utilization | 156,000,000 |

Table 24 summarizes the monthly filling capacity results associated with each fill-line scenario. It is important to note that the maximum utilization scenarios include an assumption of multi-dose filling. This is a key factor that must be taken into consideration during formulation and final product format development, as it will have a significant impact on the BDMI filling capacity.

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25.1.3 Determining Fill Line Capacity Requirements

From a capacity perspective, BDMI FFF requirements are determined by comparison of Section 23.1.1 demand estimates to Section 23.1.2 fill line capacity scenarios. Figure 52 provides a graphic comparison of filling requirements to be considered in terms of the four fill line capacity scenarios that Table 24 describes.

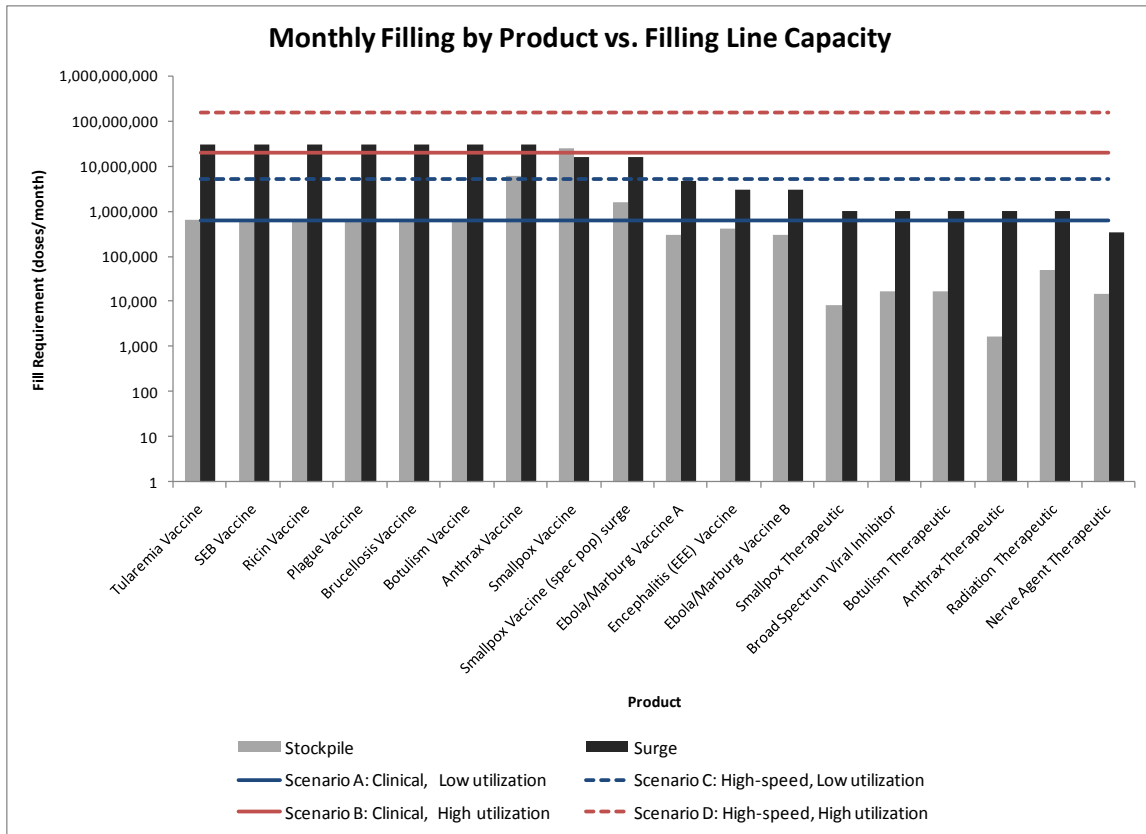


Figure 52. Comparison of product filling requirements to fill line capacity.

This comparison indicates that almost all filling requirements (28 out of 36 scenarios) could be satisfied by the capacity of a single clinical-scale filling line, and all of the filling requirements could be satisfied by a single high-speed filling line. Also noted is that for live agent products (encephalitis, smallpox, and tularemia vaccines), a clinical-scale line is capable of filling all but two scenarios, that of a smallpox vaccine stockpile (300,000,000 doses in 12 months) and a tularemia vaccine surge (160,000,000 doses in 6 months).

25.1 *Additional FFF Requirements*

In addition to filling capacity, the abilities to support formulation development work and clinical trial operations must also be considered when evaluating form/fill/finish infrastructure requirements. Assuming that these two functions will remain within the BDMI, the minimum requirement for BDMI form/fill/finish infrastructure would include any production technology that might be used eventually to produce the required array of finished dose product formats.

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As a finished product format has not yet been defined, the assumption, based on interviews and the survey of commercially available filling options, is that the BDMI should have filling capacity to support both the current most popular product format (i.e., vials) and emerging product formats (e.g., pre-filled syringes). Based on this supposition, to support the range of potential finished product formats at least two clinical-scale filling lines would be required—one capable of liquid filling into vials and the second capable of liquid filling into pre-filled syringes. In addition, lyophilization capability was mentioned as a technology that should be considered for inclusion in the BDMI, as it currently is a commonly used product format.

25.2 Cost and Size

In order to estimate the required cost and sizing of adding FFF capability to the BDMI, a survey of publicly available data regarding FFF capacity was conducted. Table 25 summarizes the survey results:

Table 25. Survey of form/fill/finish capacity and cost.

| Company | Location | Facility Size (sq ft) | Capacity (vials/shift) | Cost |
|-------------------------------|----------------------------|--------------------------|---------------------------|---------------|
| Baxter | Bloomington, IN | 162,000 | 183,000 | \$116M |
| Hyaluron | Burlington, MA | 60,000 | 75,000 | Not Available |
| GSK | Marietta, PA | 3,920,400 | Not Available | \$300M |
| Excelvion | Hettlingen, Switzerland | 7,750 | Not Available | \$9M |
| Cangene | Manitoba, Canada | 125,000 | 50,000 | Not Available |
| Chesapeake Biological Labs | Baltimore, MD | 70,000 | 100,000 | Not Available |
| Genzyme | Waterford, Ireland | 73,927 | 576,000 | \$ 358M |
| Elan | Dublin, Ireland | 42,000 | 54,800 | \$44. 8M |
| Genentech | Hillsboro, OR | 1,089,000 | Not Available | \$250M |
| Acambis | Rockville, MD | 58,000 | Not Available | \$7.5M |
| Elan | Athlone, Ireland | 42,000 | 20,000 | \$41M |
| IntegrityBio | Camarillo, CA | 2000 | 10,000 | Not Available |

Based on the Table 25 survey data, aseptic filling capacity costs ~\$1100 per sq ft, with clinical operations requiring approximately 30,000 ft². Given these assumptions, the cost of adding infrastructure for clinical-scale FFF capability to the BDMI would be on the order of \$33M.

26 Form/Fill/Finish Outsourcing Decision-Making Criteria

As analysis of the study identified, integration of bulk manufacturing with form/fill/finish capabilities is critical to the ultimate success of fulfilling MCM requirements¹⁸¹. Therefore, the decision as to whether such capabilities should be included in the dedicated BDMI or outsourced merits further consideration. Developing an appropriate form/fill/finish strategy for biologic MCMs requires optimizing the competing benefits and

¹⁸¹ Industry Outreach report, Section 6, 28.

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risks associated with each strategic option in respect to achieving the USG biodefense mission.

26.1 *Considerations in the Outsourcing Decision*

In discussions with industry experts regarding the outsourcing of FFF functions, several key considerations were highlighted:

- **Co-location with R&D:** Having the form/fill/finish capabilities and capacity integrated within the BDMI allows for cross-communication and efficient internal technology transfer. This would minimize formulation development challenges that may otherwise arise from outsourcing to CMOs during the development and enhancement of MCMs.
- **Clinical lot production priority:** Prioritization for clinical lot production needs to be addressed, in addition to having readily accessible clinical lot production capacity. If clinical lot production is outsourced, the USG may have to compete with commercial alternatives. Interviews suggested that engaging CMOs to perform clinical-scale fills would be challenging, most likely resulting in delays to the development of new MCMs. At a minimum, the BDMI would require clinical-scale (20-30k vials per shift) in-house form/fill/finish capability to support development and avoid potential delays in achieving product licensure.¹⁸²
- **Surge Capacity:** Recent trends point towards the availability of some degree of overcapacity,¹⁸³ and industry interviews suggest that in-house form/fill/finish capacity may be needed only to fulfill 20% of surge requirements at a maximum while the remaining 80% could be outsourced (Appendix G). CMOs may be an appropriate option to secure capacity for large-scale surge and stockpile bulk-conversion scenarios, though they would need to be chosen ahead of time based on capability, cost, volume, contract terms and conditions, and filling techniques. Establishing pre-existing agreements will enable rapid surge response capability.
- **Cost:** Building infrastructure for in-house capacity would incur significant upfront costs, in addition to the operating costs. However, paying CMOs upfront for capacity may not be cost effective, as the USG may not use the dedicated capacity that was paid for. Finding a balance between the two scenarios, where small-scale and live agent filling is performed in-house while large scale filling is outsourced would be cost effective.

¹⁸² Steering Team Member, Telephone Interview, 18 February 2009.

¹⁸³ Jim Miller, "Biomufacturing pendulum swings toward overcapacity," *BioPharm*, 01 May 2008, 22 Feb. 2009.

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- **Access for Live Agent F/F/F:** A significant hurdle to outsourcing form/fill/finish operations is live agent filling. The market capacity for this function is limited, as many CMOs refuse to run live agents for fear of losing other customers.¹⁸⁴ Commercial customers will often be reluctant to have their products run on the same line as that used for live agent filling, due to cross-contamination concerns. For this reason, investment in clinical-scale FFF capacity for the BDMI may facilitate development of live agent products. Live agent filling in a surge situation was not seen as an obstacle, as invoking the Defense Production Act (DPA) would allow USG to utilize external filling capacity to support surge production requirements.

26.2 *Form/Fill/Finish Options*

Broadly, there are several options available for FFF operations in the production of MCM products:

1. **100% In-house capability:** All FFF operations are conducted in-house.
2. **100% Outsourced:** All FFF are outsourced to a third party. Two approaches in terms of this type operating model were identified in discussions with industry experts:
 - a. Existing CMO capacity is used
 - b. A caveat expansion with “first access” clause to grant USG unconditional access in surge
3. **Hybrid:** Some FFF capacity is maintained in house, and a CMO network is established to provide additional external capacity.

These FFF options are compared in Table 26 with respect to addressing the considerations identified earlier in Section 28.1:

¹⁸⁴ Steering Team Member, Telephone Interview, 19 February 2009.

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Table 26. Evaluation of form/fill/finish outsourcing scenarios.

| | 1. 100% In-house Capability | 2a. 100% Outsourced (No Special Control) | 2b. 100% Outsourced (Preferred Capacity of Select CMOs) | 3. Hybrid |
|---|--|---|---|---|
| Co-location with R&D | Enables better F/F/F development | Formulation development may face additional challenges | Formulation development may face additional challenges | Enables better F/F/F development |
| Clinical Lot Production Priority | Easy access and higher prioritization | Time to licensure may extend as small scale lots compete with commercial alternatives | Small scale clinical lot production prioritized through contract with CMO | Easy access and higher prioritization |
| Surge Capacity | Viable, but much capacity will be idle | May require DPA | Viable, but may pay premium for access | Viable, but may pay premium for access |
| Cost | High to maintain surge capability | Only pay for capacity when needed | May not use dedicated capacity that was paid for | Efficiently allocates production between in-house and CMO |
| Access for Live Agent F/F/F | Available to run internally | Many CMOs unwilling to run live agents | Many CMOs unwilling to run live agents | Available to run internally |

Pro
Con
Neutral

Making a final decision regarding the appropriate operating model for FFF operations clearly requires that several competing criteria be weighed in order to determine the optimum operating model.

27 Conclusions and Recommendations

This study, conducted over the period from January 2009 to March 2009, came to the following conclusions and recommendations regarding the inclusion of FFF capacity in the BDMI in support of USG objectives:

- The BDMI design should include form/fill/finish capacity, especially in support of three types of filling activities:
 - Formulation development: Advanced development includes development of final dosage product formats. Having capacity for this activity in-house will facilitate dose format development activities.
 - Clinical-scale filling: The potential difficulty in terms of securing external capacity for clinical-scale filling was noted. Having internal capacity for clinical-scale filling would ensure a high degree of control in production scheduling.
 - Live agent product filling: CMOs are reluctant to fill live agent products due to cross-contamination concerns on the part of their other customers. Having internal capacity for live agent filling would ensure access to filling capacity for these products. FFF capacity requirement evaluations should assume live

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agent filling would be conducted in house, with the exception of surge scenarios where the DPA could be invoked.

- Product format is a critical aspect of formulation development that has a high impact on fill/finish capacity. The BDMI should have an in-house capability to fill any potential format used for MCM products. In order to minimize the complexity of the final product portfolio, finished dose formats should be standardized whenever possible. For products where high number of doses are required in a short period of time (e.g. universal mandatory vaccination with smallpox vaccine), multi-dose product formats should be considered as they can significantly increase the capacity of filling equipment.
- Adopting a hybrid strategy for FFF outsourcing has the potential to reduce both the infrastructure investment and the product-supply risk. In addition, supply risk could be reduced further through advance establishment of a CMO network for the purpose of securing high-volume form/fill/finish capacity.
- The cost and square footage required to include clinical-scale filling capacity as part of the BDMI are estimated to be on the order of \$30,000,000 for 30,000 ft² of space. Actual cost and square footage requirements will vary depending on the final design of the facility.
- FFF technologies have matured and are in widespread use throughout industry.
 - Utilizing disposable FFF technology may provide cost savings and reduce overall change-over times

28 Appendices

A. Industry Interview Participants

| Company | |
|--------------------------|--------------------------------|
| Alnylam | Integrated Biotherapeutics Inc |
| Amgen | Merck & Co., Inc |
| Astra Zeneca (MedImmune) | Meridian |
| Avecia | Novartis |
| Bavarian Nordic | Novartis |
| Baxter | Pharmathene |
| EBS | Sanofi-Aventis |
| Functional Genetics | Human Genome Sciences |
| Glaxo SmithKline | |

B. Roundtable Discussion Participants and Discussion Questions

Roundtable Discussion Participants

| Participant | Title |
|--------------------------------------|---|
| Carol D. Linden, Ph.D. | Principal Deputy Director, Office of the Biomedical Research and Development Authority, HHS |
| M. Javad Aman, Ph.D. | President and CSO, Integrated BioTherapeutics Inc |
| John D. Grabenstein, R.Ph., Ph.D. | Sr. Director, Adult Medical Affairs Vaccines & Infectious Diseases, Merck |
| James Matthews, Ph.D. | Sr. Director, Public Policy, Health and Science Policy, Sanofi Pasteur |
| Michael Kurilla, M.D., Ph.D. | Director, Office of Biodefense Research Affairs; Associate Director, Biodefense Product Development, NIAID, HHS |
| RADM Boris D. Lushniak, M.D., M.P.H. | Assistant Commissioner Counterterrorism Policy, Office of Counterterrorism and Emerging Threats, Office of Policy, Planning, and Preparedness, Office of the Commissioner, FDA, HHS |

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| Participant | Title |
|-----------------------------------|---|
| Aubrey Keith Miller, M.D., M.P.H. | CMO and Captain, US Public Health Service, Office of Counterterrorism, US FDA |
| Curran M. Simpson, M.S. | SVP, Operations, Human Genome Sciences |
| Michael Goldblatt, Ph.D., J.D. | President and CEO, Functional Genetics, Inc. |
| Darrell R. Galloway, Ph.D. | Director, Chemical and Biological Technologies; Directorate, Defense Threat Reduction Agency, DoD |
| Keith H. Wells, Ph.D. | Sr. Consultant, Process Development and Manufacturing, Biologics Consulting Group, LLC |
| Thomas V. Inglesby, M.D. | COO and Deputy Director, Center for Biosecurity, UPMC |

Roundtable Discussion Questions

(1) Integrated Advanced Development and Multi-Product Manufacturing

Industry representatives proficient in commercial operations agree that the integrated advanced development and manufacturing concept is advantageous. Co-locating advanced development and manufacturing would enable more continuity in development from clinical and process development through production—thereby streamlining the technology transfer process.

Questions

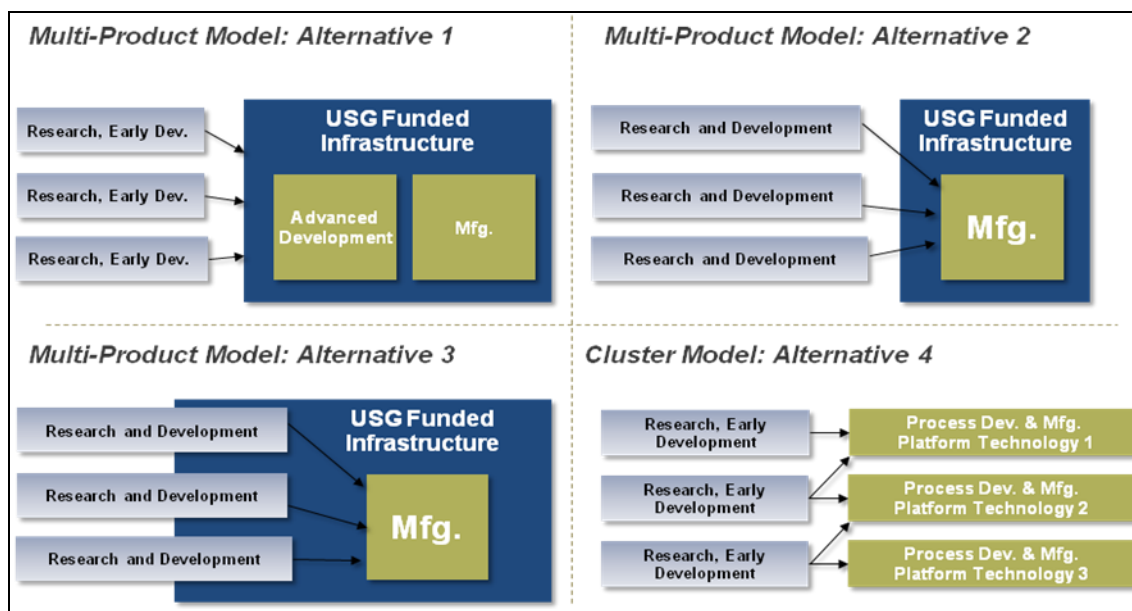
- Is integrating advanced development and manufacturing an efficient and effective approach to meet low-volume biodefense biologics requirements?
- What are the pros and cons of transferring technology at different stages of development (i.e. preclinical, advanced development, and manufacturing)?



(2) Advanced Development and Manufacturing Operating Model

Three multi-product advanced development and manufacturing operating models were presented during the individual industry outreach meetings to provide a framework for discussion and solicit input. Three of these models are shown below as Alternatives 1-3. Based on feedback received from industry, Alternative 4, the “Cluster model,” was devised. Under Alternative 4, industry partners would develop and manufacture USG biodefense biologics requirements that coincide with their expertise in a particular platform technology. This model does not require a dedicated USG-funded facility.

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Industry participants provided substantive commentary on the operating models, including strengths, weaknesses, and alternatives. A consensus was not expressed on the most effective and efficient model. In general, contract manufacturing organizations believe they can effectively provide advanced development and manufacturing assistance to meet the USG's requirements using existing infrastructure; however, the issue of surge could not be addressed. Some innovators expressed interest in Alternative 3 because it would enable greater control for the innovator throughout the product development process. It would also enable a better learning environment to encourage greater innovation as innovators learn from manufacturing outcomes. On the other hand, large biopharma indicated that Alternative 3 would be very challenging to manage whereas Alternative 1 would be more operationally efficient. Specific pros and cons of each model will be discussed during the roundtable session.

Questions

- What are the most important factors to consider when choosing an operating model?
- How can you mitigate the risks and challenges associated with your preferred operating model? Please consider alternative models to the four presented when addressing this question.

(3) Keys to Success

Industry participants were asked during the interviews to characterize the barriers that would preclude their participation in a USG-funded biodefense enterprise and the incentives that would encourage their participation. Common barriers expressed included: (1) the unfavorable economics: uncertain demand, low margins, and monopsonistic market, (2) USG contracts: the complexity and duration of the contracting process, and (3) ambiguous regulatory requirements for biologics.

Questions

- Are these the most significant barriers?
- How can government alleviate these barriers?

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According to information compiled during the industry interviews: The most value-added incentives would bolster, while not disrupting, the stakeholder company’s commercial business—including, but not limited to, use of the facility’s excess capacity for commercial production, preferred status with the FDA for participants, long-term commitments, and rights to sell licensed products in commercial markets.

Questions

- Does this statement accurately characterize the necessary incentives needed to encourage industry participation?
- What are the challenges and possibilities for providing these types of incentives – are some easier than others?

C. Supply vs. Demand in Determining Excess Capacity

Model Assumptions: Domestic mAB capacity

Annual domestic production capacity was calculated as the product of bioreactor capacity, titer, purification yield, and bioreactor turns:

Table 14. Domestic mAB capacity assumptions.

| Scenario | Domestic Bioreactor Volume (L) | Bioreactor Titer (g/L) 185 | Purification Yield (%) 186,187,188 | Bioreactor Turns per year |
|---------------------|--------------------------------|-------------------------------|---------------------------------------|---------------------------|
| Low Efficiency | 1,200,000 | 0.5 | 60 % | 7 |
| Moderate Efficiency | 1,200,000 | 1.0 | 70 % | 12 |
| High Efficiency | 1,200,000 | 1.5 | 75 % | 20 |

Current domestic bioreactor volume is estimated by a summation of publicly available information on domestic commercial capacity.

Model Assumptions: Demand Assumptions

Global demand in 2009 is 5,800kg per year and is expected to reach 11,800kg per year by 2013.¹⁸⁹

Current (2009) US demand for mAB therapeutics is estimated as the product of the average annual US demand per mAB drug (46kg)¹⁹⁰ and the current number of FDA-approved mAB drugs (25)¹⁹¹ or 1,150 kg.

¹⁸⁵ Aforementioned industry best is 5 g/L, but many current production processes utilize dated but proven methods that result in lower titers.

¹⁸⁶ Kelly, "Very large scale monoclonal antibody purification: the case for conventional unit operations," 997.

¹⁸⁷ Butler, "Animal cell cultures: recent achievements and perspectives in the production of biopharmaceuticals," 283.

¹⁸⁸ Birch and Racher, "Antibody production," 683.

¹⁸⁹ Levine, "Challenges and solutions for biopharmaceutical manufacturing," 21

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Applying the global demand growth ratio (11,800kg : 5,800 kg) to the 2009 estimate of US annual demand (1,150kg), US annual demand in 2013 can be estimated at 2,339kg.

The annual peak demand for mAB-based MCMs was calculated as the product of the peak number of required doses outlined in the HLCD model (750,000 doses) and the baseline quantity of mAB required per dose, with mAB dose strength estimated at 3 mg per dose or 800 mg per dose.

Table 15. Peak annual mAB-based MCM requirement scenarios.

| Scenario | Dose Strength (mg/dose) | Peak Annual mAB Requirement (kg) |
|---------------------|-------------------------|----------------------------------|
| Conservative | 800 | 600 |
| Baseline/Aggressive | 3 | 2.25 |

D. Domestic Bioreactor Volume

Table 15 summarizes, by company, publicly available information on domestic bioreactor capacity:¹⁹²

Table 16. Survey of domestic bioreactor volume.

| Company | Location | Cost | Sq. Ft. | Bioreactor capacity |
|----------------|---------------|---------------|---------------|-------------------------|
| Genentech | California | \$250 M | 310,000 | 96,000L total capacity |
| ImClone | New Jersey | \$53 M | 80,000 | 30,000L total capacity |
| Biogen | N. Carolina | \$175 M | 245,000 | 90,000L total capacity |
| Amgen | Rhode Island | \$500 M | 500,000 | 180,000L total capacity |
| Genentech | California | \$380 M | 470,000 | 90,000L total capacity |
| ImClone | New Jersey | \$260 M | 250,000 | 99,000L total capacity |
| Genentech | California | \$600 M | 380,000 | 200,000L total capacity |
| GSK | S. Carolina | Not Available | 30,000 | Not Available |
| GSK | Pennsylvania | \$14 M | 656,000 | Not Available |
| Sanofi-aventis | Pennsylvania | \$160 M | Not Available | Not Available |
| Novartis | N. Carolina | \$600 M | 300,000 | 20,000L total capacity |
| Merck | N. Carolina | \$300 M | 272,000 | Not Available |
| Merck | Not Available | \$100 M | 115,000 | Not Available |
| BMS | Massachusetts | \$750 M | Not Available | 120,000L total capacity |
| Lonza | New Hampshire | Not Available | 315,000 | 61,500L total capacity |
| Abgenix | California | \$125 M | 100,000 | 32,000L total capacity |

¹⁹⁰ Farid, "Established antibody bioprocesses as a basis for future planning," 28.

¹⁹¹ UPMC Scientist, In-Person Interview, 16 February 2009.

¹⁹² Internet search of multiple newsletters and press releases.

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| Company | Location | Cost | Sq. Ft. | Bioreactor capacity |
|--|-----------------|------------------|------------------|--|
| Wyeth | N. Carolina | \$17.5 M | 37,000 | Not Available |
| Wyeth | Massachusetts | | 1,100,000 | 7,500L total capacity |
| IDEC Pharma | California | \$10 M | 12,500 | Not Available |
| Boehringer Ingelheim | Missouri | \$50 M | 56,000 | Not Available |
| CMC Biologics | Washington | Not Available | 15,000 | Small scale (2L, 15L, 40L), large scale (150L, 350L, 750L, 1600L, 3000L). Note: we will be bringing in extra capacity (two 4000L bioreactors) in 2010. |
| KBI Biopharma | N. Carolina | \$65 M | 341,300 | 510L total capacity |
| SAFC Protein Group | Missouri | Not Available | Not Available | 520L total capacity |
| SAFC Viral Group | California | Not Available | Not Available | 250L total capacity |
| Univ. of Nebraska, Lincoln Biological Process Development Facility | Nebraska | Not Available | Not Available | 226L total capacity |
| Xcellerex | Massachusetts | Not Available | 40,000 | Commercial disposable bioreactors and fermentors are produced at Xcellerex, hence number is not a constraint. Bioreactor range – 200L, 500L, 1000L, 2000L, (5000L coming soon). Fermentor range – 50L turbo, (200L turbo coming soon) |

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E. List of Interviewees

| Company | Interviewee(s) | Title |
|-------------------------------------|--|--|
| Sartorius Stedim | Elizabeth Hodnicki | Sales Representative |
| ThermoFisherScientific (Hyclone) | Eric Isberg (formerly with ThermoFisher Scientific) | Manager, Single-Use Process Systems, BioProcess Container Systems, BioProcess Production |
| Univ. of Maryland, Baltimore County | Govind Rao | Professor |
| ATMI | Jeff Craig | Global Director, Strategic Marketing and Business Dev. |
| | Philip M. Mantey | Global Director, Finance & Strategic Planning |
| SAFC | Carolyn Bailey | Marketing Product Manager |
| Millipore | Bob Shaw | Program Director –Vaccines & Emerging Biotech |
| | Thomas Janko | Field Marketing Manager for Disposable Solutions |
| | Stephanie Wilson | Group Product Manager |
| | Mani Kushnan | Product Manager of Mobius Product Line |
| | Mark McGinnis | Sales of Mobius Product Line |
| CRB USA | Marc Pelletier | Director |
| | Kim Nelson, PhD | Director |
| Novavax | Jim Robinson | Vice President, Technical & Quality Operations |

F. Interview Guide

1. What are the current trends in disposable manufacturing equipments?
2. At the different stages of process development (i.e. upstream, downstream, manufacturing & fill finish), what are the most popular products?
3. What new technologies/products are currently in the development pipeline, and when will they become available?
4. How well is the disposable equipment being accepted by various stakeholders
 - Private companies (Pharmas/Biotechs)?
 - Public labs (Academia)?
 - Gov. (NIH, FDA)?
5. What are the current technology gaps in disposable equipment?
6. What are the performance challenges with the current technology?
7. What are the current regulatory issues/concerns with disposable technology? How are these being addressed by your company?
8. What are some ROI concerns of your customers?

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9. Has a cost-savings analysis been performed for disposables? If so, can you provide the results?
10. Can you provide references of companies (Pharma/Biotech, CMOs) that currently use your disposable products?

G. Availability of Form/Fill/Finish Capacity

Two schools of thought exist regarding the availability of excess capacity in the form/fill/finish field. On one side, industry experts such as Dr. Terry Novak, Executive VP and Chief Marketing Officer at DSM Biologics & Pharma, claim there is ample capacity in the market. On the other side, industry experts like Craig Mastenbaum, VP of Manufacturing and Business Development at HollisterStier, believe there is an “overall shortage of available capacity.”¹⁹³ In addition, recent trends observed amongst the “big five” in biopharma (Sanofi-Pasteur, GlaxoSmithKline, Merck, Wyeth and Novartis) suggest that they are moving to secure dosage form capacity, primarily in pre-filled syringes.

The top fifteen biopharma companies are building up their portfolios of mABs, vaccines, and recombinant proteins. Most of this work is done through technology and candidate in-licensing and outright acquisitions.

Figure 54 represents their expenditure.

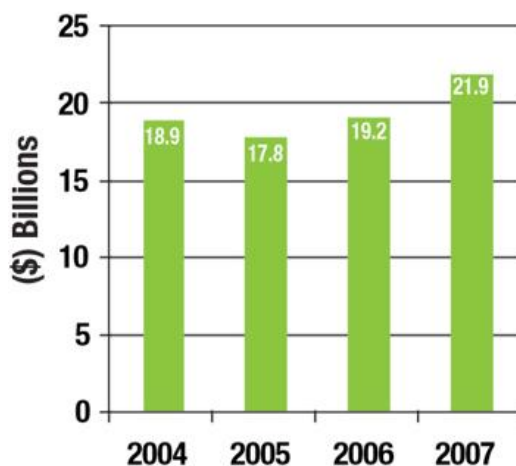


Figure 54. Capital expenditures by the 15 largest bio/pharmaceutical companies

Capital expenditures by the 15 largest bio/pharmaceutical companies in new manufacturing and laboratory facilities was \$24.9 billion in 2007, representing a vast 27% increase over the \$19.6 million spent in 2006, and 40% more than 2005 expenditures.¹⁹⁴ There was a 14% increase in expenditure by the top 15 from 2006 to 2007, and a 23% increase in expenditure by top the 15 from 2005 to 2007. Studies indicate that much of the expenditure is going toward internal fill/finish facilities as companies move towards vertical integration for biologic products.

¹⁹³ Gil Roth, "How will a growing market affect the contract manufacturing business?" *Bio News & Views: Vaccines and CMOs, Contract Pharma* (2007).

¹⁹⁴ Miller, "Biomufacturing pendulum swings toward overcapacity."

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Table 27. Capital expenditures by biopharmaceutical companies for different projects in various geographical areas.¹⁹⁵

| Company | Project | Location | Cost (\$ million) |
|---------------------------|---|--|-------------------|
| Abbott | Biologics API | Puerto Rico | 450 |
| Amgen | Biologics API Fill/finish expansion Biologics API expansion | Puerto Rico Rhode Island, US | 1,200 |
| AstraZeneca/ Medimmune | Biologics API Biologics API | Canada Maryland, US | |
| BMS | Biologics API Parenteral fill/finish | Massachusetts, US Puerto Rico | 750 200 |
| Genentech | Biologics API | Oregon, US | |
| GSK | Vaccine manufacturing Vaccine fill/finish Vaccines antigens | Singapore France Hungary | 200 680 136 |
| Eli Lilly | Biologics facility Fill/finish expansion Biologics pilot plant Biologics API | Ireland Indiana, US Indiana, US Puerto Rico | 560 |
| Merck | Vaccine manufacturing Parenteral fill/finish Vaccine fill/finish | Virginia, US France North Carolina, US | 40 114 300 |
| Novartis | Biologics API expansion Vaccines manufacturing Biologics API expansion | California, US North Carolina Germany | 600 |
| Pfizer | Biologics API expansion | Missouri, US | |
| Roche | Parenteral fill/finish Parenteral fill/finish | Germany Switzerland | 68 68 |

The expectation is that large-molecule and small-molecule programs will be integrated from clinical development through manufacturing. BioProcess Technology Consultants noted that, “Big Pharma is not really embracing outsourcing so much as it is redeploying assets in conjunction with a wholesale strategy makeover.”¹⁹⁶ This move to vertical integration will concomitantly create new opportunities for CMOs as they pick up manufacture of older active pharmaceutical ingredients and dosage forms along with some of new small molecule launches but overall the move to vertical integration is expected to leave excess capacity in the CMO market.¹⁹⁷

While it may be too early to assess if this is a short-term or long-term trend, there is evidence to support shifts in the industry. As the market enters a period of transition it is difficult to quantify the extent of excess capacity, but the general sense in industry is that recent trends point towards the availability of some degree of overcapacity.¹⁹⁸

^{196, 197, 198} Miller, “Biomanufacturing pendulum swings toward overcapacity.”

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