DEVELOPING BIODEFENSE COUNTERMEASURES:
LESSONS FROM THE ORPHAN DRUG ACT AND PROJECT BIOSHIELD
ANTHRAX CONTRACTS

by

Dominique Duong
A Dissertation
Submitted to the
Graduate Faculty
of
George Mason University
in Partial Fulfillment of
The Requirements for the Degree
of
Doctor of Philosophy
Biodefense

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Date: March 25, 2011

Spring Semester 2011
George Mason University
Fairfax, VA

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DEDICATION

This is dedicated to my family who is the light of my life and the most loving and solid support system anyone could ever dream of.

ACKNOWLEDGEMENTS

I could not have done this without my soulmate Alan. Not only did he take the time to correct the grammar and style of this dissertation, but he also pushes me to think outside of the box. I would like to thank him for the peace and happiness that he gives me through passion and endless support. He also gave me priceless time to find inspiration and write my dissertation.

I am fortunate to have my sister and best friend Christine in my life. She helped me with the final logistics of this dissertation, but also makes life beautiful because we can enjoy the little things together, because she grounds me when things get chaotic, because she gives me unconditional love and support.

I would not be here without Mammy and Papa. They inspire me to always seek an intellectual challenge and to strive to make a positive impact. They taught me that I can reach for the stars and gave me the tools and instruments to get there. They also taught me the meaning of sacrifice and unconditional love.

The support of my best friend and soul sister Chau was dear to my heart. She always is my guiding and comforting light even in the darkest times. I would like to thank her for providing me with sound advice, not only on the style and grammar of this dissertation, but also on everything and nothing about the adventures of life.

I would like to thank Adeola, Tristan, Angela, Dr. Harbour, Zack, Duane, Papa, and Amelia, for helping me with the inception, evolution, and/or correction of this dissertation.

Last but not least, I am grateful for my committee, Dr. Koblentz, Dr. Kahn, and Dr. Baker. I would like to thank Dr. Baker for giving me time, encouragement, and dedication. I am thankful for Dr. Kahn for his enthusiasm and for giving me inspiration and guidance. Finally, I am deeply appreciative of Dr. Koblentz, the Chair of my committee, for giving me vision, direction, and insightful mentorship.

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LIST OF ABBREVIATIONS

AIG ..... Anthrax Immune Globulin
AVA ..... Anthrax Vaccine Adsorbed
BARDA ..... Biomedical Advanced Research and Development Authority
AVIP ..... Anthrax Vaccine Immunization Program
BAT ..... Botulinum Antitoxin Heptavalent
Biopharma ..... Biopharmaceutical
BioShield ..... Project BioShield
Biotech ..... Biotechnology
BLA ..... Biologics License Application
BSL ..... Biosafety level
CBRN ..... chemical, biological, radiological, and nuclear
CDC ..... Centers for Disease Control and Prevention
CDER ..... Center for Drug Evaluation and Research
CEO ..... Chief Executive Officer
Cipro ..... ciprofloxacin
CRDA ..... Cooperative Research and Development Agreement
DOD ..... Department of Defense
DHS ..... Department of Homeland Security
Dr. ..... Doctor
EMEA ..... European Medicines Agency
EU ..... European
EUA ..... Emergency Use Authorization
EUAWG ..... Emergency Use Authorization Working Group
FDA ..... Food and Drug Administration
FD&C ..... Food, Drug and Cosmetic
FR ..... Federal Register
GAO ..... Government Accountability Office
HGS ..... Human Genome Sciences
HHS ..... Department of Human and Health Services
IND ..... Investigational New Drug Application
IP ..... Intellectual Property
JVAP ..... Joint Vaccine Acquisition Program
Kg ..... kilogram
mAb ..... monoclonal antibody

MBPI.....Michigan Biologics Products Institute
Mg.....milligram
MVA ..... Imvamune
N/A.....Not applicable
NBSB .....National Biodefense Science Board
NDA.....New Drug Application
NIAID ..... National Institute of Allergy and Infectious Diseases
NIH .....National Institutes of Health
NORD .....National Organization for Rare Disorders
NPS .....National Pharmaceutical Stockpile
ODA.....Orphan Drug Act
ORD ..... Office of Rare Diseases
PAHPA .....Pandemic and All-Hazards Preparedness Act
PDUFA .....Prescription Drug User Fee Act
Pharma .....Pharmaceutical
PHEMCE .....Public Health Emergency Medical Countermeasure Enterprise
PHS .....Public Health Service
P.L. ..... Public Law
PREP .....Public Readiness and Emergency Preparedness
R&D.....Research and Development
rPA .....Recombinant Protective Antigen
SAFETY ..... Support Anti-Terrorism by Fostering Effective Technologies
SNS ..... Strategic National Stockpile
US .....United States
USAMRIID.....US Army Medical Research Institute of Infectious Diseases
VICP .....National Vaccine Injury Compensation Program
vs. ..... versus

ABSTRACT

DEVELOPING BIODEFENSE COUNTERMEASURES:
LESSONS LEARNED FROM THE ORPHAN DRUG ACT AND PROJECT BIOSHIELD ANTHRAX CONTRACTS

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George Mason University, 2011

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US preparedness for a potential bioterrorist attack must include a comprehensive stockpile of countermeasures against biological agents. The Project BioShield Act was enacted in 2004 to promote the development of biodefense countermeasures. Under the act, however, only a limited number of such products have successfully been developed and none have yet received regulatory approval. This dissertation seeks to understand the barriers and ineffective incentives that challenge the development of such countermeasures by analyzing the following: 1) Evaluation of factors (technical, regulatory, economic, legal, political and military) surrounding the development of biodefense products; 2) Comparison of the impact of two acts with the aim to incentivize the development of products with little market appeal: Project BioShield and the Orphan Drug Act; and 3) Comparison of four companies with a BioShield anthrax contract in a

multiple-case study. The purpose of these analyses is to identify opportunities to remove barriers that challenge the development of biodefense countermeasures.

This dissertation finds that the most critical barriers to the successful development and approval of biodefense countermeasures are regulatory and political. The regulatory pathway is still unproven, and the political barrier is apparent because the government is not only the sole customer, but also the regulator, legislator, and collaborator of the biodefense industry. Radical strategies to lower the regulatory and manufacturing barriers have been proposed but still need to be implemented by the Department of Health and Human Services. This initiative suggests, however, that without significant federal funding and keen involvement, the development of biodefense countermeasures could be stumped. This dissertation proposes an alternative model where the resources and burdens are shared between the private industry, the government, and a third contractor party on standby. Additional opportunities to remove barriers include the need for federal commitment to maintain biodefense and BioShield funding, continuous improvement of federal coordination and communication, using a simplified acquisition procedure as opposed to the current approach favoring full and open competition, investment in biodefense product(s) and associated technological platforms, and the promotion of a government-industry-academia-military partnership. The alternative model enhancement to the biodefense drug model suggested in this dissertation along with BioShield can create the necessary foundation to stimulate the development of biodefense countermeasures for preparedness against potential bioterrorist attacks.

CHAPTER 1: INTRODUCTION AND METHODOLOGY

Preparedness in the face of a potential bioterrorist attack is essential to the protection of the population in the United States (US) and the rest of the world. Nine years after the 2001 anthrax letters attack, the country finds itself with a still inadequate and uncertain supply of biodefense countermeasures. The lack of incentives to engage the pharmaceutical industry in devoting scientific expertise, development and manufacturing capabilities is detrimental to providing biodefense countermeasures to the national stockpile. This dissertation seeks to understand the barriers and incentives impacting the process for biodefense product development under Project BioShield. Part of the analysis will include a comparison to the Orphan Drug Act (ODA), another policy incentivizing the market of products with limited market appeal.

The Project BioShield Act was enacted in 2004 to develop and make available countermeasures against potential bioterrorist agents. The Act has been considered slow at creating countermeasures for the Strategic National Stockpile (SNS), and has not yet seen the regulatory approval of a novel product. On the other hand, the ODA is considered to be a successful policy for encouraging the development of orphan drugs, vaccines and therapeutics for rare diseases that have a limited market and therefore a limited commercial appeal. The dissertation project uses an evaluative and comparative

approach to better understand the biodefense product development process and to connect the effectiveness of the ODA to the ongoing evolution of BioShield. This dissertation should be of interest to high-level decision makers, specifically in the Department of Human and Health Services (HHS), to private and public organizations that wish to pursue a biodefense contract under BioShield, and to scholars of public health policy.

The remainder of this dissertation is organized as follows: I first present a brief review of the history of the US biodefense program before and after the pivotal 2001 anthrax letters attack. Next, I introduce Project BioShield and the ODA. ODA is used as a tool to further understand the development of products with little commercial appeal. I will then perform three assessments to further understand the barriers and incentives surrounding the development of biodefense countermeasures and to ultimately determine if there are lessons that can be learned to incentivize the development of such products. First, I discuss the different factors (technical, regulatory, economic, legal, political and military) surrounding the biodefense product development. I then compare the product types and company types under BioShield and ODA, as well as the impact of each act on regulatory approval. Furthermore, I compare four companies with a BioShield anthrax contract in a multiple-case study. Finally, in the discussion and conclusion sections, I determine the lessons to incentivize the development of biodefense countermeasures after 1) evaluating the factors surrounding such development process, 2) comparing impact of BioShield and ODA on such process, and finally 3) comparing the experience of four companies with a BioShield anthrax contract.

1.1 US biodefense program pre-2001

In 1997, the United States government renewed efforts to develop a biodefense program, which was first started in the 1940s (Hoyt 2006). The efforts continued with the Department of Defense's (DOD) Joint Vaccine Acquisition Program (JVAP), a program that transferred promising vaccine leads from military researchers to an outside contractor for development. The first company to win a contract under JVAP was DynPort Vaccine Co., a British-American joint partnership based in Frederick, Maryland. The company was awarded a $322 million dollar (ten-year) contract to develop and obtain licenses for eighteen vaccines for the military, including smallpox and a new recombinant version of the anthrax vaccine. (Cohen and Marshall 2001) On December 15, the Pentagon took an unprecedented step to counter the threat of germ warfare when it announced that it would mass vaccinate the military against anthrax with the old vaccine. The cost for the six-year long program was estimated at $130 million. The efforts to develop a biodefense program were increased when, in 1998, President Clinton presented his plan for germ defense, urging for the first time in the nation's history for the creation of a national stockpile of vaccines and antibiotics to protect the public. (Miller et al, 2002)

The implementation of the plan to develop a stockpile began in 1999, when Congress charged HHS and its Centers for Disease Control and Prevention (CDC) with the

establishment of the National Pharmaceutical Stockpile (NPS). Later in 2003, the NPS would be renamed the Strategic National Stockpile (SNS) and would be put under the joint management of the Department of Homeland Security (DHS) and HHS, per the Homeland Security Act of 2002 (P.L. 107-296). When the Project BioShield legislation was enacted in 2004 (P.L. 108-276), the oversight of SNS would return to HHS. The SNS is a national repository of essential medical assets, including antibiotics, chemical antidotes, vaccines, antitoxins, life-support medications, intravenous administration and airway maintenance supplies, and medical/surgical items. The mission of SNS is to deliver pre-packaged supplies during an emergency to states and communities within twelve hours of the federal decision to deploy. Within two years of its inception, the SNS response capacity was tested. (CDC 2008)

In October 2001, anthrax-containing letters were sent through the US postal office system and reached targets in Congress and the media, injuring seventeen and killing five people. During the 2001 attacks aftermath, the federal government determined that the country was unprepared for a major biological attack, especially since there was a lack of effective medical countermeasures. (Mayer 2007) There was a significant need for a more extensive and comprehensive vaccines and therapeutics stockpile to prepare against future biological attacks. This was highlighted in the 2001 Third Annual Report to the President and Congress presented by the Advisory Panel to Assess Domestic Response Capabilities for Terrorism Involving weapons of Mass Destruction, when the panel concluded that “[l]imited research, development, and production capability for certain

vaccines is one of the largest hurdles currently facing military and civilian responders as they prepare for biological threats." (Mayer 2007)

1.2 US biodefense program from 2001 to Project BioShield

1.2.1 Bioterrorist attacks of 2001

After the 2001 anthrax attack, there was concern that the US lacked vaccines and therapeutics against chemical, biological, radiological, and nuclear (CBRN) threats. To address this, President Bush announced the creation of Project BioShield in his State of the Union address on 28 January 2003, where he proposed a budget of "$6 billion to quickly make available effective vaccines and treatments against agents like anthrax, botulinum toxin, Ebola and plague." The proposal aimed to stimulate the development of countermeasures to the previously identified agents of interest and to procure them for the SNS. On July 21, 2004, President Bush signed the Project BioShield Act of 2004 (P.L. 108-276).

1.2.2 Legislation of Project BioShield

The Project BioShield Act of 2004 established a 10-year program to acquire civilian medical countermeasures to CBRN agents for the SNS. The government recognized that many medical countermeasures against potential bioterror agents do not have a natural market and, therefore, do not attract significant commercial interest. Provisions of this act were designed to encourage private companies to develop these countermeasures by guaranteeing a government market for successfully developed countermeasures.

Project BioShield has three main provisions:

(1) Relaxing regulatory requirements for some CBRN terrorism-related spending, including hiring and awarding research grants.

(2) Guaranteeing a federal government market for new CBRN medical countermeasures.

(3) Permitting emergency use of unapproved countermeasures.

The Act did not appropriate any money. However, it authorized the appropriation of up to a total of $5.6 billion for countermeasures procurement. (Gottron 2007a) The US government dedicated $5.6 billion, provided by the Homeland Security Appropriations Act, 2004 (P.L. 108-90) over ten years to guarantee the purchase of successful vaccines, drugs, and other therapies.

Federal incentives for drug product development can be divided into “push” and “pull” mechanisms. Push mechanisms help to reduce R&D costs, and are typically used to motivate early-stage research. Pull mechanisms help to increase revenues from completed products, through financial rewards or intellectual property extension, and are typically used to motivate late-stage development and manufacturing. (Matheny et al 2007) Project BioShield’s first provision can be considered a push mechanism, while the last two provisions represent pull mechanisms.

In order for a sponsor to obtain a BioShield contract for a product, the HHS must first issue a request for proposal seeking a specified product. HHS can then choose to select a company out of many competitors in a full and open competition. The expedited procedures, a push mechanism, consist of relaxed Federal Acquisition Regulation procedures for HHS to follow when funding CBRN countermeasures research and development. These expedited procedures reduce paperwork and the potential for oversight. The act also increases the maximum amount, from $100,000 to $25 million, for contracts awarded under simplified acquisition procedures. It allows these purchases using other than full and open competition. (Gottron 2010) Market guarantee, a pull mechanism, is the guarantee that the government will buy new, successfully developed, but not yet approved biodefense countermeasures for the SNS. This incentive is important because it promises a market when commercial appeal is low or non-existent. BioShield operates in a centralized funding approach in which the government officials pick the winners and the losers for contract awards. Finally, another pull mechanism is the possibility of temporary authorization by the HHS secretary of the emergency use of medical products that are not yet approved by the Food and Drug Administration (FDA). The conditions for emergency use of unauthorized products through the Emergency Use Authorization (EUA) include: 1) the product is indicated for a serious or life-threatening disease; 2) the product may reasonably be believed to be effective in detecting, diagnosing, treating, or preventing the disease; 3) the known and potential benefits of the product outweigh its known and potential risks; 4) and no adequate alternative to the product is approved and available. (FDA 2007)

1.2.3 Impact and evolution of Project BioShield and related efforts

Project BioShield has 3 main provisions, including expedited procedures, market guarantee, and emergency use of unapproved products. Although the latter two provisions have been extensively used (HHS 2007, HHS 2008), the first provision has not. The Government Accountability Office (GAO) (GAO 2007b) determined that HHS used the simplified acquisitions procedure authority for five contracts, all executed between 2004 and 2005. Through December 2009 (HHS 2007, HHS 2008, HHS 2010a), HHS had not exercised its authority to use anything other than full and open competition. Meanwhile, the conditions for procurement would allow payment once the products are delivered, and upon receipt of FDA approval, licensing or clearance. (Ferrari 2007) The companies would be responsible for the cost of advanced development and manufacturing of the product as well as product approval. Because Project BioShield Act did not include any indemnification provisions, the private industry was concerned with the risk of litigation caused by the adverse effects to their products. (Gottron 2007a) Congress attempted to address these concerns by passing the Public Readiness and Emergency Preparedness (PREP) Act as part of the 2006 Defense Appropriations Act (P.L. 109-148), which includes liability protections for manufacturers of security and pandemic countermeasures.

The government continued over the years to re-address its strategies to try and meet the conditions for effectively producing biodefense countermeasures. Two years after

BioShield was implemented, Congress passed the Pandemic and All-Hazards Preparedness Act (PAHPA, P.L. 109-417), also nicknamed BioShield II. This Act amended Project BioShield and provided measures designed to further advance the federal government's efforts to develop and acquire CBRN countermeasures. President Bush signed it on December 19, 2006. Under the act, HHS is authorized to use about $5.6 billion in a Special Reserve Fund to procure the countermeasures. The act also created the Biomedical Advanced Research and Development Authority (BARDA) within HHS, rendering BARDA a single point of authority for the acquisition of products for the SNS. (HHS 2007b) The mission of BARDA is to accelerate the development of new products by fostering collaboration, to support research, to encourage innovation, and to offer technical guidance among governmental and private sector entities. (Hodge et al 2007) This legislation also amended the payment provisions of BioShield to authorize milestone payments of 5% each for reaching specific milestones in product development, up to 50% of the total contract amount. (HHS 2007b) This approach of providing milestones-based payments of up to half of the total award before delivery represents a push mechanism providing regular financial rewards to companies that were able to make progress in the development process. PAPHA also authorized the appropriation of more than $1 billion through the Biodefense Medical Countermeasure Development Fund for development of biodefense products. (P.L. 109-417)

Further federal effort to clarify strategies and requirements include the April 2007 Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) Implementation Plan,

where HHS and other federal departments defined and prioritized requirements for biodefense countermeasures. (HHS 2007) Additionally, in October 2007, the White House released Homeland Security Presidential Directive 21 (HSPD-21) establishing a "National Strategy for Public Health and Medical Preparedness." The directive established a national strategy based on biosurveillance, countermeasure distribution, mass casualty care, and community resilience to protect the American people against all kinds of disasters. (White House 2007) Another example of federal evolution is the Integrated National Biodefense Medical Countermeasure Portfolio Initiative (Linden 2009). This initiative joins together the national biodefense portfolio for medical countermeasures between HHS and DOD, therefore minimizing duplication of projects and monitoring progress of all candidates in the portfolio. In February 2010, the National Biodefense Science Board (NBSB 2010a) pointed out that the drug industry, contracting with the government, viewed its partner to be slow, unwieldy, expensive and opaque. The industry was frustrated with the increased risk and was less willing to participate due to the lack of clear requirements, the indecisiveness in potential procurement size, the undefined regulatory review, and the non-reliability of sustained funding. In March 2010, the NBSB (NBSB 2010b) identified three critical concepts for the development of biodefense products: prioritization, synchronization (coordination across government agencies), and anticipation (clear and realistic plans). The NBSB is a Federal Advisory Committee established in December 2006 by the PAHPA, and provides expert advice and guidance to the Secretary of HHS. Finally, in August 2010, HHS published a report called "Public Health Emergency Medical Countermeasures Enterprise Review:

Transforming the Enterprise to Meet Long-Range National Needs" (HHS 2010b), which was sparked by the disappointing performance of the pharmaceutical industry in producing sufficient vaccine in a timely manner to address the 2009 H1N1 pandemic. In this report, Kathleen Sebelius, secretary of HHS, led an extensive review of all aspects of product development for biodefense. The report also proposes new strategies to modernize the countermeasure production process, and to create a system that can respond to any threat at any time. The report recommends new infrastructure initiatives as well as enhancements to the current system. The new initiatives included: 1) innovative regulatory science and oversight; 2) flexible manufacturing and advanced development partnerships based on new platforms for innovative product development and manufacturing; 3) enhanced product pipeline with new scientific concepts and addressing product multi-use; and 4) development of an independent strategic investment firm. Enhancements to the current system included: 1) strategic leadership, program, and administrative changes; 2) updated requirements for current and future products; and 3) multi-year budget planning process. The new strategy would be a capabilities-based approach and would require a much more active role by the government in establishing partnerships, removing barriers to innovation, clarifying the regulatory pathway, and repositioning the government as a strategic partner and investor. The report also identifies needs for improved coordination and communication across federal departments, and addressed leadership and management practices to produce an integrated and successful program. The report also provides recommendations for the establishment of manufacturing centers to provide rush production capacity for

biodefense products, and the establishment of an independent strategic investment firm to assist small companies and private investors. The strategy proposed by HHS recognizes that the federal government must be much more creative in helping inexperienced companies by providing access to advanced development services, including product and manufacturing, scale-up, pivotal clinical study assistance, and navigating the regulatory process. The report indicates that the industry uniformly agreed that the most important incentives would be to strengthen capacity and investment in regulatory science and review, and to revisit aspects of the current regulatory and policy framework.

The development of biodefense countermeasures requires coordination between the industry and the government. The different examples demonstrating the importance of the public-private partnership and the power of government influence over critical incentives indicate that the biodefense drug market is a sole customer-driven market where the government is the customer, the regulator, the legislator and the partner.

1.3 Orphan Drug Act

This dissertation compares Project BioShield to the Orphan Drug Act, another legislation whose mission is to incentivize the development of products with little to no market. An orphan drug is a pharmaceutical product that has been developed to treat rare diseases, which afflict fewer than 200,000 patients in the United States. Rare diseases are oftentimes life threatening or chronically debilitating. Meanwhile, drug development for rare diseases is restricted because the understanding of uncommon and infrequent

diseases is usually limited, and because novel pharmaceuticals with poor commercial appeal will most likely incur significant costs of investment and development. (Wastfelt et al. 2006)

1.3.1 Legislation of the Orphan Drug Act

The ODA (P.L. 97-414) was designed to encourage the development of drug products with limited commercial appeal, and more specifically products for the treatment of rare diseases and conditions. The ODA defines two classes of orphan drugs: In the first category are diseases that affect fewer than 200,000 persons in the US; in the second class are diseases that affect more than 200,000 persons in the US, but for which the product has no potential recovery costs from its US sales. The ODA was passed on January 4, 1983 (FDA 2009) after the government recognized there was a lack of orphan drugs (i.e. drugs that have been abandoned or 'orphaned' by major drug companies). (Wastfelt et al. 2006) The purpose of this act was to encourage the pharmaceutical manufacturers to develop drugs, biotechnology drugs, and medical devices to treat rare diseases.

The Orphan Drug Act provides three main incentives:

(1) Seven-year market exclusivity.

(2) Tax credit of 50 percent of the cost of conducting human clinical trials.

(3) Federal research grants for clinical testing of new therapies to treat and/or diagnose rare diseases.

The ODA provides both push and pull mechanisms. The push mechanisms include a 50% tax credit on clinical trials undertaken in the US, a clinical research program administered by the FDA that focuses on early clinical development, and finally, FDA advice and counseling with sponsors on orphan drug protocols. The pull mechanism is a guaranteed 7-year market exclusivity that runs concurrently with any patent-exclusivity terms applicable to particular drugs.

The first push mechanism is the 50% tax credit, which lowers the cost of conducting human clinical trials. As of 2007, the tax credit cost nearly $2 billion, and was projected to cost $1.9 billion between 2008 and 2012. (Office of Management and Budget 2007) It is an efficient incentive because the program operates in a decentralized market, meaning this incentive is applicable to any approved orphan drug after receiving designation.

Additionally, the FDA created the Office of Orphan Products Development (OOPD), who administers the major provisions of the ODA. The OOPD also administers the Orphan Products Grants Program, which provides funding for early clinical development in rare diseases. (FDA 2010a) Finally, a critical incentive is the FDA advice and counseling incentive to sponsors on orphan drug protocols. Recently, the agency continued efforts to increase availability and support to potential sponsors. (Marcus 2010) In 2010, the FDA set up workshops where government officials provide on-the-spot regulatory advice to potential sponsors. Unfortunately, these workshops do not

provide an alternative pathway to orphan-drug designation, but rather provide regulatory advice for critical issues when filling out an application, therefore, increasing the chance for designations. (Marcus 2010) Additionally, the FDA waived the fee established by the Prescription Drug User Fee Act (PDUFA) that sponsors pay when submitting their marketing application.

Finally, the market exclusivity, a pull mechanism, allows drugs with orphan status to benefit from market exclusivity for seven years following the date of the drug's marketing approval. Designation of a drug could also be requested for a previously unapproved drug or for an already marketed drug. The purpose of the market exclusivity provision is to address the limited revenue potential of rare disease drugs and to allow companies to extend the period of marketing rights provided under patent law.

1.3.2 Impact and influences of the Orphan Drug Act

Although some have denounced the high profits that some drug companies have made using the ODA (Maeder 2003), few argue against the fact that the Act led to the introduction of numerous products for rare diseases that would otherwise not be available. Many, including the FDA (FDA 2009, Haffner 2006; HHS 2001), the biopharmaceutical industry (see section 3.2.2 Orphan drug companies), academic and non-profit research groups such as the Tuft Center for the Study of Drug Development and the National Academies (Milne 2002 and Wizemann et al. 2008), and patient advocacy groups (Meyers 2000) view the ODA program as very successful. Indeed,

more than 300 drugs and biological products for rare diseases have been approved and brought to market since 1983 for more than 2000 orphan designations. In contrast, the decade prior to 1983 saw fewer than ten such products come to market. (Borda 2008) The success of the ODA in the US also inspired the adoption of similar legislation in several countries around the world, including Japan, Australia, and Europe. (Villa et al. 2008) For example, the European Parliament approved the European Orphan Drug Regulation (EODR) in December 1999. (EU Regulation 141/2000 2000) Before the legislation was in place, there were nearly no EU-developed orphan products. (Wastfelt et al. 2006) The first 5 years of the EODR yielded 21 marketing approvals for 369 designated orphan drugs. (Haffner et al. 2008)

It is interesting to note that the field of rare diseases and orphan drugs is uniquely impacted and influenced by patient advocacy groups. Advocacy groups were central to the introduction of the ODA in the US, and these organizations remain key players in providing patient perspective on rare diseases, both to manufacturers and to the government. (Wastfelt et al 2006) Generally, close collaboration with lead users can foster high rates of innovation because it provides the developer with valuable insights about product development and user needs. (Von Hippel 1988) Two of the largest advocacy groups are the National Organization for Rare Disorders (NORD) and the Genetic Alliance. NORD is a federation of voluntary health organizations dedicated to helping people with rare orphan diseases. NORD has funded academic researchers (up to $4.5 million) who study new treatments or diagnostics for rare diseases. Researchers

then apply for larger government grants or attract a commercial sponsor for manufacturing and marketing. Genetic Alliance is a coalition of more than 600 patient organizations and lobbies for patients affected by genetic diseases. In addition to lobbying, which increases awareness and promotes legislation with the government, advocacy groups also push insurance companies and governments to provide full reimbursement of the products, despite their high unit prices. (Wastfelt et al. 2006) At first though, advocacy groups and manufacturers were adversaries, due to conflicting interests and different goals: manufacturers pursue profitable products and aim to prevail over competition, while advocacy groups push for the development of as many treatment options as possible for the patients they represent. But the manufacturers of orphan drugs eventually understood the importance and the influence of these support groups. (NORD 1999) The pharmaceutical industry benefit from advocacy groups' reach to both the scientific community and to patients needed for clinical trials, as well as their lobbying efforts with the government. Meanwhile, the support groups representing the patients need the manufacturers to develop the products. In conclusion, the progress of orphan drug development since 1983 could be credited to a strong partnership between the federal government, the pharmaceutical industry, academia, and consumer organizations. (NORD 1999) This intricate collaboration and the influence of advocacy groups demonstrate that the orphan drug market is a customer-driven market where the customer is a defined patient population.

1.4 Relevance of Orphan Drug Act for biodefense countermeasures development

The analysis comparing Project BioShield to the Orphan Drug Act will be used to understand the difficulties of developing products with limited commercial appeal. This comparison should be relevant to biodefense products because they can be designated as orphan drugs. However, additional barriers inherent to the development of biodefense products might impede the growth of the BioShield program. For example, some differences between orphan drugs and biodefense products include the fact that orphan drugs have a small but defined patient population market, while biodefense products would be sold solely to the government for stockpiling and might never be put to use. Orphan drugs have a small and defined patient population market, which can easily be tapped for clinical trials, while biodefense products are designed to counter agents that are uncommon or non-existent in nature. This means that clinical trials for biodefense products are challenging due to additional technical restrictions, less established regulatory requirements, and a non-existent patient population for clinical trials. Additionally, biodefense products cannot be tested for efficacy in humans for ethical reasons, and instead researchers have to rely on animal models that also lack an established clinical and regulatory approval pathway. Further differences and issues surrounding the development of biodefense products will be discussed in the following sections.

CHAPTER 2: EVALUATION: ISSUES SURROUNDING BIODEFENSE DRUG DEVELOPMENT

The dissertation will evaluate technical, regulatory, economic, legal, political and military factors surrounding the development of biodefense countermeasures. The goal is to understand the barriers and incentives challenging the development of such products. Before examining influences surrounding biodefense products, the barriers and incentives contributing to the development of any new drug need to be explored for further understanding.

2.1 Issues surrounding the drug development process

The development of new drugs is inherently challenging, and is impeded by technical, regulatory, economic, and legal factors.

2.1.1 Technical and regulatory

The development of a drug is a lengthy and costly process involving basic research and discovery, pre-clinical and clinical development (including clinical evaluation and manufacturing), and rigorous regulatory approval, not to mention post-marketing surveillance (Figure 1).

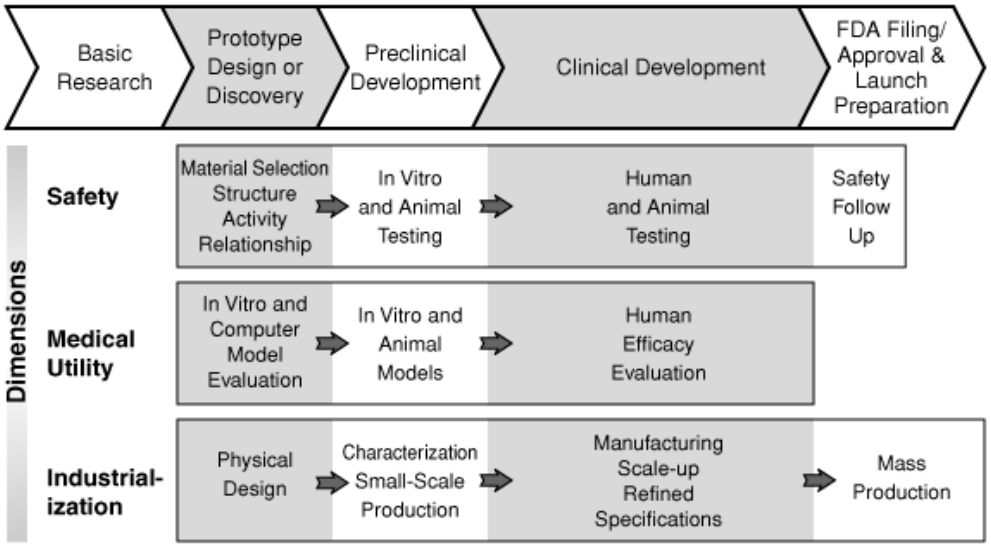


Figure 1 - Drug Development Pathway

Source: FDA 2004

When focusing on pre-clinical and clinical development, the initial step is the pre-clinical trial phase, involving the producer completing synthesis and purification of the drug and conducting limited animal testing. If the compound appears promising enough, the producer can file for an Investigational New Drug Application (IND) with the FDA. After approval of the IND, the process then involves three phases of clinical trials. In Phase 1, trials are small, typically involving twenty to eighty healthy volunteers, and last about twenty months. The purpose of Phase 1 trials is to understand the product's basic properties and safety profiles, and to identify common side effects. Some of the product's basic properties that are evaluated include absorption, distribution, metabolic effects, excretion, and toxicity of the compound. Next, Phase 2 trials are larger, typically involving hundreds to thousands of volunteers of the target population, and last about

twenty nine months. The purpose of Phase 2 trials is to gain additional information on safety and efficacy. Following this, Phase 3 trials are large-scale trials, involving thousands to tens of thousands of volunteers, and last about thirty three months. The purpose of Phase 3 trials is to measure efficacy, typically in randomized double-blind controlled trials. They can also detect common adverse events and are usually the pivotal trials for regulatory approval. (Hinman et al, 2006) Table 1, a subset of Figure 1, examines the preclinical development, clinical development, and FDA regulatory review stages. It describes the transition probabilities, failure rates, and approval rates that the product faces during its progress through each clinical stage. The transition probabilities were determined to differ slightly depending on the producer being a pharmaceutical or a biotechnology company. Pharmaceutical and biotechnology companies are differentiated by their business core. The core of a large pharmaceutical company is marketing and selling drugs. Because drugs have life cycles, this means that the companies must constantly invest in building their product pipeline. On the other hand, biotechnology companies are founded around a specific, unique, and proprietary technology. Biotechnology companies can be divided into two types: those who develop technology and sell it to pharmaceutical or other biotech companies, and those who use the technology to develop the drugs themselves. (Taunton-Rigby 2001) A biopharmaceutical company exhibits characteristics from both a pharmaceutical and a biotechnology companies, through mergers, acquisitions, collaborations, etc.

Table 1 - Drug product development time, test population, and costs

Stage	Preclinical development	Clinical development			FDA regulatory review
		Phase 1	Phase 2	Phase 3	
Length (in months)	**52**	**19.5**	**29.3**	**32.9**	**16**
Test population	Laboratory and animal studies	20–80 healthy volunteers	100–2000 patient volunteers	1,000–10,000 patient volunteers	Review process/ approval
Purpose	Assess safety, biological activity, and formulations	Determine safety and dosage	Evaluate efficacy, side effects	Evaluate efficacy, adverse reactions from long-term use	
Costs (in millions of 2005 dollars)	615	626			
Transition probabilities for biotech		83.7%	56.3%	64.2%	
Transition probabilities for pharma		71.0%	44.2%	68.5%	
Failure rate		30.8%	58.8%	21.5%	
Approval success rate		22.6%	32.7%	78.5%	

Source: Adapted from DiMasi 2001, DiMasi et al. 2003, DiMasi and Grabowski 2007, Hinman et al 2006

Once all the trials are completed and demonstrate that the product is safe and efficacious, the producer can file a New Drug Application (NDA) or Biologic License Application (BLA). An NDA is a document submitted to the FDA to request approval to market a new drug. The Biologic License Application (BLA) requests approval to market a biologic. The differences between traditional drugs and biologics are outlined in Table 2. After product launch, the FDA commonly requests post-marketing studies and follow-up studies to determine the effect of use on extended populations, or for potential side effects with other medications already in use. These additional studies are referred to as Phase 4. These large follow-up studies have become a standard requirement for products such as vaccines. (Salinski and Werble 2006)

Table 2 – Biologics vs. traditional drugs

	Biologics	Traditional drugs
Composition	Large molecules (3,000 to 5,000 atoms)	Small molecules (20 to 100 atoms)
	Interrupt disease processes to prevent disease/symptoms	Treat symptoms
	More targeted than traditional because of robust binding with specific protein sites	More restricted binding capability
Delivery	Administered via injection or infusion	Administered orally or transdermally
Manufacturing	Molecular biology, industrial fermentation	Medicinal chemistry, specially chemical synthesis
	Must be produced within living cells	Chemically synthesized
	Much more complex and costly production; 250 critical tests, facilities often required prior to approval	Typical drug manufacturing in a specially chemical plant; 40 to 50 chemical tests
Development process	97.7 months for development, 8% longer than traditional; 54 to 56% approval in Phase 3	65 to 75% approval in Phase 3
	22% success rate for FDA approval	30% success rate for FDA approval

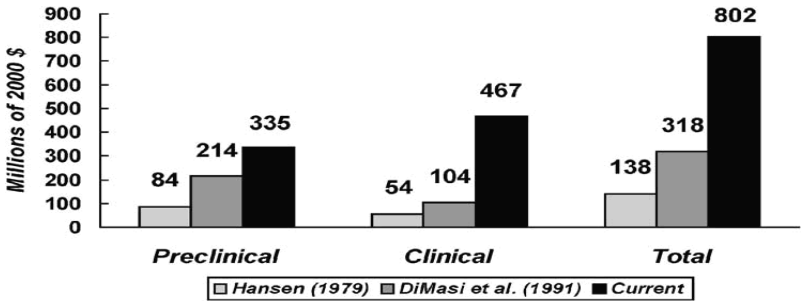
Source: Adapted from Clarke et al. 2009

Although the drug development pathway is lengthy and complicated, the FDA has developed three approaches to make drugs that treat serious diseases available as rapidly as possible: Priority Review, Accelerated Approval, and Fast Track. Priority Review reduces the time it takes the FDA to review a new drug application from a standard review time frame of ten months to a projected six months. Priority Review designations are given to drugs that offer major advances in treatment, or those that provide a treatment where no adequate therapy exists. Meanwhile, Accelerated Approval is a process that reduces the clinical trial length for drugs designed for certain serious or life-threatening diseases. Finally, the Fast Track program is designed to facilitate development and expedite the review of drugs that treat certain life-threatening or extremely serious conditions. (FDA 2010c) Not only are sponsors of Fast Track products eligible for frequent and timely interactions with the FDA, but also the product

applications are eligible for 'rolling review', which allows sections of the applications to be filed over time. Although these benefits do not affect safety or efficacy of the products, they might improve the quality of the clinical development program and marketing application, accelerate the FDA review process, and decrease the chances of commercial termination. (Reichert and Dewitz 2006)

2.1.2 Economic

The drug development process is complex and lengthy, but also costly. Costs for pre-clinical and clinical development can reach over $1.2 billion (Table 1), and seem to substantially increase over time. Figure 2 (DiMasi et al. 2003) shows total clinical costs at $138 million (from the year 2000) in 1979, $318 million in 1991, and $802 million in 2002. DiMasi et al. also approximated the total costs to increase at an annual rate of 7.4% above general price inflation. Reasons for this increasing trend include the use of more sophisticated treatments and research technologies, the treatment of more complex diseases, the demand for higher standards of safety and efficacy, difficulties enrolling patients, and the need to develop medicines for global markets. (Milne 2002)



Source: DiMasi et al. 2003

Figure 2 - Trends in preclinical, clinical, and total cost per approved new drug

On the other hand, the financial performance of the pharmaceutical industry has historically been among the highest of all industries, not only in the US but also worldwide. (Aspinall and Hamermesh 2007) This is mostly due to the industry‘s successful blockbuster drug model. The business model, developed over the last fifty years, focuses on developing and marketing drugs for as broad a patient population as possible, as opposed to developing more targeted and personalized therapies aimed at smaller subpopulations. (Aspinall and Hamermesh 2007) The model has been highly successful. In 2000, 17 drugs brought in more than $1 billion each in global sales, while 2005 saw 94 drugs meeting this threshold. (Cutler 2007) A significant factor contributing to this evolution is the aging of the population. For example, Lipitor (atorvastatin) is a mega blockbuster ($13 billion in annual sales) in part because aging baby boomers are at increasing risk for coronary disease. Additionally, increasing incomes enable people to afford not only essential medications but also “lifestyle” ones. Both trends are likely to continue, which could indicate that the industry could remain successful for years to come. (Cutler 2007) However, recent analyses suggest that the blockbuster model may not be sustainable due to technical and economic factors. First, identifying and developing new blockbuster treatments is becoming more difficult. Despite the drug industry and the federal government tripling the total R&D spending since 1990, the number of new drugs approved by the FDA has declined from an average of 33 per year during 1993–1997 to 26 during 1998–2003. (Aspinall and Hamermesh 2007) Additionally, as companies become better at discovering and producing products, more and more generic drugs are created. In the 1970s, a typical drug in a new class

enjoyed 10.2 years of market exclusivity. By the late 1990s, a new drug had only 1.2 years. (DiMasi and Paquette 2004) Generic drugs are however essential for the consumers as they keep the prices low for patients. (Cutler 2007) Finally, to further understand the blockbuster model, it might be useful to look at the most profitable types of drugs marketed by the industry. When looking at the global drug market of 2008 by sales, the top 15 drug products (Table 3) and the top 15 drug classes (Table 4) included all therapeutics. (IMS 2009)

Table 3 - Top 15 products in the world market by sales, 2008

Rank	Product	Type/Indication	Manufacturer
1	Lipitor	Lipid regulator	Pfizer
2	Plavix	Blood thinner	Bristol-Myers/Sanofi-Aventis
3	Nexium	Proton-Pump inhibitor	AstraZeneca
4	Seretide	Asthma	GlaxoSmithKline
5	Enbrel	Autoimmune	Amgen
6	Seroquel	Schizophrenia	AstraZeneca
7	Zyprexa	Schizophrenia	Eli Lilly
8	Remicade	Autoimmune	Johnson & Johnson
9	Singulair	Asthma	Merck
10	Lovenox	Anticoagulent	Sanofi-Aventis
11	Mabthera	Autoimmune, cancer	Roche
12	Takepron	Proton-Pump inhibitor	Takeda
13	Effexor	Depression	Wyeth
14	Humira	Autoimmune	Abbott
15	Avastin	Cancer	Roche

Source: IMS 2009, companies' press releases

Table 4 - Top 15 global product classes

1	Oncologics
2	Lipid Regulators
3	Respiratory Agents
4	Antidiabetics

5	Acid Pump inhibitors
6	Angiotensin II Antagonists
7	Antipsychotics
8	Antidepressants
9	Anti-epileptics
10	Autoimmune agents
11	Platelet Aggregation Inhibitors
12	HIV Antivirals
13	Erythropoietins
14	Non-narcotic analgesics
15	Narcotic analgesics

Source: IMS 2009

The blockbuster drug model has contributed to the success of the pharmaceutical industry. However as the industry is possibly headed towards a more segmented and perhaps personalized medicine, it is likely that the drug industry will change strategy.

2.1.3 Legal

The development of drug products can be discouraging for manufacturers because of potential liability. Drug companies risk substantial sums, and sometimes their whole existence, to bring products to market without any legal protection. Even when provided with legal protection, the risk remains significant, which is demonstrated by the swine flu crisis. In 1976, the death of an army recruit at Fort Dix in New Jersey was attributed to the swine flu. Experts believed that the flu threatened to turn into a pandemic. To prevent this, President Gerald Ford launched a mass national vaccination program, with Congress appropriating funds for the vaccination. Drug companies, however, raised concerns about potential liability. As a response to these concerns, on August 10, 1976,

Congress adopted a legislation (P.L. 94-380) that established the national swine flu program and provided an exclusive remedy for injury or death caused by the program. This means that lawsuits about vaccine injuries would be filed exclusively against the federal government. The manufacturers agreed to make the vaccine, and federal officials vaccinated 45 million people. However, the vaccine production encountered significant delays while the legal question was being addressed and because of unclear requirements by the government. (Begley 1977) Meanwhile, a pandemic never materialized, and about 5,700 individuals filed injury or death claims for Guillain-Barré syndrome (a rare neurological condition causing temporary muscle weakness or paralysis) and other vaccine-related injuries or deaths. These lawsuits resulted in $73 million in payouts. (Institute of Medicine 1985) The highly publicized story negatively impacted public perception about vaccines and public health announcements, and significantly damaged the vaccine production market. Another example is the National Childhood Vaccine Injury Act of 1986 (P. L. 99-660) creating the National Vaccine Injury Compensation Program (VICP) in 1986. It was created to provide an alternative compensation system for individuals injured from receiving a recommended childhood vaccine. However, the VICP does not provide liability protection for all vaccines marketed in the US, as it is generally limited to fully licensed vaccines routinely given to children, with some exceptions such as the influenza vaccine, which is also marketed to adults. Due to this, GlaxoSmithKline withdrew the Lyme disease vaccine from the market because of liability concerns. This product was not covered by VICP, and the manufacturer spent millions of dollars defending its product against claims that the vaccine caused chronic

arthritis, muscle pain, and other chronic conditions. These liability concerns, combined with limited market potential, led to the product's complete withdrawal. (Salinski and Werbler 2006)

2.2 Issues surrounding the development of biodefense countermeasures

Biodefense countermeasures development is surrounded by technical, regulatory, economic, legal, political and military factors.

2.2.1. Technical

First, developers of biodefense countermeasures face the challenge of little available information about many of these exotic pathogens. The agents are typically tropical diseases, endemic in developing countries. As such, relatively little research attention and funding has been focused on them until recently (Bolken and Hruby 2008). Biodefense products also have specific technical requirements. The type of biodefense products includes prophylactic vaccines against infectious disease agents, and therapeutics including antibiotics and antibodies for passive protection. (Hilleman 2002) Vaccines are effective at long-term protection against infections when administered before exposure to the agent, and with sufficient time for the induction of antigen-specific immunologic memory. (Valiante et al. 2003) Although vaccines can be effective for disease prevention, they are of little or no use as therapeutics. (Hilleman 2002) Vaccines

also encounter challenges such as the need to be given in advance of exposure, multiple dosing, high cost of production, and the stockpiling of vaccines that may never be used. Technically, they also have to cover different possible antigenic specificities, remain stable during storage, evoke long-term immunity, and have acceptable reactogenicity (the capacity to produce adverse reaction). (Hilleman 2002) Like vaccines, antibiotics have a long history of effective use and have the added advantage of routine use after an infection has been established. They, however, have little to no use when dealing with viruses or bacteria engineered to be antibiotic-resistant. (Valiante et al. 2003) Passive administration of antibodies may quickly provide protective antibodies to susceptible individuals from infectious diseases compared to active vaccination. Passive infusion of polyclonal or monoclonal antibody (mAb) has shown to be effective by neutralizing toxins, inflammatory molecules, or viral epitopes necessary for viral attachment or cell entry. Antibodies can also block binding to key host receptors, and facilitate clearance of bacterial infections. An added benefit to antibody therapies is that they are generally well tolerated. (Kokai-Kun and Mond 2004) MAbs represented the majority of protein candidates currently in clinical development because of their versatility as therapeutic agents (Reichert 2008), their high specificity and long half-life. They usually have little to no side effects and can synergize with antiviral and antimicrobial therapies. (Lanzavecchia et al. 2007) MAbs also recently attracted a lot of interest from the pharmaceutical industry because the regulatory pathway to establish three key features for approval - safety, efficacy and quality- is now well defined for mAbs. Additionally, physicians and patients have clearly accepted mAbs as innovative therapeutics.

Furthermore, 86% of all US-marketed mAbs were found to be indicated for cancer or immunological diseases. (Reichert 2008)

An important technical requirement is the need for biodefense products to have an extended shelf-life for stockpiling in the SNS. The expectation is a stable product with efficacy of at least three to five years and possibly longer. (Lu and Wang 2009) Since the cost of stockpiling of biodefense products is high, and the possibility of using those products is unpredictable, it is more cost-effective to stockpile products with the most extended shelf-life possible. This is a major challenge to the biodefense vaccine manufacturing process since most routine vaccines do not need to be stored for extended periods of time, and, as a result, are more often produced for use in the near future due to cost and quality control issues. (Lu and Wang 2009)

Additionally, the diseases for which biodefense products are needed occur rarely or (in the case of smallpox) never occur naturally. This means that these drugs cannot be tested for efficacy in humans for ethical reasons. The FDA established the Animal Rule in 2002 to allow efficacy to be proven in animal models (see section 2.2.2. Regulatory). These types of trials can become expensive and time-consuming, and require laboratories equipped with high levels of security and biosafety level (BSL) equipment. The availability of such containment facilities becomes more limited with the requirement of larger animals and more complex experiments, such as aerosol testing. For example, certain biological agents specifically requires BSL-4 facilities, which are available in

only a few locations in the US, such as the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), University of Texas Medical Branch Galveston, Southwest Foundation for Biomedical Research, and the CDC. Additionally, BSL-4 laboratories have limited space available to conduct animal, especially non-human primate, studies required for licensure. This limits the number and type of experiments that can be done and the statistical significance of the results. (Bolken and Hruby 2008)

Moreover, aerosol exposure is the most likely pathway of transmission for several lethal bioterrorism agents. Due to this, biodefense product development requires aerosol testing. In nature, animals are typically not exposed to aerosolized bioterrorist agents, and only a few agents (e.g. *Mycobacterium tuberculosis*, influenza) are considered obligate airborne pathogens (causing infection under natural conditions through infected aerosols deposits). Other agents, such as inhalational anthrax, are considered opportunistic, since the aerosol route is simply a means of entry into the host to cause systemic disease. (Roy et al. 2010) This means that there is little guidance from natural history for the development or characterization of animal models. (Committee 2006) During manipulations of the agents in aerobiology, specific precautions are critical to ensure safety and prevention of contamination of laboratory, equipment, and personnel. (Committee 2006) Aerobiology also requires specialized equipment, such as an aerosol generation and measurement system, an appropriate animal selection, technical capabilities, veterinary resources, and microbiological support. (Swearengen 2006) Another challenging factor of the aerobiologic experiment is the necessity to generate

reproducible exposures. This requires creating viable aerosols, exposing animals in a consistent manner, dosing appropriately, and accurately comparing results among laboratories. (Committee 2006) It is noteworthy to point out that the necessity of creating reproducible exposures in the laboratory differs from the mechanism of infection in natural cases, therefore demonstrating the complexity of extrapolating and applying laboratory data to potentially real life occurrences. Aerosol infections in nature are almost exclusively produced by the active infection of a host, which is serving as a vessel for the repeated distribution of the pathogen via the respiratory system. Microbial concentrations found in infectious bioaerosols are mainly controlled by the severity and duration of the disease. Multiple passages through many hosts can also modify the agent, either attenuating or selectively increasing virulence. (Roy et al. 2010) Finally, the development of animal models also necessitates the redesigning of the manufacturing process to match the downstream aerosol delivery equipment as well as the viability of the product due to humidity and temperature. (Lu and Wang 2009)

In summary, the development of biodefense countermeasures involves technical factors such as limited scientific knowledge, additional development requirements, specialized laboratories and equipment needs, and specialized testing.

2.2.2. Regulatory

The clinical development and approval pathway for biodefense products is complex and unproven. Since most of the pathogens are not endemic in the US and may even be

uncommon in endemic areas, it is challenging and unethical to perform human clinical trials for efficacy. The FDA recognized this challenge and created the Animal Rule. The animal rule allows such products to be approved for use in humans based on evidence of effectiveness derived only from appropriate animal studies and any additional supporting data. The Animal Rule (21 CFR Parts 314 and 601) took effect on June 30, 2002.

The rule states that in selected circumstances, when it is neither ethical nor feasible to conduct human efficacy studies, FDA may grant marketing approval based on adequate and well-controlled animal studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans. (FDA 2009b) FDA can rely on the evidence from animal studies to provide substantial evidence of effectiveness only when:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well characterized animal model for predicting the response in humans.
3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of morbidity.

4. The data or information on the (pharmaco) kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

If these criteria are met, it is reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans. In 2009, in an effort to clarify expectations, the FDA released a draft guidance on Animal Efficacy Rule (FDA 2009b). The draft guidance provides the FDA's thinking and expectations for the essential elements to support approval of products under the Rule. Essential elements identified and defined by the FDA included the characteristics of the agent that influence the disease or condition, host susceptibility and response to etiologic agent, natural history of disease (pathophysiologic comparability), trigger intervention, characterization of medical intervention, and study design considerations. The FDA also highlighted the importance of early and frequent discussion between the sponsors and FDA regarding the essential data elements for the development and evaluation of animal models.

The Animal Rule is a yet to be proven regulatory approval path for biodefense products or any novel drug, although two drugs with prior approvals have undergone this regulatory pathway: 1) pyridostigmine bromide in 2003, indicated for use after exposure to a nerve agent called Soman had prior FDA approval at a different dosage for treating myasthenia gravis; 2) hydroxocobalamin, indicated for victims of cyanide attacks as well as smoke inhalation had prior approval from France in 1996 and was already available in the US at a much lower dose. (Gronvall et al 2007)

Another important regulatory legislation is the EUA program, established by Project BioShield (P.L. 108-276). Project BioShield amended section 564 of the Food, Drug and Cosmetic (FD&C) Act creating the EUA in a provision entitled Authorization for Medical Products for Use in Emergencies. EUA permits the FDA to approve the emergency use of an unapproved medical product, or the unapproved used of an approved medical product during certain types of emergencies involving CBRN agents. Before an EUA is issued, the Secretary of HHS must declare an emergency based on the following grounds:

1. A determination by the Secretary of Homeland Security that there is a (significant potential) domestic emergency involving a heightened risk of attack with a specified CBRN agent(s);

2. A determination by the Secretary of Defense that there is a (significant potential for) military emergency involving a heightened risk to military forces of attack with a specified CBRN agent(s); or

3. A determination by the Secretary of HHS of a public health emergency under section 319 of the Public Health Service Act (PHS Act) that (has significant potential to) affect(s) national security, and that involves a specified CBRN agent(s), or a specified disease or condition that may be attributable to such agent(s).

Following the Secretary of HHS's Declaration of Emergency, the FDA commissioner may issue an EUA after consultation with the directors of the NIH and CDC after conclusion that:

1. the agent specified in the declaration of emergency can cause a serious or life-threatening disease or condition;

2. based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing: (a) the serious or life-threatening disease or condition referred to in paragraph (1); or (b) a serious or life-threatening disease or condition caused by a product authorized under section 564, or approved, cleared, or licensed under the FD&C Act or PHS Act, for diagnosing, treating, or preventing the disease or condition referred to in paragraph (1) and caused by the agent specified in the declaration of emergency;

3. the known and potential benefits outweigh the known and potential risks of the product when used to counter such disease or condition; and

4. there is no adequate, approved, and available alternative to the product for countering such disease or condition.

The first use of the EUA authority was in 2005 and exemplifies in a unique way the effective public health response to a need for large-scale use of biodefense countermeasure. The armed forces had been administering the Anthrax Vaccine Adsorbed (AVA) (later known as BioThrax), a vaccine against anthrax, since 1998, in an

effort to protect a substantial number of their members against the threat of an anthrax attack. The vaccine was licensed in 1970 but was not originally contemplated as a biowarfare or bioterrorism countermeasure. Additionally, the program had detractors and had been the subject of litigation. In late 2004, a federal court deemed use of AVA to prevent inhalation anthrax an unapproved use of an approved drug. While awaiting the decision of the court, DOD asked for an EUA to sustain military preparedness through continued vaccinations against anthrax. (Nightingale et al. 2007) After the Deputy Defense Secretary determined that there was a significant potential for a military emergency involving anthrax and requested that an EUA be issued for AVA, the HHS Secretary issued a Declaration of Emergency on January 14, 2005. On the basis of this declaration and having concluded that the criteria for issuance of an EUA were met, the FDA Commissioner, in consultation with NIH and CDC, issued an EUA for AVA on January 27, 2005. Importantly, the EUA required DOD to inform military members that they had an option to refuse the vaccine without fear of penalty under the EUA. The DOD resumed anthrax vaccinations to protect military personnel assigned to certain higher threat areas. During the period of the EUA, more than 100,000 anthrax vaccinations were given. On December 19, 2005, FDA issued a final order concluding that AVA is safe and effective for its labeled indication to protect persons at high risk for anthrax disease. This action permitted DOD to resume vaccination with AVA for its licensed indication, and an EUA was no longer required. (Nightingale et al. 2007) Additionally, the HHS Secretary issued EUAs to allow the use of certain countermeasures for the 2009 H1N1 swine influenza outbreak. (Gottron 2010)

Finally, another regulatory matter is the perception that regulatory scrutiny is higher with vaccines compared to therapeutics. The biodefense arsenal naturally will require vaccines. Because vaccines are given to healthy people, the FDA has higher regulatory expectations when it comes to health risks associated with these products. Consequently, the FDA expects much larger clinical trials, and since vaccines are typically administered in mass, the trials have to appropriately represent the broad population intended for vaccination. (Salinski and Werble 2006)

In conclusion, biodefense countermeasures encounter higher regulatory barriers because the regulatory pathway, namely the Animal Rule, is not yet proven. Vaccines more specifically are associated with higher health risks because they would be given in mass to healthy people. In case of emergency however, the EUA permits the FDA to approve the emergency use of an unapproved medical product, or the unapproved used of an approved medical product during certain types of emergencies involving CBRN agents.

2.2.3. Economic

Profits made from biodefense drugs, especially vaccines, are relatively small compared to those made from blockbuster drugs. (Kaizer 2006) Pharmaceutical companies cannot afford to make costly and lengthy investments for the development of drugs unless the companies believe there is a real and consistent market. (Lentzos 2007) Large firms are not willing to divert research from potential blockbuster drugs for chronic diseases to drugs for exotic germs like Ebola and plague, which may be stockpiled and used only in

an emergency. In addition to dealing with exotic germs, manufacturers of biodefense products have to also produce vaccines, which are inherently less profitable than therapeutics. This is demonstrated by examining the global drug market of 2008. Sales of the top 15 profitable products did not include vaccines (Table 3), and the top 15 drug classes were all therapeutics (Table 4). (IMS 2009) On a worldwide scale, vaccines contribute a small portion of the global pharmaceutical market, representing approximately 1.5 percent of all pharmaceutical revenues. However, although it is small, the vaccine market seems to be growing at a modest but steady rate. (Salinski and Werble 2006) Despite increasing incentives to manufacturers to produce bioterrorism countermeasures, the pharmaceutical industry however does not perceive the biodefense market as a long-term growth market. In 2004 at a NIH-sponsored meeting, Wyeth Executive Vice President George Siber indicated that vaccine stockpiles, even large ones for two to three hundred million doses for bioterrorism vaccines, were not an attractive commercial investment for major companies. Investors want to see growth in the company that they invest. A bioterrorism vaccine for stockpile, followed by a rotation of the stockpile, does not have potential for growth. Because of the one-time nature of the government's need in this field, the Wyeth executive stated "I don't believe we will see large industrial firms flocking to make bioterrorism vaccines." (Salinski and Werble 2006) The limited market potential for vaccine products, as measured by total revenue, is a key reason why vaccines have little appeal. This market limitation is driven by both volume and price considerations. (Salinski and Werbler 2006) Additionally, the costs of product development, particularly Phase 3 trials, are generally thought to be higher for

vaccines than for therapeutics. This is caused by the requirement of larger clinical trials to accurately represent the broad population intended for vaccination and to satisfy a higher regulatory scrutiny regarding potential side effects. (Salinski and Werble 2006) Fundamentally, the business models for biodefense development compared to venture capitalists are incompatible. (Lentzos 2007) For example, the rate of return for the industry is about thirty percent for successful biotechnology companies, compared to about nine percent for major defense contractors. When companies undertake research, they voluntarily put their capital at risk. If the rate of return for biodefense research is much less than for non-biodefense research, then the companies will most likely choose the model that is likely to return a higher profit. The biotechnology industry's business-and-investment model is based on high risk and high reward: although funding for R&D has a relatively small probability of success, it still provides a potentially large payout if it is successful. Companies that have aspirations to develop biodefense products, however, have to adapt to a business model resembling more defense contracting, with lower margins, smaller markets and with one-time product sales, rather than continuous revenue. Additionally, they face a high-risk/low-reward paradigm-where margins are limited by government pricing, but significant risks remain, including legal liability, lack of intellectual property (IP) protection, and indeterminate market size. (Lentzos 2007)

Perhaps, the most important factor influencing the development of biodefense products is the availability of funding. The market is limited and involves one sole customer. However, the government can choose, and has done so in the past, to reallocate monies

from the appropriated budget for Project BioShield (Matishak 2010, Gottron 2010). In 2004 and 2005, Congress removed approximately $25 million from the budget through rescissions included in the Consolidated Appropriations Act, 2004 (P.L. 108-199) and the Consolidated Appropriations Act, 2005 (P.L. 108-447). In 2009, Congress transferred $412 million to support countermeasure advanced research and development and pandemic influenza preparedness and response in the Omnibus Appropriations Act of 2009 (P.L. 111-8). The Consolidated Appropriations Act of 2010 (P.L. 111-117) transferred $609 million to support basic research and advanced countermeasure development. It also transferred the remaining Project BioShield funds from DHS to HHS. The Disaster Relief and Summer Jobs Act of 2010 (H.R. 4899) would rescind up to $2 billion of Project BioShield funds. For the budget of 2011, President Obama has requested the transfer of at least $476 million from this account. (Gottron 2010) All actual and proposed rescissions and transfers from 2001 to 2011 are listed in Table 5.

Table 5 - Project BioShield rescissions and transfers: 2001 to 2011 (actual and proposed)

Fiscal year	Public Law	Purpose	Amount (in $ millions)
2004	P.L. 108-199	Rescission	5
2005	P.L. 108-447	Rescission	20
2009	P.L. 111-8	Transfer for advanced development	275
		Transfer for pandemic flu preparedness	137
2010	P.L. 111-117	Transfer for advanced development	305
		Transfer for basic research	304
2011	H.R. 4899	Rescission	2000
	President's budget request	Transfer for advanced development and administration	476
		Total actual and proposed rescissions and transfers	3,522

Source: Adapted from Gottron 2010

2.2.4. Legal

Manufacturers of biodefense products face high liability concerns, especially with vaccines, which are truly challenged for efficacy and side effects when administered to healthy individuals during a mass vaccination event. Because the biodefense vaccines would be given in mass to healthy people during a crisis, this could generate higher liability risks than routine administration of fully licensed products during non-emergency times. In an attempt to alleviate liability concerns for biodefense products, the government has implemented many measures to assist health authorities in dispending biodefense medical countermeasures from the Strategic National Stockpile (SNS) during an emergency. For example, the EUA program allows FDA to authorize the use of an unapproved medical product or the unapproved use of an approved medical product during certain types of emergencies involving CBRN agents. Additionally, the Public Readiness and Emergency Preparedness (PREP) Act (P. L.109-148), enacted in 2005, addresses some of the liability concerns by providing limited immunity from tort liability for individuals and entities involved in a range of countermeasure activities, such as manufacturing, testing, development, distribution, and dispensing. The HHS Secretary may make a PREP Act declaration when he or she finds that a disease or other threat constitutes a public health emergency or that there is a credible risk of such a threat. (Binzer 2008) Under PREP Act declarations, HHS Secretary removes financial risk barriers for everyone in the "vaccination chain," (MDH 2009) therefore establishing a mechanism for compensating individuals who are injured as a result of the administration or use of countermeasures that are covered in declarations. The first declaration was

issued in January 2007 for the H5N1 Pandemic Influenza Vaccine (72 FR 4710). Additional declarations were made as part of emergency preparedness and planning efforts in order to provide targeted liability protections for biodefense countermeasures based on a credible risk of a biodefense threat. In 2008, there were PREP Act declarations for anthrax (73 FR 58239), *Botulism* (73 FR 61864), influenza pandemic (73 FR 61861), Acute Radiation Syndrome (73 FR 61866), and smallpox (73 FR 61869) countermeasures. In 2009, the PREP Act declaration was amended to include the H1N1 vaccine. (MDH 2009) Further legislation providing liability protection for some biodefense products includes the Anti-Terrorism by Fostering Effective Technologies (SAFETY) Act, which is part of the 2002 Homeland Security Act (P.L. 107-296). The SAFETY Act provides some liability protection for providers of certain anti-terrorism technologies, and provides incentives for the development and deployment of these technologies using a system of risk and litigation management.

Threats to intellectual property from the government can arise if the government needs to pressure the company for different reasons. For example, Bayer was forced to sell ciprofloxacin (Cipro), the only agent with a label indication for treatment of anthrax, at a quarter of its market price due to potential challenges by the government of Bayer's patents rights to ciprofloxacin (see section 2.2.5 Political).

In summary, producers of biodefense countermeasures face high liability risks. However, the federal government has enacted legislation to alleviate some of the liability concerns,

including the EUA, the PREP Act and the SAFETY Act. The PREP Act has been used to break down liability barriers associated with biodefense countermeasures development, deployment, and administration. This is provided that the countermeasures, such as anthrax and smallpox, are covered by the PREP Act declarations.

2.2.5 Political

The biodefense market is limited and involves one sole customer, the government. Partnerships between public-private organizations aim to share the same goal, in this case, to develop biodefense countermeasures; however, their potentially conflicting and competing interests, due to diverging scope, structure, or function can create additional obstacles. Additionally, the biodefense market is further complicated because the government is not only the customer (composed of different departments and sub-departments such as DOD, HHS and BARDA within HHS) but also the regulator, legislator, and collaborator. One of the concerns of biodefense companies is the possibility that the government will change its mind on a sale, due to shifting priorities and/or policies. For example, Hollis-Eden Pharmaceuticals, a San Diego biotechnology company, was developing a treatment for acute radiation syndrome (a blood sickness caused by a dirty bomb or nuclear explosion) by the name of Neumune and had already spent $85 million on the drug development. (Hollis 2007) The company was expecting a dose order for 12 million to 24 million people. In 2005, however, the government declared its intention of only buying 100,000 treatments. (Thompson 2006) This news highlighted the perceived fickleness of the government. In 2006, HHS reassured Hollis-

Eden that its proposal was the only one being considered and that no additional safety and efficacy data was needed. A year later, however, HHS suddenly rejected the drug deeming it "technically unacceptable" and no longer in the competitive range. This was despite the continuous endorsement by DOD for Neumune. No other justification was provided. (Hollis-Eden 2007) Following the government announcement that there would not be an order for a product like Neumune, the company's stock plunged and never recovered. Such example is demoralizing for companies that would have the inclination to develop countermeasures. Richard Hollis, then Chief Executive Officer (CEO) of Hollis-Eden Pharmaceuticals, testified multiple times before Congress criticizing Project BioShield by stating: "HHS is not implementing the BioShield legislation as Congress intended. Additionally, Project BioShield will continue to fail unless it can attract private sector participation—and that is the result of the lack of transparency, missed timelines, poor communication and the inexperience of agency representatives." (Hollis 2007) In an interview with CBS News "60 Minutes", Representative Tom Davis, committee chair of Project BioShield, stated that biodefense products will never be developed if the government fails to recognize that companies like Hollis-Eden need government funding and proper application of the incentives provided by legislation. (Schorn 2006) Hollis-Eden eventually cut its workforce, fired Richard Hollis, and the company's shares, which peaked at $33.25 in September 2003, closed at 48 cents. (Habor BioScience 2010, Hollis-Eden 2009) In February 2010, the company changed its name to Harbor BioScience. (Harbor BioScience 2010)

Additionally, the government, as a sole customer and only market for biodefense products, can put pressure on companies. For example, Bayer, Germany, was forced to make a price cut for their product Cipro during the anthrax attacks of 2001. The demand for the company's product Cipro sharply rose during the emergency. To force the company to lower the drug price, the government threatened to use an existing law to issue a compulsory purchase order suspending Bayer's patent. This would allow other companies to manufacture and sell generics of the product, offering a lower price to the government. (Shaffer 2010) Three drug manufacturers (Bristol Myers Squibb, Johnson & Johnson, and GlaxoSmithKline) offered to supply large quantities of their antibiotics free if the FDA approved their anthrax treatment. Eli Lilly and Pfizer also offered to provide drugs at cost. (Charatan 2001) The threat was credible, and Bayer lowered its already wholesale price for the drug. Although the compulsory purchase order was never issued, private companies certainly remember the lesson. (Shaffer 2010)

Additionally, due to the government's position as a monopsony (a situation where there is a single buyer and many sellers) in the biodefense drug market, private firms compete fiercely for government biodefense contracts. An example demonstrating this is the battle of Emergent to prevent two companies, VaxGen and PharmAthene, from breaking its monopoly on the supply of anthrax vaccine to DOD and HHS. Emergent produces BioThrax, the only vaccine approved by the FDA for the prevention of anthrax infection. As the sole source for the vaccine, Emergent stood to lose if more modern products by other companies were awarded contracts from the government, especially since BioThrax

was its principal source of revenue. BioThrax in the meantime encountered resistance from its main market, the military, due to the requirement of six shots over eighteen months for full immunity, adverse reactions, lawsuits and negative publicity. Due to this, the government needed to find a safer and faster alternative to the old vaccine. In 2004, the government awarded a $877 million BioShield contract to VaxGen. VaxGen's vaccine was based on the old vaccine that had been genetically re-engineered by Army scientists to render it safer and faster (three shots instead of six). (Lipton 2006) VaxGen with limited drug development experience soon encountered many problems related to formulation, stability and expertise (see section 4.1 Multiple case study 4.1.1 VaxGen). Meanwhile, Emergent intensified its lobbying pushing the government to purchase more vaccine, which was readily available as opposed to VaxGen's product (Willman 2007). From 2004 through June 2007, Emergent used 52 lobbyists at a cost of $5.29 million. VaxGen responded by spending $720,000 on six lobbyists. (Mundy 2010) On Dec. 19, 2006, HHS canceled VaxGen's contract, which resulted in VaxGen eventually laying off 90% of its workforce and terminating all development work. On May 5, 2008, VaxGen sold its anthrax vaccine candidate to its rival Emergent. (VaxGen 2008) The second time the government requested bids for an anthrax vaccine, a heated competition developed between Emergent and PharmAthene. PharmAthene had developed a second-generation recombinant protective antigen (rPA) anthrax vaccine called SparVax, which required three injections over 60 days. In 2008, PharmAthene began competing for a contract worth $600 million from BARDA to develop and sell its anthrax vaccine for the SNS. But in December, the government suddenly withdrew its contract proposal after

assessing that neither company could produce a licensed product within the required eight-year time frame. The company's stock took a tumble. (Mundy 2010) Emergent made significant political contributions and lobbying to maintain its monopoly, spending over $3 million on political lobbying in 2009 and beginning of 2010, while PharmAthene Inc. spent $ 763,000 in 2009. (Mundy 2010) On February 23, 2010, HHS (BARDA) modified its existing research and development contract with PharmAthene to provide an additional $78.4 million to advance SparVax to a stage where it will be eligible for a Project BioShield procurement contract. (PharmAthene 2010) On March 3, 2010, Emergent BioSolutions objected to the contract modification and filed a protest with the Government Accountability Office (GAO). During review of the protest, PharmAthene's development process was halted until GAO rendered a decision. GAO denied the protest in June 8, 2010, stating that some flexibility should be allowed in contracts because of "unanticipated changes due to the lack of definitiveness of the government's requirements." (GAO 2010) Emergent will retain its monopoly over the anthrax vaccine until a new one is ready. This could take years. (Mundy 2010)

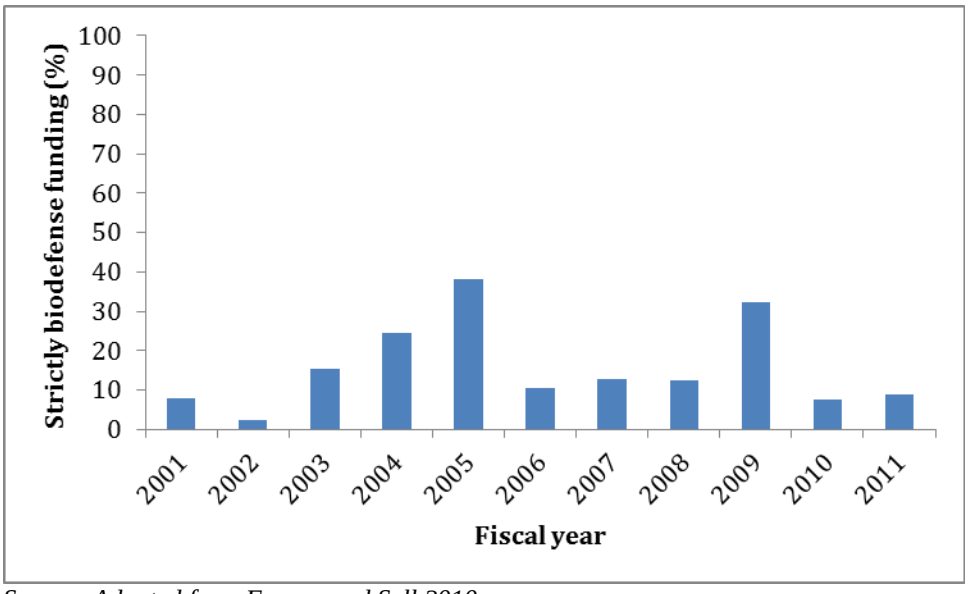
The strong political influence in biodefense product procurement is further illustrated by Emergent's lobbying force that is not only strong in dollars but also in federal ties. The lobbying roster includes former high-ranking health officials, who sometimes have close ties to the Bush administration. Two former officials with HHS, Jerome Hauer (former Acting Assistant Secretary for Office of Public Health Emergency Preparedness of HHS) and Dr. Louis Sullivan (former HHS Secretary under former President George H.W.

Bush) sit on Emergent's board of directors. (Emergent 2010a) Before being invited to sit on the board, both Hauer and Sullivan worked as paid lobbyists in an aggressive and well-connected lobbying effort to secure the BioThrax contracts. (Weisberg 2007) In their former administration posts at HHS, both Hauer and Sullivan helped oversee the SNS and were instrumental in policy development and drug procurement related to countering bioterrorism. (Weisberg 2007) Another former Bush administration official, former Federal Emergency Management Director Joe Allbaugh, joined Emergent's board in June 2006. Allbaugh had been George W. Bush's chief of staff when he was governor of Texas and was the national campaign manager for the 2000 Bush-Cheney campaign. (Weisberg 2007) Emergent's lobbying roster demonstrates the significance of political influence in the development of biodefense countermeasures.

Finally, the most important factor influencing the development of biodefense products perhaps is inadequate and inconsistent funding from the government (see Table 5 in section 2.2.3. Economic). In certain cases, some BioShield money was diverted to address more pressing threat such as the pandemic flu. Additionally, perhaps due to the economic downturn and consequently overall tighter budgets, the administration was forced to reallocate appropriated funds instead of requesting new money from Congress for non-biodefense programs. Moreover, Franco and Sell have detailed federal agency biodefense funding for fiscal years 2001 to 2011. Funding for biodefense programs for the year 2011 across the federal government was proposed to increase 4% or $271.3 above the previous year's estimates, for a total of $6.48 billion for civilian biodefense

programs. Of that total, $5.9 billion (91%) is budgeted for programs that have both biodefense and non-biodefense goals and applications. These programs are intended to address a range of public health, healthcare, national security, and international security issues in addition to biodefense. Programs with both biodefense and non-biodefense goals and applications include those that fund basic scientific research in infectious disease pathogenesis and immunology, programs to improve planning and operations related to public health preparedness, and programs to improve preparedness and response for a range of other diseases. Meanwhile, $577.9 (9%) is budgeted for programs that deal strictly with biodefense. Furthermore, over the last 11 fiscal years $11.28 billion (18%) of the $61.86 billion total in biodefense funding has gone to programs devoted solely to biodefense. (Franco and Sell 2010) Table 6 shows that from 2001 to 2011 (proposed), an inconsistent and non-significant funding has been dedicated solely to biodefense out of the total government civilian biodefense funding.

Table 6 - Percentage of strictly biodefense funding out of total government civilian biodefense fund



Source: Adapted from Franco and Sell 2010

In summary, the influence of politics over the development of biodefense countermeasures is mainly driven by the fact that the government is the sole customer and only market. This gives the customer the power to change its mind to fit its needs and shifting priorities and the power to put pressure on companies in times of crisis. Additionally, due to the government's position as a monopsony, private companies compete fiercely for government biodefense contracts. In one case, an established biodefense company, Emergent, can resort to powerful lobbying to maintain its monopoly over the market. Finally, the biodefense market is further complicated because the government is not only the customer (further divided into different departments) but also the regulator, legislator, and collaborator.

2.2.6 Military

Successful development of vaccines has been demonstrated during World War II through a synergistic collaboration between academia, the industry, and interestingly, the military. The vaccines developed during this collaboration were indicated for diseases, natural or intentional, that the military could potentially face during wartime. Hoyt points out that the participation of the military significantly contributed to the innovation of vaccines during the war because the military is the lead user of vaccine technologies. Generally, close collaboration with lead users can foster high rates of innovation because it provides the developer with valuable insights about product development and user needs. (Von Hippel 1988) Additionally, the participation of entire military units made clinical trials more controlled and designated than those with volunteers. (Hoyt 2006) Furthermore, military scientists and physicians had extensive experience with communicable disease and thus, could provide clear direction on research objectives and development needs. They also had the advantage over their academic counterparts, as they typically shared the industry's product development path. They could bridge the gap between early- and late-stage development by developing vaccine candidates that would later be scaled-up for large-scale testing and licensing by industrial engineers and scientists. The military-academic-industrial teams overcame hurdles of the vaccine development process because they worked together. (Hoyt 2006) Another important factor to vaccine innovation is the spirit of collaboration in the face of a crisis. During World War II, many of the ideological and practical barriers to closer collaboration between academia, the industry, and the military subsided under threat of war. Industry opposition to low-margin

contracts, academic opposition to disrupted research and teaching schedules, and government and military opposition to a technocratic reorganization of the federal research and development system were lowered under a common threat. (Hoyt 2006) Additionally, selecting the appropriate management structure was essential in ensuring the success of the development project. In the successful examples of the development of the pneumococcal and influenza vaccines, a top-down management structure eliminated intervening layers of bureaucracy and contributed to speed and efficiency by rapidly integrating and applying existing knowledge to vaccine production. This also ensured that research objectives met military needs, and in some cases in fact, research and military objectives were so well coordinated that some vaccines were developed for specific missions. However, the top-down management was sometimes inappropriate for other projects with a different requirement profile. For example, the anthrax vaccine program lacked a clear and basic understanding of the disease and the organism, as well as development needs. Under a top-down management structure, the program failed. Because of the lack of basic knowledge, the program yielded to a less efficient but more flexible bottom-up decision-making processes and investigator-initiated structure, which is characteristic of basic research programs. Finally, it is important to note that despite the proven safety and efficacy of the successful vaccines that came out of WWII development programs, many of them were commercial failures. The military often encouraged industry to develop vaccines well before commercial markets could support the industry participation and the US market needs never caught up with military needs. (Hoyt 2006)

Three examples of collaboration between the industry and the military are discussed in this dissertation: 1) VaxGen's genetically modified anthrax vaccine by army engineers (see section 4.1 Multiple case study 4.1.1 VaxGen) that was taken over by Emergent BioSolutions after VaxGen failed BioShield contract; 2) Emergent BioSolutions' narrow and prolific relationship with the military through the anthrax vaccine program (see section 4.1 Multiple case study 4.1.2 Emergent BioSolutions); and 3) Cangene's anthrax therapeutic created with the support of the military (see section 4.1 Multiple case study 4.1.4 Cangene). Another relevant example is Elusys Therapeutics and USAMRIID. Both partners are performing collaborative research under a Cooperative Research and Development Agreement (CRDA) to develop therapeutics against anthrax and other unspecified biowarfare agents, using Elusys' Heteropolymer Antibody technology. The technology chemically joins two antibodies together and has the ability to rapidly remove the pathogen from the blood, potentially reducing the high mortality rate of bloodstream infections. CRDA is designated under the Federal Technology Transfer Act of 1986 (P.L. 99-502) and promotes technology transfer by authorizing government-operated laboratories to enter into cooperative research agreements with a private company. The private partner agrees to provide funds, personnel, services, facilities, equipment or other resources while the federal government provides similar resources, but not funds, directly to the partner. CRDA also allows flexibility in patenting and patent licensing between the government and the collaborating partner. Elusys' work in biodefense in collaboration with USAMRIID began in 2000 with the anthrax therapeutic, Anthim.

With funding from the DOD and NIH for both Anthim and the Heteropolymer Antibody technology, Elusys has since advanced Anthim into clinical development and the company hopes to obtain a contract under Project BioShield. The Heteropolymer Antibody technology offers interesting prospects for more biodefense applications because it is a new approach for the treatment of antibiotic resistant infections. The technology platform uses immune system mechanisms to clear pathogens and provide a means to develop novel drug candidates targeted against bacterial, viral and fungal infections. (Elusys 2006)

In summary, the collaboration between military and the industry has yielded some inspiring stories in biodefense countermeasures development. The success of some of WW II vaccine development programs was achieved when it was possible to consolidate and apply existing knowledge to a set of clearly defined and prioritized development objectives. Because of its role as lead users and also with the interdisciplinary knowledge of its military research scientists, the military contributed valuable insights about product development, about user needs. Additionally, they provided more controlled and designated clinical trials, and could bridge the gap between early and late stage of vaccine development. Barriers to developing vaccines to well-understood diseases were therefore not scientific but organizational in nature and were best overcome by the coordination provided by targeted research and development programs. On the other hand, the collaboration between Elusys and USAMRIID through a CRDA demonstrates that joining forces and investing in not just a product but also a

technological platform could not only yield a potential countermeasure for the SNS, but also a technological platform that can be applied to more biodefense and possibly non-biodefense applications.

2.3 Summary

The environment surrounding the drug development process includes technical, regulatory, economic and legal features (Table 7). Additional technical, regulatory, economic, legal, political, and military aspects contribute to the development of biodefense countermeasures.

Table 7 - Qualitative analysis summary: Environment surrounding new drug and biodefense products

	Drug product process development	Biodefense product process development
Technical	Complex and lengthy	More complex and requires novel approaches
Regulatory	Complex and lengthy	Non-established pathway
Economic	Costly but potentially large pay-off	Little to no market
Legal	Some liability protection	Some liability protection
Political	N/A	Single customer
Military	N/A	Lead users and important contributors

CHAPTER 3: COMPARISON BETWEEN PROJECT BIOSHIELD AND ORPHAN DRUG ACT

The quantitative comparison section evaluates the history of ODA and Project BioShield. Twenty six years (from 1983 to 2009) of orphan drugs development history using data were obtained from the FDA's Orphan Drug Product designation database (FDA 2010b) in order to understand the factors behind the success of the ODA. The BioShield law was enacted in 2004 and the program has contributed seven years' worth of analysis (up to 2010) for this dissertation. Factors such as type of products, type of companies, and impact of the act on regulatory approval were evaluated to determine the contribution of the legislation to the successful development of products with limited commercial appeal.

3.1 Product type

Orphan drugs and BioShield drugs were divided into prophylactics (vaccines), therapeutics (antibiotics, antiviral drugs, and antibodies), diagnostics, or other types of products. It is important to note that some products can have multiple indications (both prophylactic and therapeutics), and this analysis only used the main indication for evaluation. The majority of BioShield drugs and orphan products are therapeutics. Vaccines make up about 33% of BioShield products and about 8% of orphan drugs

(designations and approvals) (See Table 8). Approval of a product under Project BioShield has not yet occurred.

Table 8 - Product type for Orphan Drug designations and approvals, and for BioShield products

Product type	Orphan designations		Orphan approvals		BioShield products	
	Number	%	Number	%	Number	%
Therapeutics	1882	*90*	302	*89*	6	*67*
Prophylactics	159	*8*	26	*8*	3	*33*
Diagnostics	42	*2*	11	*3*	0	*0*
Other	14	*1*	1	*0*	0	*0*
Total	2097	*100*	340	*100*	9	*100*

Source: Compiled data obtained from FDA 2010 and Gottron 2010

3.1.1 Product type of BioShield products

Biodefense countermeasures can be divided into two main categories: prophylactic (vaccines), and therapeutics (antibiotics, antiviral drugs, and antibodies for passive protection). (Hilleman 2002) The majority of BioShield products (Table 8) are therapeutics (67%), while the remaining products are vaccines (33%). Out of the therapeutics, the most common products were antibodies therapeutics (~33%) (Table 9). Interestingly, two of the antibodies have obtained orphan designation. Meanwhile, although vaccines make up a minority of biodefense countermeasures, they still contribute to a significantly higher percentage than observed in orphan drugs (8%). Compared to all new drugs, a Tufts Center for the Study of Drug Development study (Reichert 2006) determined that a total of fifteen new vaccines were approved during 1996–2005, which represents less than one-quarter of the number of new drugs approved in the same period. The Tufts study also determined that only four of the fifteen vaccines were indicated for a previously unmet medical need. The remaining eleven vaccines

were approved for prevention of influenza and childhood illnesses. The study stated that the scarcity in the vaccine market is due to little market appeal and few incentives to develop new or innovative vaccines. Additionally, Table 3 and Table 4 demonstrate that vaccines were not amongst the most profitable drugs or drug classes globally, by sales in 2008. Vaccines also have additional technical, economical, regulatory, and legal matters (see section 2.2 Issues surrounding the development of biodefense countermeasures). Due to this, it is possible that biodefense vaccines have more barriers to overcome.

Table 9 - Project BioShield contracts

Company	Product	Type	Orphan designation	Contract status
VaxGen	rPA vaccine	Recombinant Protective Antigen Vaccine	No	Cancelled 19-Dec-06
Emergent BioSolutions	BioThrax	Anthrax Vaccine Adsorbed	No	Prior approval
Human Genome Sciences	Raxibacumab	(Human) Monoclonal antibody therapeutics	Yes 11/12/2003	Complete response
Cangene Corp.	Anthrax Immune Globulin	Polyclonal antibody therapeutics (derived from plasma)	Yes 7/29/2008	Animal Rule studies
Bavarian Nordic A/S	Imvamune	Vaccine, based on a live non-replicating strain of virus.	No	Phase 3 in 2011
Cangene Corp.	Botulinum Antitoxin Heptavalent	Heptavalent botulism antitoxin (antibodies)	No	Phase 2
Fleming Pharmaceuticals	ThyroShield (liquid Potassium Iodide)	Thyroid blocking therapeutics	No[1]	Prior approval
Akorn, Inc.	Ca-DTPA	Anti-radiation therapeutics	No	Prior approval
	Zn-DTPA	Anti-radiation therapeutics	No	

Source: Companies' press releases and public documents

1. *Orphan Designation for pediatric use on 11/17/2004, and approval on 1/12/2005. No exclusivity granted. (FDA 2010)*

Table 10 shows the pipeline for anthrax countermeasures funded by the government as a whole, including HHS, National Institute of Allergy and Infectious Diseases (NIAID), and DOD. The evaluation was performed to complement the analysis of BioShield products. The pipeline is composed of early development products, and most of them

include therapeutics, and more specifically antibodies. Interestingly, all anthrax antibodies have obtained orphan designations.

Table 10 – Federal anthrax countermeasures contracts

Company	Product	Orphan drug status	Cost ($ million)	Government contract	Contract status
VaxGen, Inc.	rPA vaccine, recombinant protective antigen	No	878	BARDA (BioShield)	Cancelled 19-Dec-06
Emergent BioSolutions	BioThrax, Anthrax Vaccine Adsorbed	N/A	690	BARDA (BioShield)	Prior approval
Human Genome Sciences	Raxibacumab, anti-toxin human mAb_1	11/12/2003	315	BARDA (BioShield)	Complete response
Cangene	AIG, anti-toxin polyclonal antibody, derived from $plasma_1$	7/29/2008	144	BARDA (BioShield)	Phase 3
Emergent BioSolutions	AV-7909, BioThrax combined with VaxImmune	N/A	448	BARDA and NIAID	Phase 2
Emergent BioSolutions	rPA vaccine, recombinant protective antigen	NA	187	BARDA and NIAID	Phase 2
Emergent BioSolutions	AVP-21D9, human anthrax mAb_1	11/04/2010	24	BARDA and NIAID	Phase 1
Emergent BioSolutions	Anthrivig or AIG, polyclonal anthrax immunoglobulin (antibody)	9/3/2009	13	BARDA and NIAID	Phase 2
Elusys Therapeutics	Anthim, prophylactic and therapeutic anti-toxin mAb_1	6/9/2006	143	DOD, NIH and BARDA	Phase 1
PharmAthene	SparVax, recombinant protective antigen (vaccine)	N/A	4	NIAID and BARDA	Phase 2
Medarex (Bristol-Myers Squibb and PharmAthene)	Valortim, prophylactic and therapeutic anti-toxin mAb_1	2/16/2006	1	DOD, NIAID, and BARDA	Phase 1
Advanced Life Sciences	Restanzam, antibiotic	N/A	4	DOD	Preclinical

Source: Shaffer 2010, Center for Biosecurity 2007, and companies' press releases

1. *Fast-track*

This analysis shows that BioShield products are mostly therapeutics (66%), with a significant remainder of vaccines (33%). Vaccines can encounter more barriers to development than therapeutics. Most therapeutics under BioShield and under contract with another branch of the federal government are antibodies. Interestingly, all anthrax antibodies, whether under Project BioShield or under contract with another branch of the federal government, received designation under the Orphan Drug Act.

3.1.2 Product type of orphan drugs

Table 8 shows that the majority of orphan designations are therapeutics (90%). Analyses by the Office of Orphan Products Development at the FDA show that the two largest types of products are indicated for rare forms of cancer, such as ovarian cancer or hairy-cell leukemia, and for metabolic disorders, which account for 31% and 11% of all orphan drugs, respectively. (Haffner et al. 2002) The most common approvals, in decreasing order, were given to products for cancer, metabolic disorders, infectious diseases, neurologic disorders, hematologic disorders, pulmonary diseases, and poisoning. (Haffner 2006) Similarly, the significant percentage of orphan drugs being indicated for cancer is reflected in Table 4, which demonstrates that oncology products were among the top 15 global therapeutic classes by sales in 2008 (Haffner et al. 2002).

The success of ODA is perhaps driven by the fact that development of novel therapeutic approaches for rare diseases can sometimes be applicable for the treatment of more common diseases (Wastfelt et al. 2006) and vice-versa. This has proven true for large therapeutics areas such as cancer, where a profitable strategy is to acquire approvals for multiple related orphan and non-orphan indications. One example is Gleevec from Novartis, which was a kinase-targeting drug originally approved for chronic myelogenous leukemia under orphan designation. A year later, Novartis received another orphan drug approval for gastrointestinal stromal tumors. The company continued its efforts to gain approvals for multiple orphan indications. Gleevec, a blockbuster drug with more than $2.5 billion in revenues, is projected to grow at a rate of 10–12%

generating more than $4 billion in sales by 2011. (Ariyanchira 2008) Gleevec has marketing approvals for seven orphan indications and 10 indications overall. (Novartis 2009) Another example is Epogen produced by Amgen. Epogen was originally granted orphan status and approved to treat anemia caused by kidney failure and anemia associated with HIV. Later, the product was approved for anemia caused by chemotherapy, a large and lucrative market. (Conway 2010) The product had sales over $2.5 billion in 2009, mainly from its non-orphan cancer indication. (Amgen 2010, Conway 2010) In both examples, Novartis and Amgen benefited from the initial orphan indication for their product, as it was a launching platform for more orphan and non-orphan indications, which created a potentially lucrative return for the company. This indicates that the ODA can have an important benefit in promoting multiple indications for both orphan but also more common diseases.

ODA incentives advanced approaches for developing products for rare diseases that can be applied to more common and potentially profitable diseases, such as indications for cancer, and vice versa. This characteristic of the ODA, in addition to incentivizing the market of orphan drugs, most likely contributed to the act's success and the profitability of some of its products. This aspect perhaps is not completely relevant to BioShield products because the type of product - cancer-related drugs - that makes possible the success of the ODA is not a disease covered by BioShield. However, the principle of generating broader applications can be used to promote the success of BioShield. Finally, it is interesting to note that all anthrax antibodies under BioShield or another

federal program have orphan status. This is probably due to antibodies' demonstrated success as orphan and non-orphan drugs thanks to their defined structure, interactions, and regulatory pathway. Perhaps the most direct way of applying a successful aspect of ODA is to apply ODA benefits to all BioShield products.

3.2 Company type

This section evaluates the type of companies pursuing the development of BioShield drugs or orphan products. The type of companies pursuing either product could have an impact on the product development process, regulatory approval, and market definition.

3.2.1 BioShield companies

All of the products currently under BioShield contract are held by small to mid-sized biopharmaceutical or biotech companies (Table 11). The size of companies under Project BioShield in Table 11 was determined according to the standards stated by Dev Pradhuman (2000) as follows:

1) Small-sized companies have a market capitalization of under $1.5 billion.
2) Mid-sized companies have a market capitalization of under $4.5 billion.
3) Large-sized companies have a market capitalization of over $4.5 billion.

Table 11 – Profile of companies with BioShield contracts

Company	Market capitalization (in $ millions)	Employees
Emergent BioSolutions	489	> 600
Human Genome Sciences	4640	> 800
Cangene	347	~ 800

Bavarian Nordic A/S	2519	> 400
Fleming Pharmaceuticals	Privately held	< 100
Akorn, Inc.	309	> 300

Source: Companies' press releases, Yahoo Finance, Bloomberg. Market capitalization obtained through Yahoo Finance as of June 2010

All of the companies are small to mid-sized companies, according to the standards described above, except for Human Genome Sciences (HGS) and Fleming & Company. HGS has a market capitalization of around $4.5 billion, but since it does not have products marketed or approved as of February 2011, it is also considered as small to mid-sized company. Fleming Pharmaceuticals is a privately held company and therefore does not disclose financial results. However, examining a company's staff size can provide some important clues in terms of company type and situation. Fleming is categorized as being a small-sized company since it employs less than a hundred individuals.

The absence of large companies in this analysis can be explained by understanding the type of product and expected profit margin required for biodefense development. As seen in Section 3.1.1 Product type of BioShield products, a significant number of those products are vaccines. The technical complexities of producing vaccines, in addition to the challenges of large-scale manufacturing, require both specialized facilities and highly trained personnel. Consequently, only a limited number of companies, with the necessary capital and expertise, have the capabilities to produce vaccines. Although 11 manufacturers now hold vaccine product licenses, only four large pharmaceuticals produce the majority of vaccines: Sanofi Aventis, GlaxoSmithKline, Merck, and Wyeth.

(Salinski and Webler 2006) Whether developing vaccines or therapeutics, large pharmaceutical companies typically have the resources but are less willing to invest in smaller profit-margin products since they are restricted by their responsibility to shareholders. They also usually have much more profitable options available and the opportunity costs of engaging in biodefense activities are considered too high for large biopharmaceutical companies. Small biotech companies seem more willing than large pharmaceutical companies to invest in innovative and risky projects since such companies are usually financed by a group of risk-taking investors and venture capitalists. (Villa et al. 2008) However, they have to heavily rely on government funding. Additionally, their limited experience in advanced development, licensing and producing can contribute to a higher risk of failure.

Large pharma companies have the necessary resources to develop drugs such as biodefense countermeasures, but they are less willing to invest in potentially less profitable products with no to little market. Consequently, the biodefense industry is made up of several small biotechnology firms and depends on continued government funding to maintain an active biodefense research and development program.

3.2.2 Orphan drug companies

Almost 1000 companies hold at least one orphan designation and over 150 companies have received FDA have received FDA marketing approval for at least one orphan drug (data not shown) (FDA 2010). It is (FDA 2010). It is important to note that I have taken into account to the best of my knowledge all mergers up to knowledge all mergers up to August 2010. The 10 companies that received the most orphan designations were

orphan designations were all large pharma and biopharma companies holding between 22 to 62 designations to 62 designations (Table 12). The 10 companies that received the most orphan drug approvals included most of the same major companies in Table 12 with 7 to 19 orphan drug approvals (

Table 13). None of the top companies discussed above have pursued a BioShield contract.

Table 12 - Top 10 companies holding the most designated orphan drugs

Company	Type of company	Designated orphan products
Roche Group	2	62
GlaxoSmithKline	1	40
Novartis	1	39
Pfizer	1	37
Merck	1, 2	32
Amgen	2	30
AstraZeneca	1	27
Genzyme	2	25
Bayer	1	22
Bristol-Myers Squibb	1	22

1. Top 20 pharmaceutical companies based on 2009 revenues. (Roth 2010)
2. Top 10 biopharmaceutical companies based on 2009 revenues. (Roth 2010)
Source: Derived from data provided by FDA 2010

Table 13 - Top 10 companies holding the most approved orphan drugs

Contact company	Type of company	Approved orphan drugs
Novartis	1	19
GlaxoSmithKline	1	18
Roche Group	2	15
Amgen	2	14
Pfizer	1	11
Bayer	1	9
Genzyme	2	9
Bristol-Myers Squibb	1	8
Novo Nordisk	2	7
Merck	1, 2	7

1. Top 20 pharmaceutical companies based on 2009 revenues. (Roth 2010)
2. Top 10 biopharmaceutical companies based on 2009 revenues. (Roth 2010)
Source: Derived from data provided by FDA 2010

Large pharma companies account for 53% of the orphan drug market, while biotech companies account for 37%, with the rest comprising of small- to mid-sized companies (Figure 3). (Ariyanchira 2008) Large pharma companies are probably active in the orphan drug market because they usually enter the picture once the drug had already passed the discovery and early development stages. Actually academia and biotech companies are typically the main players during the early stages. (Ariyanchira 2008) Both lists of top 10 companies also show a dominance of large pharma over biotech companies. However, some large pharma companies held a high position on the lists after acquiring biotech companies with a strong history in orphan drug development. Large companies often choose to acquire or collaborate with biotech companies rather than start a new drug development program targeting an orphan disease. This strategy has provided needed funding to biotech companies. (Ariyanchira 2008) For example, AstraZeneca, a large pharma company, is shown in Table 12 to hold 27 designations. However, before acquiring MedImmune, a large biotech company, AstraZeneca held five designations and no approvals. MedImmune complemented AstraZeneca's pipeline with 22 orphan designations and five approvals. Large pharma companies such as Novartis, Eli Lilly, Pfizer, and GlaxoSmithKline have also specifically invested in active orphan drug development programs. For example, GlaxoSmithKline launched a dedicated unit specializing in orphan drug research in February 2010. (Ariyanchira 2010) Small biotech companies have always and first supported the development of orphan drugs. Several biotech companies such as Genentech (now part of Roche Group), Amgen, and Genzyme, stepped into the market and blossomed into large companies with an orphan

drug as their first approved product. (Haffner et al., 2002) In fact, Genzyme specializes in rare diseases, and 48% of the company's 2007 revenues were estimated to come from rare diseases. (Senior 2007) Meanwhile, Genentech was actually the first biotech company to enter the market with its growth hormone products, Protropin and Nutropin, in 1985. (Ariyanchira 2008) All three big biotech companies can be found in both lists of the top 10 companies to hold orphan drug designations and approvals.

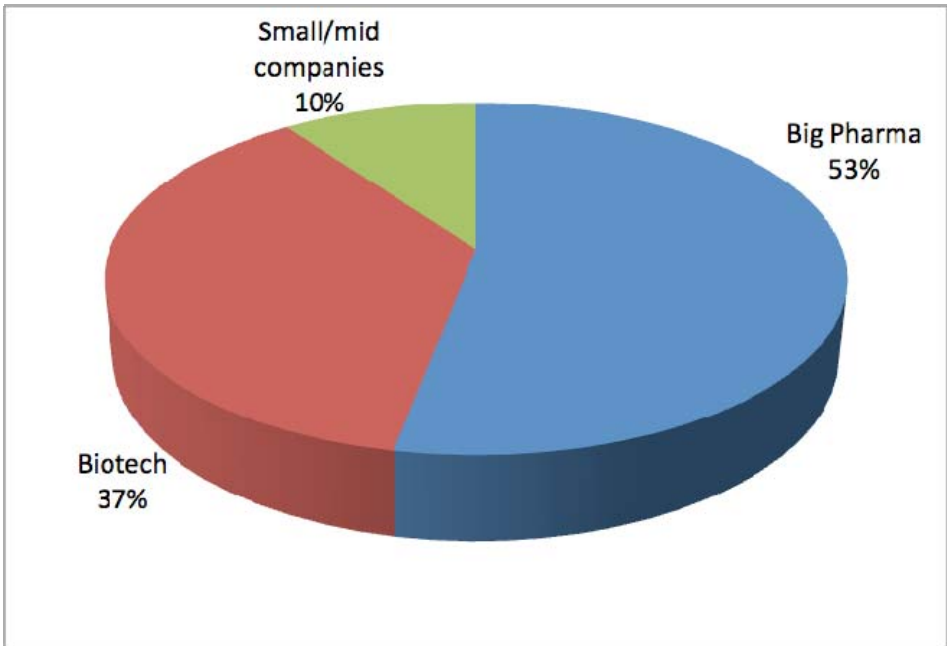


Figure 3 - Type of companies within orphan drug market

Large pharma companies constitute a main player in the market of orphan drugs through mergers with smaller biotech companies or through investments in the later stages of orphan drugs development. This successful aspect of ODA is not applicable to BioShield products because they are still in the early years of history and/or in early stages of

development. However, as discussed in section 1.3.2 Impact and influences of the Orphan Drug Act, the success of orphan drugs is significantly impacted by the support of advocacy groups, a critical yet understated player in the orphan drug market. Although advocacy groups lack in hands-on capacity such as research and manufacturing, they can provide access to clinical and commercial patients, potential collaborators, resources and lobbying. This link in the orphan drug model is critical to the ODA success and can be applied to the biodefense drug model. Parallel to this, a critical but understated partner in the biodefense drug model is the military, as discussed in section 2.2 Issues surrounding the development of biodefense countermeasures 2.2.6 Military.

3.3 Impact on Regulatory Approval

This section analyzes the impact of each act on the regulatory approval process based on three criteria: approval rate, trend in approval/designation, and clinical and approval times

3.3.4 Approvals under Project BioShield

Approval under BioShield has not taken place yet, although HGS has submitted a BLA in May 2009. The FDA delivered a complete response after about seven months of regulatory review and follow-up is expected soon. When evaluating all BioShield products, there were four out of nine total products that received approval (Table 14). However, all four products were already approved before being awarded a BioShield contract. The remaining BioShield products are in Phase 2/Phase 3 of clinical trials.

When evaluating only biological BioShield products, there is only one approved product out of six. However, that product (BioThrax) was also already approved before receiving a BioShield contract. Because of the small sample size under Project BioShield, other anthrax countermeasures in development with the government beyond HHS were examined. Most products were in pre-clinical development, Phase 1 and Phase 2 (Table 10). Few of those products will likely reach the market within the next few years. Because no approval has yet occurred under Project BioShield, it is too early to determine the impact of Project BioShield on regulatory approval. Finally, Figure 4 shows that a surge of contract awards, including follow-on order awards, occurred in 2006, while the remaining years saw only or two awards per year. The small number of awards after the surge in 2006 might coincide with the discouraging and messy contract cancellation of the first and largest BioShield award to VaxGen for the development of an anthrax vaccine on December 19, 2006.

Table 14 – Project BioShield contracts within HHS: milestones and progress

Company	Product	Award date	First delivery	Delivery to SNS	Contract status	Doses[2]	Cost (in $ millions)
VaxGen	rPA vaccine	11/04/04	N/A	N/A	Cancelled 19-Dec-06	75,000	878
Emergent BioSolutions	BioThrax	05/04/05 05/04/06 09/25/07 10/01/08[1]	Before BioShield	02/12/06, 02/22/07 ongoing	Approved before BioShield	48,250	1220[1]
Human Genome Sciences	Raxibacumab	06/19/06 07/29/09	02/09	ongoing	BLA: Complete Response	65	315
Cangene	Anthrax Immune Globulin	07/27/06	08/07	ongoing	Animal Rule Studies	10	144
Bavarian Nordic A/S	Imvamune	06/24/07	07/10	ongoing	Phase 3 in 2011	20,000	505

Company	Product	Award date	First delivery	Delivery to SNS	Contract status	Doses[2]	Cost (in $ millions)
Cangene Corp.	Botulinum Antitoxin Heptavalent	06/01/06	09/07	ongoing	Phase 2	200	416
Fleming Pharmaceuticals	ThyroShield	03/17/05 02/08/06	03/05	09/05 07/07	Approved before BioShield	4,800	18
Akorn, Inc.	Ca-DTPA	12/30/06 04/13/06	04/06	04/06	Approved before BioShield	395	22
	Zn-DTPA		04/06			800	22

Source: Companies' press releases

1. *According to Gottron 2010, the last contract awarded by HHS to Emergent on October, 1, 2008 amounting to $405 million contract for 14.5 million doses of BioThrax was funded by the CDC funds rather than the Project BioShield special reserve fund.*
2. *Doses in thousands*

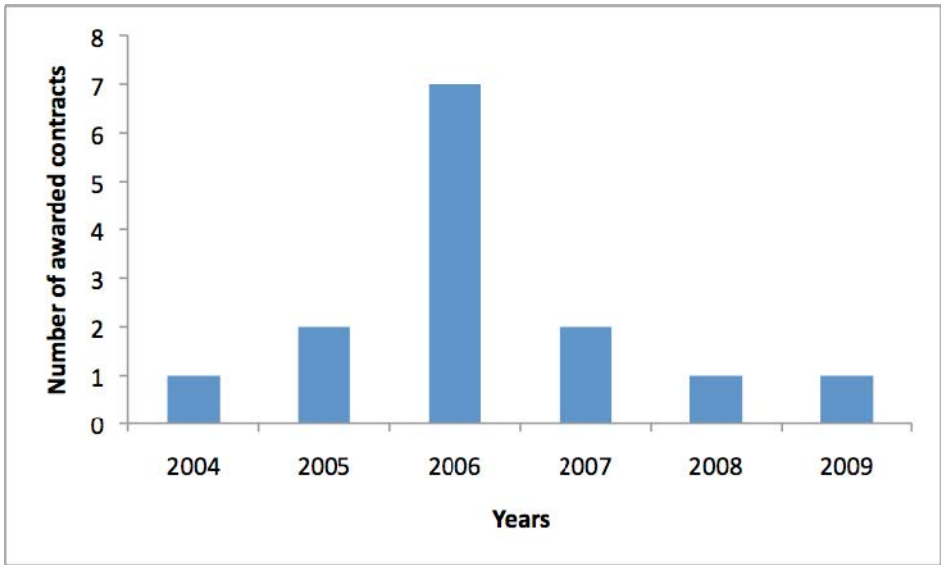


Figure 4 - BioShield contract awards

3.3.2 Approvals under Orphan Drug Act

Between 1983 and 2009, the Orphan Drug Act led to the approval of 346 orphan drugs out of 2112 designations, yielding a 16.4% approval rate (FDA 2010b). This compares to a 21.5% probability of success for drugs entering clinical trials in the 1980s and 1990s.

(DiMasi et al. 2002) This indicates that an orphan drug designation does not contribute to increased chances for regulatory approval.

Figure 5 compares the number of orphan designations vs. the number of orphan approvals from 1983 to 2009. (FDA 2010b) Products that had prior approvals before designation were removed from analysis. A visible upward trend indicates more designations being submitted over time, while the number of approvals remains consistent (with a slight increase). This suggests that either the FDA might have limited resources, therefore approving a finite range of products per year, or manufacturers adopted the strategy of designating products with existing approvals for new indications, as opposed to developing novel orphan drugs from start to finish and submitting them for approval. Finally, this could also suggest that the ODA stimulated designations of orphan drugs. The statistical significance (R-squared, or how likely the correlations may be due to chance in the form of random sampling error) of this increasing trend was about 66% for designations, and 44% for slightly increasing but consistent number of approvals (See Figure 5). Although this indicates that the ODA might stimulate more orphan designations, it does not seem to contribute to increased chances for regulatory approval.

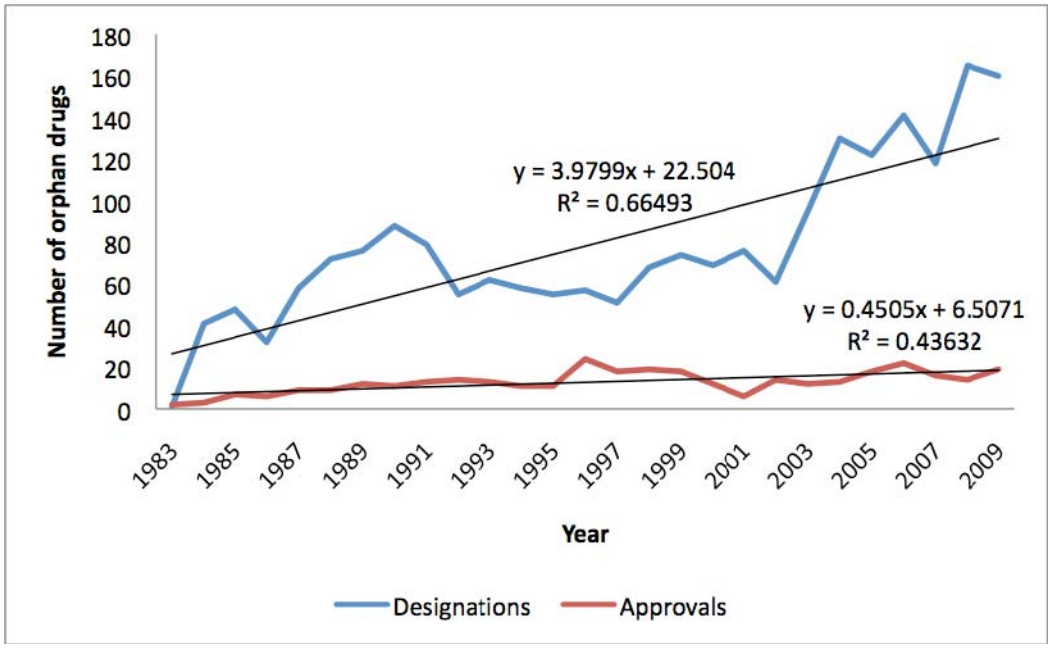


Figure 5 - Orphan designations and approvals over years

Next, results form a Tufts study (Milne 2002) are examined to determine how the clinical and approval times seen in orphan drugs compare to non-orphan drugs. Table 15 shows mean and median times of orphan vs. non-orphan drugs for clinical and approval phases, regardless of designation time, between 1994 and 2001. The results suggest a shorter approval phase for non-orphan drugs, whether in standard or priority review. However, the total development phase for orphan drugs is generally shorter due to a shorter clinical phase. According to Milne, clinical time for orphan drugs is shorter due to the facilitation of patient recruitment through active advocacy groups, close relationships between specialist doctors and patients, and by a strong market demand due to the scarcity or non-existence of a treatment. This study, however, indicates that an orphan drug designation does not seem to improve the chances for regulatory approval times.

Table 15 - Development times for orphan versus non-orphan drugs approved by FDA (1994 - 2001)

		Standard review		Priority review	
	In years	Orphan (n = 6)	Non-orphan (n = 19)	Orphan (n = 13)	Non-orphan (n = 7)
Clinical phase	Mean	3.8	5.1	5.7	5.5
	Median	3.7	4.8	5.4	6.2
Approval phase	Mean	2.3	1.8	1.0	0.7
	Median	2.3	1.5	0.9	0.5
Total development	Mean	6.1	6.9	6.7	6.1
	Median	5.3	6.4	6.5	6.8

Source: Adapted from Milne 2002

In conclusion, three analyses were made to determine the impact of orphan designation on regulatory approval: 1) comparison of the approval rate of orphan (16.4%) vs. non-orphan drugs (21.5%); 2) comparison of the number of orphan designations (increasing) vs. approvals (slightly increasing to constant); and 3) (non-superior) comparison of approval times of orphan vs. non-orphan drugs. These results indicate that although the ODA did not seem to improve the chances for regulatory approval, it did stimulate the development of orphan drugs, as seen by the increase of designations. This is probably fostered by close FDA counseling and advice in obtaining designation and developing orphan drugs. A similar approach for BioShield contracts might generate more sustained interest for the industry to develop biodefense countermeasures. This aspect is however limited by the fact that an orphan designation and a BioShield contract are awarded in very different manners: an orphan designation is obtained when an application is submitted and approved; meanwhile, in order for a sponsor to obtain a BioShield contract, the HHS must first issue a request for proposal, then choose to select a company out of many competitors or can choose to retract its request. The full and open

competition also adds another layer of complexity and uncertainty as variables such as pricing, doses and criteria for acceptable product have to be defined. This additional barrier of full and open competition can be lowered if simplified acquisition procedures are favored instead.

3.4 Summary

The quantitative comparison evaluates factors that could be contributing to successful development of products with limited commercial appeal. The analysis compares types of products, types of companies and approval chances of biodefense countermeasures under Project BioShield and orphan drugs under the Orphan Drug Act (Table 16).

Table 16 - Quantitative analysis summary: Product type, company type, and approval timelines

Type	Aspect	BioShield	ODA	Notes	Lessons
Product type	**Category**	Therapeutics	Therapeutics	Therapeutics = most profitable and developed product category	Oncology products have contributed to the success of ODA because this type of product lends itself to broader and potentially more lucrative applications. This aspect can be applied to BioShield if products with potentially broader applications are promoted. Additionally, ODA benefits should be applied to all BioShield products.
	Indication	Anthrax	Oncology	Oncology = top orphan product class. Anthrax = main biodefense priority. All anthrax antibodies and no vaccines have orphan status.	
Company type	**Size**	Small	Large	Small biotech = involved in early stages of orphan and BioShield drugs. Larger pharma = involved in later stages of orphan drugs or through mergers.	An important partner for orphan drugs is the advocacy groups. The positive impact of advocacy groups can be translated for biodefense drugs into collaboration with the military.
	Pharma/ Biotech	Biotech	Pharma Biopharma		

Approval	**Approval rate**	N/A	16.4% for orphan vs. 21.5% for non-orphan	No positive ODA impact on regulatory approval.	Increased orphan designations probably fostered by close FDA advice and counseling. This approach can be applied to biodefense drugs to promote interest in pursuing BioShield awards. However, the limitation of this approach lies in the fact that BioShield contracts are awarded through open and full competition. This barrier can be alleviated by favoring the use of simplified acquisition procedures.
	Number of awards/ designations vs. approvals	N/A	Increasing designations but constant approvals	No positive ODA impact on regulatory approval. Positive ODA impact on designations.	
	Clinical and approval times	N/A	Shorter clinical but longer approval times for orphan vs. non-orphan drugs	No positive ODA impact on regulatory approval.	

CHAPTER 4: COMPARISON: PROJECT BIOSHIELD ANTHRAX CONTRACTS MULTIPLE CASE STUDY

This chapter evaluates four companies that were awarded contracts for developing an anthrax countermeasure under Project BioShield by HHS. As shown in Table 17, two companies with anthrax vaccine contracts and two companies with anthrax therapeutics contracts are examined. The companies with an anthrax vaccine contract include: VaxGen, Inc., with Recombinant Protective Antigen (rPA), and Emergent BioSolutions, with BioThrax. The companies with an anthrax therapeutics contract include: Human Genome Sciences, Inc., with raxibacumab, Cangene Corporation, with Anthrax Immune Globulin (AIG). The criteria evaluated in each case study include: 1) the company profile and fitness for a BioShield contract, 2) the development stage of the product and its progress within the BioShield program, and 3) the federal and military ties to the project.

Table 17 – BioShield anthrax countermeasures contracts (HHS)

	VaxGen	Emergent	Human Genome Sciences	Cangene
Product	rPA	BioThrax	Raxibacumab	AIG
Market capitalization (in $ millions)	11	489	4640	347
Company type	small biopharma	small biopharma	small/mid biopharma	small biopharma
Year founded	1995	1998	1992	1984
Approval history	N/A	1	no approval	5 approvals in US and/or Canada

	VaxGen	Emergent	Human Genome Sciences	Cangene
Disease focus	Infectious diseases	Infectious diseases	Immune diseases, infectious diseases	Infectious diseases
Product focus	N/A	Vaccines and therapeutics	Therapeutics	Therapeutics
BioShield contract	1	1	1	2
Anthrax product type	Vaccine	Vaccine	Therapeutics	Therapeutics
Contract (in $ millions)	878	690	315	144
Approval	Cancelled contract	Prior approval	Complete response	Phase 2
SNS	Cancelled contract	Product in SNS	Product in SNS	3 products in SNS

Source: Companies' press releases and public documents. Market Capitalization obtained through Yahoo Finance as of June 2010

4.1 Multiple case study

4.1.1 VaxGen

VaxGen, founded in 1995 in Brisbane, CA, was the first recipient of a BioShield contract on November 4, 2004. The contract was awarded at $877 million over a five-year period for 75 million doses of a recombinant protective antigen (rPA) vaccine against anthrax. It remains the largest contract awarded under the program. However, because of multiple product development delays and contract modifications, the contract was terminated on December 19, 2006.

VaxGen was a spin off from Genentech with a specific mission to develop vaccines. The main focus of the team, composed of late stage vaccine developers, was a HIV vaccine. The company tried bringing in everything in-house and eventually felt secure in VaxGen's ability to perform from manufacturing to quality assurance to regulatory and clinical. After the 2001 anthrax attacks, VaxGen saw a strong opportunity to develop

biodefense products since the structure and production of the rPA vaccine would be similar to the company's HIV vaccine. The rPA vaccine was the old but only approved anthrax vaccine re-engineered by Army scientists to make it safer and faster, with an administration of three shots instead of six. (Lipton 2006) The company finally gave its full attention to biodefense products, more particularly the anthrax vaccine after termination of the HIV vaccine program in 2003 due to failed clinical trials (VaxGen 2010). VaxGen became the first recipient of a BioShield contract on November 4, 2004 for $877 million. Many criticized the government choice to award the anthrax vaccine contract to a company that never made a licensed vaccine, had a recent history of failed AIDS vaccine, had limited funding, and had been delisted from the NASDAQ stock in 2004 after managers uncovered accounting errors. (Lipton 2006) Soon enough, VaxGen experienced some setbacks during the vaccine development process. Because an ingredient in the formulation caused the vaccine to degrade quickly, the vaccine was not stable and therefore could not meet the expiry requirements for the SNS. The reformulation of the product therefore required additional development and testing, which the company had to fund itself. At the time, milestones payments during the development process were not yet an option. This consequently caused delays in delivery of the product. (Lipton 2006) In fact, the company was two years behind in the delivery schedule for the vaccine. After several contract modifications to account for development delays, VaxGen finally failed to meet a significant milestone imposed by HHS requiring a clinical trial of the vaccine candidate by December 18, 2006. On December 19, 2006, HHS terminated the contract for failure to provide 75 million doses

of a modern anthrax vaccine for civilian biodefense. (VaxGen 2006) Because the company did not deliver a vaccine and because milestone payments were not an option at the time, VaxGen did not receive the payment of $877 million. After VaxGen announced the contract termination, Lance Ignon, VaxGen's vice president for corporate affairs, stated: “We find it, I think, regrettable that we were unable to have an open and productive dialogue with HHS about how to ensure all the work that's gone into this could result in an anthrax vaccine.” (Roos 2006) Following the cancellation of the BioShield contract, VaxGen announced on January 5, 2007, that it had restructured the company and that Lance K. Gordon, had resigned as VaxGen's President, CEO and Executive Director. The company decreased workforce by approximately 51% directly following the cancellation of the BioShield contract. (VaxGen 2007a) On May 24, 2007, the company announced discontinuation of further development of its recombinant anthrax vaccine. It also underwent a second round of lay-offs, directly and indirectly associated with the vaccine program. (VaxGen 2007b) After more layoffs months later, resulting in a total of 90% workforce reduction, VaxGen ended all product development programs and is currently seeking to sell all remaining assets. (VaxGen 2010) The company stock steadily declined during the anthrax vaccine program. The stock started around $15.60 in November 2004 and fell to 29 cents in August 2010. VaxGen eventually sold its rPA vaccine to its rival Emergent on May 5, 2008. Emergent paid VaxGen $2 million for the transfer of the vaccine assets, with maybe an additional $8 million in milestone payments, plus specified percentages of future net sales. (VaxGen 2008)

A report by the GAO (2007a) identified three major factors contributing to the failure of this contract: 1) the contract was awarded when the rPA vaccine was still at an early stage of development and critical manufacturing issues had not been addressed; 2) the company took unrealistic risks when accepting the contract terms; and 3) the key parties did not clearly articulate and understand the critical requirements. Additionally, VaxGen was a small biotech company with limited staff, limited technical expertise, unavailable funding for unexpected costs, and with no regulatory approval experience. The GAO also pointed out that the contract was issued before the EUA guidance was released, which contributed to the perception that critical requirements and expectations were not yet articulated.

In the case study of VaxGen, the capabilities of the company were limited to successfully develop a product under Project BioShield. The company was awarded the first and largest BioShield contract. However, it had limited staff and high turnovers, low capacity, and had never gone through a full regulatory approval process. The product itself, a genetically modified version of the only licensed anthrax vaccine by the US Army, was at an early stage of development. Additionally, the company had difficulties and lacked funding when addressing product development issues, including formulation and stability problems within the deadlines imposed by HHS. Finally, the expectation that a small company, or any other company whether large or small, could develop, manufacture, and deliver 75 million doses within two to five years is unreasonable. The

VaxGen story, full of setbacks, lack of communication, lack of clear expectations, and the company's eventual demise, could be a deterrent to potential biodefense companies.

4.1.2 Emergent BioSolutions

Emergent BioSolutions, founded in 1998 and based in Rockville, MD, received its first BioShield contract in May 6, 2005 for its product BioThrax® (Anthrax Vaccine Adsorbed), the only licensed vaccine against anthrax. Upon success of product delivery to the SNS, the company received additional contracts on May 05, 2006, and on September 25, 2007. (Emergent 2008) The contract totaled 28.750 million doses worth $690 million. BioThrax, the only approved product of the company, was approved before the contract awards.

Emergent BioSolutions actually used to be named BioPort, which was formerly the Michigan Biologics Products Institute (MBPI). MBPI was part of the Michigan's state government and was the only facility in the US that had been producing the only licensed anthrax vaccine, AVA, later known as BioThrax. MBPI's anthrax vaccine, licensed since 1970, was administered to all active duty personnel as part of a program implemented in 1997 called the Anthrax Vaccine Immunization Program (AVIP). The institute portfolio included development, research, and commercialization of biologic products. The products targeted products against biodefense agents (anthrax and botulinum and smallpox) as well as more commercial vaccines (diphtheria, tetanus, and rabies). (Scott 2007) In 1998, BioPort paid $3.8 million in cash for MBPI, financing the rest of the $25

million cost with loans from the state of Michigan. Eleven days after the sale was finalized, in September 1998, DOD awarded BioPort a $45 million contract to supply anthrax vaccine to the US armed forces. In September 1998, eleven days after the MPBI became BioPort, the DOD extended the company a $29 million contract to supply anthrax vaccine to the US armed forces under the AVIP. The contract required the government to pay for up to 75% of the cost of the vaccine, even if the vaccine failed to receive market approval. (Weiss et al. 2007) Meanwhile, the company faced many challenges during vaccine development, including quality problems with the vaccine and failed FDA inspections. Those issues were actually inherited from MPBI. The company requested additional funding in June 1999, arguing that there were significant difficulties bringing an undercapitalized former state health laboratory up to current FDA standards for vaccine manufacturing. The Army, which cited national security, eventually granted the request, and increased the contract price by $24 million. (Weiss et al. 2007) In 2001, Congress and the Pentagon considered terminating the BioPort contract for multiple reasons including the fact that DOD had so far invested in only one source of the anthrax vaccine for anthrax. Additionally, DOD had foregone opportunities to improve or diversify the vaccine production program. It also continued to make substantial investment in a vaccine that could prove inadequate with multiple quality issues, lack of private funding, and several manufacturing inspection failures. (Committee 2000) Furthermore, the vaccine encountered resistance from the principal market, the military. The resistance stemmed from the stringent requirement of shots, adverse reactions, and negative publicity. According to Drugs.com, BioThrax is administered through a series

of six shots, which takes about 18 months to establish full immunity in an individual. This means that only those inoculated well in advance of an event would be protected. Additionally, the individual would need a yearly booster shot to maintain immunity. Furthermore, there have been reports among military personnel of six deaths and serious complications, including lymphoma and multiple sclerosis. The military stopped mandatory vaccinations in 2004 after some soldiers recoiled and filed lawsuits. (Lipton 2006) In October 2006, DOD announced the reinstatement of mandatory anthrax vaccinations. (Gottron 2007b) Meanwhile, the company made acquisitions of intellectual properties and products in an attempt to diversify the portfolio, which was heavily focused on biodefense. The company wanted to include more commercial products and wanted to diminish reliance on the US government as a sole customer. (Scott 2007) Currently, the portfolio includes 11 products in development with the majority in biodefense and some with commercial purposes (Emergent 2009a). Revenues generated from biodefense contracts with HHS and DOD made up about 97.2%, 95.7%, and 99.6% of the company's total revenues in the years 2007, 2008, and 2009, respectively (Emergent 2009b). The majority of the company's biodefense revenues however come from BioThrax and its continued use in the vaccination program. To date, over 9.5 million doses of BioThrax have been purchased and administered to more than 2.4 million of individuals, mostly military personnel. (Emergent 2010b) Furthermore, delivery to HHS and DOD since 1998 is expected to reach over 48 million doses by September 2011. (Emergent 2009a) The high volume is derived from DOD's immunization program and HHS' civilian biodefense program. Due to this, the company

has a strong motivation to prevent competitors from breaking its monopoly over the supply of anthrax vaccine to DOD and HHS. Emergent has actually already battled two companies: VaxGen and PharmAthene (see section 2.2.5 Political). Finally, Emergent is developing a second-generation anthrax vaccine, VaxImmune (combination of BioThrax and a new adjuvant), and two therapeutic products against anthrax including Anthrivig (Anthrax Immune Globulin (AIG)), and AVP-2109. Additionally, Emergent BioSolutions acquired VaxGen's rPA vaccine in 2008. (Emergent 2008) All four products have received support from BARDA and NIAID (see Table 10). On October 9, 2008, Emergent announced that BioThrax and AIG have been included as covered countermeasures under the PREP Act pursuant to a declaration issued by HHS. The declaration will remain in effect until December 31, 2015. Additionally, in 2006 BioThrax was certified under the SAFETY ACT. (Emergent 2008)

The case study of Emergent BioSolutions showed the company's capabilities ranging from development to commercialization even before acquisition in 1998. The company had extensive experience raising funds and addressing FDA concerns after multiple facility inspection failures as well as vaccine quality deviations. By the time the company was awarded the BioShield contract, it was prepared for product development, manufacturing and commercialization of the vaccine, which had been approved in 1970. The company also had a long history of product acquisition through DOD for the military. Additionally, Emergent BioSolutions was actually built upon a former state health department entity. BioThrax remains the only approved anthrax vaccine on the

market, allowing Emergent to capitalize on its monopoly over the anthrax vaccine through expertise, funding, coordination, collaboration, lobbying, and maintenance of a strong anthrax vaccine and therapeutics pipeline.

4.1.3 Human Genome Sciences

Human Genome Sciences (HGS), founded in 1992 and based in Rockville, MD, received its first BioShield contract on June 16, 2006 for 20,000 doses of raxibacumab, a human monoclonal antibody drug for the treatment of inhalation anthrax, for $165 million. Upon completion of product delivery to the SNS, the company was awarded an additional contract worth $151 million on July 29, 2009 for an additional 45,000 doses to be delivered over a period of three years, beginning at the end of 2009. (HGS 2010)

HGS has a technological platform derived from progress made during the Human Genome Project. The company's focus was originally on discovery, with US patents covering genes, proteins, antibodies and proprietary technologies. The technical platform included the discovery and understanding of human genes and their biological functions, as well as the discovery and development of human protein and antibody drugs. Over the years, HGS has concentrated its efforts on commercialization of late-stage products, including products for systemic lupus and inhalational anthrax. The portfolio includes drugs to treat other autoimmune diseases and cancer. HGS has been able to gather funds to develop products through collaborations with large pharma companies such as GlaxoSmithKline and Novartis, as well as the US government. (HGS 2010) The

company has not yet received approval from the FDA for any product as of February 2011.

Raxibacumab is a human monoclonal antibody that interacts directly with the anthrax toxin, more specifically the protective antigen that is the binding moiety, and inactivates it. The product obtained Fast Track Product designation from the FDA, as well as Orphan Drug Designation. The company filed a BLA with the FDA in May 2009. The application was subsequently accepted and granted priority review. It is the first new drug developed since the 2001 anthrax attacks to be considered for approval under the Animal Rule. For products that cannot be ethically or feasibly tested on humans, the Animal Rule allows efficacy studies to be demonstrated in one or more animal models. HGS evaluated the efficacy of raxibacumab as a prophylactic and therapeutics agent in rabbits and monkeys. To determine the efficacy of raxibacumab, the company designed a multi-step experiment. First, the company developed challenge studies, which quantified the aerosol concentrations of *Bacillus anthracis* after delivery in BSL-3 facilities at the Battelle Biomedical Research Center in Columbus, Ohio. Next, the prophylactic studies tested the efficacy of the antibody to protect animals exposed to aerosolized anthrax spores that was approximately 100 times the median lethal dose. Furthermore, the anthrax infection was characterized in both animal models to determine the markers of the disease progression and to identify an optimal time window for therapeutic intervention. Additionally, the therapeutic efficacy studies evaluated the efficacy of raxibacumab in rabbits and monkeys after exposure to aerosolized anthrax spores that

were approximately 200 times the median lethal dose. The primary end point was defined as the percentage of animals that survived at day 28. Finally, after determining the dose of raxibacumab (40 mg/kg) that provided survival benefits in animals, HGS assessed the safety of that dose in 333 human patients. The study concluded that a single dose of raxibacumab improved survival in rabbits and monkeys with symptomatic inhalational anthrax. (Migone et al. 2009)

The Animal Rule has critical requirements described in Section 2.2.2. Regulatory. The company (Migone et al. 2009) discussed how the development program of raxibacumab met all requirements under Animal Rule:

1. Raxibacumab was shown to bind protective antigen with high affinity and specifically blocks the binding of protective antigen to its receptor, preventing anthrax toxin–mediated damage.

2. and 3. Studies in rabbits and monkeys showed that the course of inhalational anthrax has pathophysiological features and outcomes that are similar to those in humans. Raxibacumab was shown to improve survival among rabbits and monkeys with evidence of systemic disease after exposure of 200 times the median lethal dose of inhaled anthrax spores. In both rabbits and monkeys, raxibacumab significantly increased the overall survival rate and time to death.

4. The dose of 40 mg of raxibacumab per kg in humans results in levels of serum raxibacumab that are similar to or greater than those that provide a survival benefit in animal models. The safety profile in humans provides support for the

use of raxibacumab, particularly in the clinical setting of immediately life-threatening inhalational anthrax disease.

The study described above included two efficacy studies that tested raxibacumab in rabbits and monkeys and comparing the efficacy against a placebo. Both studies demonstrated that the 40 mg/kg dose was superior to placebo. Two subsequent efficacy studies were performed to evaluate the efficacy of raxibacumab plus antimicrobial (a fluoroquinolone) versus antimicrobial alone in the treatment of anthrax. The effects were also compared to placebo. The purpose of these studies was to determine the effect of combining both the antibody and antimicrobial (levofloxacin in rabbit and ciprofloxacin in monkey). However, an additional purpose was to assess whether raxibacumab made a contribution to the efficacy of the combination (raxibacumab and antimicrobial) and whether the efficacy of the combination was higher than the efficacy of antimicrobial alone. Unexpectedly, the efficacy of the antimicrobial was 95-100%. Combining raxibacumab and antimicrobial also saw similar high rates of efficacy. Because antimicrobials alone demonstrated high efficacy, the FDA determined that it was not possible to demonstrate a contribution of raxibacumab to the efficacy of the regimen. This raised the question about the need for an animal model that more closely approximates the 55% survival seen in 2001 in the patients with inhalational anthrax. The FDA questioned the fitness of the animal models designed by HGS, and consequently, the results. The FDA also doubted that efficacy in humans could be predicted from this data. (CDER 2009a) On October 27, 2009 the Anti-Infective Drugs

Advisory Committee to the FDA met to discuss certain aspects of the BLA. (HGS 2009b) The original purpose was for the FDA to seek advice about HGS data based on all four criteria of the Animal Rule. During site inspections, the FDA had identified issues that raise important concerns about the quality and reliability of human pharmacokinetic data in HGS' application. These data were deemed essential to link raxibacumab human to animal pharmacokinetic exposure for dose selection, which is Criterion 4 of the Rule. The FDA therefore instructed the advisory panel to focus only on the animal efficacy studies and raxibacumab safety and to disregard the human pharmacokinetic data. The FDA also chose not to ask the committee for a recommendation on approval of the product, since a complete judgment could be not made without reliable human pharmacokinetic data. (CDER 2009b) The majority of the panel believed that all the criteria of the Animal rule were met and agreed that HGS' animal studies could be used to indicate efficacy in humans. The panel was split on determining whether the antibody did not diminish the efficacy of the antimicrobials. The panel also recommended that HGS provide more evidence that raxibacumab makes a contribution to the efficacy over antimicrobials alone. (CDER 2009c) Then again, a report by the NBSB (2010b) raised concerns about the FDA interpretation of its own Animal Rule. When FDA asked members of the Committee whether additional evidence of efficacy beyond currently approved antibiotics should be requested, NBSB points out that the request contrasts with the rule. In the rule, FDA states that its staff has "decided to eliminate the requirement that 'products would be expected to provide meaningful therapeutic benefits of patients over existing treatments,' as well as the limitation that the

toxic agent be 'without a proven treatment'" (FDA 2002). On November 16, 2009, the company announced that it received from the FDA a Complete Response Letter, which is a request for additional information needed to complete BLA review. In the press release, Sally D. Bolmer, Senior Vice President, Development and Regulatory Affairs, said: "We have responded to all of FDA's previous questions. We plan to address the current questions as well. In certain respects, the Complete Response Letter appears to be inconsistent with the FDA's published final rule governing the development of new drugs when human efficacy studies are not ethical or feasible." (HGS 2009a) The company would receive an additional $10 million under the contract upon licensure. (HGS 2010) The FDA approval for marketing is independent from the government's stockpiling the SNS for emergency use. As of February 2011, the regulatory review process is still ongoing.

The case study of Human Genome Sciences showed the company's capabilities ranging from development to pre-commercialization, with a technological platform derived from the Human Genome Project. The company seemed prepared for product development, and manufacturing, although it has not yet taken a product through regulatory approval before receiving the BioShield awards. It is safe to assume that expectations and requirements were somewhat not completely delineated since agreement on what satisfies the Animal Rule is still being debated. Because this is the first product to undergo regulatory approval review under the Rule, it is possible that the FDA offers more scrutiny before granting approval under a yet not proven regulatory path. Due to this, it

is also possible that interpretation of the Animal Rule by FDA is therefore somewhat variable and inconsistent. However, raxibacumab is already in the SNS after completion of the initial BioShield contract and will continue to be delivered for the next couple of years.

4.1.4 Cangene

Cangene, founded in 1984 and based in Canada, received a BioShield contract worth $144 million on July 28, 2006 for 10,000 doses of its product Anthrax Immune Globulin (AIG), therapeutics for anthrax. Cangene also received another BioShield contract worth $416 million on June 1, 2006 for 200,000 doses of its product Botulism Antitoxin Heptavalent (BAT), therapeutics for botulinum toxins. (Gottron 2010) The focus in this report for analysis purposes will be on AIG.

Cangene is an export-driven Canadian company focusing on the development, manufacture, and marketing of blood-based and biotechnology-derived pharmaceutical products. The company's pipeline is composed of products that target infectious and biodefense diseases. (Cangene 2010) Cangene's international business is divided into two operating segments: commercial and contract-services. The main commercial biopharmaceutical product segment provides revenue from approved product sales. The contract-services business is dominated by large government biodefense contracts and generates a somewhat uneven revenue stream that still provides significant benefits once the product is delivered. (Cangene 2010) The company initiated biodefense work in

1999, with an established track-record with BARDA, CDC, and DOD for three products: Vaccinia Immune Globulin (VIG), a therapeutics for smallpox licensed by FDA and Health Canada, Anthrax Immune Globulin (AIG), which will be discussed below, and Botulism Antitoxin Heptavalent (BAT), which is an investigational drug against botulinum toxins. All three products have been used to treat human cases, and have been delivered to the SNS. (Cangene 2009) In the last years, Cangene has established partnerships with many types of organizations including commercial distributors, governmental organizations and national Ministries of Health, and has successfully undertaken product registration in a number of countries including Ireland, the United States, Poland, Australia and the United Kingdom. (Industry Canada 2008) The company's portfolio includes products that are hyperimmunes, which are purified antibody products from blood plasma targeted towards infectious diseases such as hepatitis B, botulism, and anthrax. This makes many of their products applicable to biodefense programs. The company has five products already approved in the United States and/or Canada (with four approved by the FDA), and three products have been accepted into the SNS: VIG against smallpox, BAT, and AIG. (Cangene 2010)

Cangene's anthrax product is the AIG, which is an investigational product derived from plasma obtained from donors immunized with the anthrax vaccine. Donors must have received at least four doses of the vaccine. AIG is a hyperimmune purified antibody product specific for *Bacillus anthracis*, the bacteria that cause anthrax. (Cangene 2009) On August 11, 2004, the DOD and HHS announced that the military would support the

CDC effort to create AIG. Anthrax-vaccinated military personnel at Army installations were invited to donate some of their blood plasma to support this effort. The secretary of HHS asked for the assistance of DOD in requesting plasma from anthrax-vaccinated troops because most of the people in the country vaccinated against anthrax are US military personnel. (DOD 2004) In 2006, Cangene had the opportunity to test the efficacy of AIG in a human patient. A patient with a case of naturally acquired inhalation anthrax presented to a local hospital in Pennsylvania with symptoms of mild respiratory distress and initially received aggressive antibiotic treatment as well as other critical support. When the patient's condition deteriorated, he was treated with adjunct AIG therapy under an Emergency Investigational New Drug use protocol based on a recommendation by the CDC. The patient eventually recovered. The addition of AIG to the treatment protocol may have been beneficial, but additional and controlled studies using appropriate animal models are necessary to confirm that this response was due to the infusion of anthrax immunoglobulins. (Walsh et al. 2007, Schneemann and Manchester 2009) Currently, AIG is in Phase 2 clinical trials. The company obtained Fast Track designation and Orphan Drug status from FDA and European Medicines Agency (EMEA). Cangene developed this product under contract to the US government and has supplied the product to the SNS. (Cangene 2010) The product has so far been used in two human patients for naturally acquired inhalational anthrax. (Cangene 2009) Cangene is expected to submit a BLA by the end of 2012, with a decision in possibly 2013. (Leonardzehr 2010)

The case study of Cangene showed that the company has capabilities ranging from development to commercialization, as well as previous FDA approvals, before receiving the awards. The company has an established track record with the US government, such as the CDC and DOD, in addition to HHS and BARDA, as well as the military, and has delivered three products into the SNS.

4.2 Multiple case study comparison

The criteria that were used to assess the impact of BioShield on successful product development included: 1) the company profile, 2) the drug development progress within BioShield program, and 3) the federal and military collaborations (besides HHS) (Table 18 assesses the profile of the company and its product, as well as its impact on the potential success of the BioShield contract.

Table 18 –Multiple case study comparison

Company	Project BioShield anthrax contract			
	Company readiness	**Development and approval progress**	**Product in SNS**	**Federal and military ties, in addition to HHS**
VaxGen	Small, limited resources and expertise.	Contract terminated	No	US Army genetically modified old anthrax vaccine.
Emergent BioSolutions	Experience raising funds, strong expertise, and successful development process, regulatory approval, and commercialization.	Previously approved product (in 1970)	Yes	DOD, US Army vaccination program and political lobbying ties. Formerly a state health department entity.
Human Genome Sciences	Experience raising funds, strong expertise, and successful development process. No regulatory approval or commercialization experience.	First novel product under Animal Rule. Complete Response by FDA.	Yes	No
Cangene	Experience with development process, regulatory approval, and commercialization.	Advanced development, and manufacturing capabilities.	Yes	DOD, CDC, armed forces during creation and development of AIG

CHAPTER 5: DISCUSSION

The analyses in this dissertation yielded many essential observations. First, the analysis developing an understanding of the development process of biodefense countermeasures showed that the most critical barriers to the process are regulatory and political. On the one hand, the current legislations affecting biodefense products have provided important incentives such as removing liability barriers (through the EUA, PREP Act, and to some extent the SAFETY Act) and the amendment of the original Project BioShield Act to include milestone payments as means to provide regular financial rewards to companies making progress in the development process. On the other hand, the most critical barriers that were identified are regulatory and political. First, the regulatory pathway is still unproven. Because it is neither ethical nor feasible to test biodefense products for efficacy in humans, the FDA created the Animal Rule in 2002. The rule allows FDA to grant marketing approval based on adequate and well-controlled animal studies. However, no new drug has yet received approval under this rule. Additionally, although one company holding a BioShield contract (for an antibody treatment against anthrax disease) has managed to navigate the development process under the rule, the FDA still responded with a Complete Response letter. During the Anti-Infective Drugs Advisory meeting, the FDA raised questions regarding the contribution of the antibody to the efficacy over antimicrobials alone. NBSB points out that the request contrasts with the

requirements of the rule. These differing interpretations might or might not have contributed to the withholding of regulatory approval but yet they demonstrate the difficulties in implementing a rule that has no precedent to rely on during the development and approval process. Moreover, many political barriers hinder the efforts of developing biodefense products. Those barriers are apparent because the government is not only the sole customer for the biodefense market but it is also the regulator, the legislator, and the collaborator. First, the customer is segmented into many departments and sub-departments that do not always communicate and coordinate within or amongst each other. They also typically have their own goals and budgets to manage. Additionally, while the government is the sole customer, the companies competing for the contracts are many, therefore creating a monopsony where competition can get heated. Furthermore, it is understood and accepted that the government must adapt to ongoing events and therefore must shift its priorities and needs. This leaves the biodefense market with an unreliable customer. Finally, the government as both the customer and the legislator also has demonstrated that the guaranteed market provided by Project BioShield is actually not always guaranteed. Biodefense funds, including budget allocated specifically to BioShield, have been provided inconsistently and actual estimates show distribution of only a fraction of the allocated budget. To complicate the matter further, the government is also the regulator and legislator of the biodefense market.

There are opportunities, however, to improve the chances for successful development of biodefense countermeasures. For instance, as a customer, the government can decrease the negative impact of the monopsony by exercising its authority to use a simplified acquisition procedure as opposed to full and open competition. Second, as a regulator, the government can commit to promote a closer relationship with the industry by providing advice and counseling, as seen with orphan drugs. The regulatory pathway for biodefense drugs is still unproven and, therefore, requires intensive communication and coordination between the industry and the regulatory agencies, in addition to clearer guidance on expectations for approval. For example, closer collaboration of the FDA with orphan drug companies generated more interest for companies to pursue orphan drug development. Third, as a legislator, the government must continue to adapt and amend legislation to promote the essential environment for successful development of biodefense products. Finally as a collaborator, the government can continue to follow the CRDA model of public-private partnership, which allows for a synergistic collaboration between federal and non-federal companies, including technology and knowledge transfer, facilities and equipment sharing, etc. The most interesting aspect of the CRDA examples illustrated in the dissertation (Elusys' Heteropolymer Antibody technology and Cangene's hyperimmunes) is the investment in a product targeted for biodefense acquisition and also its associated technological platform that promises more products with biodefense and non-biodefense applications. This is a critical approach because it would benefit not only the customer (in this case the government) thanks to additional potential products, but also the producer thanks to a drug model resembling the

blockbuster orphan drug model. This approach might also be appealing to large pharma as well since this approach could be a valid alternative business model to the shifting blockbuster drug model. Additionally, the government as a legislator could provide additional incentives to promote this approach, such as market exclusivity to products coming out of this platform. Furthermore, the government, as both the customer and the legislator, needs to understand that when a market is guaranteed, it is guaranteed. Although priorities will shift, and so will needs, the budget allocated to biodefense and specifically BioShield should be maintained for its purpose. When Congress appropriated $5.6 billion through the Special Reserve Fund over ten years, it did so to provide producers with a guaranteed market for biodefense countermeasures. This promise has been broken because of the multiple transfers out of this budget over the years, even if the reallocated monies are replaced. Additionally, the small companies that make up the biodefense industry are capable of developing biodefense products, as demonstrated in the BioShield anthrax contracts study, but they depend heavily on continued funding and support from the government to maintain an active biodefense program. A mandate guaranteeing that the budget will not be reallocated should be made if more appropriations are authorized once the funds expire in 2013. Finally, the biodefense industry would benefit from continuous improvement in federal communication and coordination. As the government (customer, regulator, legislator and collaborator of the biodefense industry) becomes more synchronized, the development of biodefense countermeasures will become smoother.

Moreover, this dissertation yielded an interesting lesson from the ODA analysis: similarly to advocacy groups' positive impact on the development of orphan drugs, the military is an understated link to incentivize the development of biodefense countermeasures. The military is typically the lead users of biodefense products in the absence of an emergency crisis because they run a credible threat risk of exposure to a biological agent, whether natural or biowarfare-related. Because of this, they can offer invaluable insights into the market needs as well as feedback for the development progress of the product. The military has also historically shown to be a more controlled and designated patient base for clinical trials. Additionally, military researchers and scientists have strong expertise in biodefense agents and diseases and can help bridge the gap between early stages of basic research/development and late stages of drug development. Finally, the military can promote a productive collaboration by sharing knowledge, basic research, and product development but also with resources such as laboratories, and development and manufacturing capabilities. A lucrative biodefense drug model would involve a synergistic government-industry-academia-military partnership, which would mirror the synergistic and successful collaboration of government-industry-academia-advocacy groups for orphan drugs. The positive impact of the military on the development of biodefense products was also demonstrated in the BioShield anthax contracts case study. Lessons from comparing Project BioShield to the Orphan Drug Act and from comparing BioShield anthrax projects are delineated in Table 19.

Table 19 - Developing biodefense countermeasures: Lessons from the Orphan Drug Act and Project BioShield anthrax contracts

Factors	Lessons from ODA	Lessons from Project BioShield and other federal anthrax contracts		Comments for developing biodefense countermeasures
		Barriers	Opportunities	
Technical	Basic disease/ product knowledge from a targeted market	Potentially limited knowledge of exotic germs that rarely or never naturally occur	Possible technology and knowledge transfer from government, academia or military	**More systematic technology and knowledge transfer from government, academia or military.**
	N/A	Special requirements due to exotic germs such as labs, personnel, equipment	Possibility of sharing available resources from the government through CRDA	**Collaboration between federal labs and industry.**
Regulatory	No observed approval benefits, but increasing designations. FDA counseling.	Unclear regulatory requirements and expectations	Animal Rule established to allow for ethical efficacy trials	**Clarifications of regulatory requirements and expectations. Stronger FDA advice and counseling.**
	N/A	Product has to be covered under EUA declaration	BioShield permits the emergency use of unapproved countermeasures	**Importance of EUA.**
Economic	Small but strong market need	Guaranteed federal government market if awarded BioShield contract in response to no to little market	BioShield guarantees a federal government market	**Market for biodefense countermeasures includes government and military.**
	N/A	Guaranteed market is actually not guaranteed as the budget can sometimes be reallocated	N/A	**Allocated budget needs to remain appropriately allocated.**
	Blockbuster model could shift towards targeted, perhaps personalized medicine	Large pharma companies historically prefer the blockbuster drug model	Potential to attract large pharma: CRDA collaboration for a specific product and a potentially larger and lucrative technological platform	**Collaboration and investment in product and associated technological platform.**
	Synergistic partnership between government, industry, academia and consumer organizations	Difficult partnership between different government branches and industry	Some productive partnership between industry and military	**Potential for synergistic partnership between government, industry, academia and military. Need for synchronization of federal departments.**
	N/A	BioShield originally only provided financial reward upon contract completion	BioShield was amended to provide milestone payments	**Importance of milestone payments.**

Factors	Lessons from ODA	Lessons from Project BioShield and other federal anthrax contracts		Comments for developing biodefense countermeasures
	N/A	BioShield Fund reallocated for other priorities	BioShield is funded though BioShield Fund	**Budget allocated for biodefense should be reserved for biodefense. Other priorities needing resources should be funded on their own right.**
	N/A	Funding for projects strictly related to biodefense is slated to be 9% in 2011, 18% over the last 11 years	N/A	
	N/A	Full and open competition. Monopsony	BioShield allows awarding of contracts under simplified acquisition procedures	**Simplified acquisition procedures incentive over open and full competition.**
Legal	Liability concerns lessened due to patients suffering from severe to lethal diseases	Liability concerns	EUA, PREP Act, SAFETY Act	**Alleviated liability concerns.**
Political	N/A	Government is customer, regulator, legislator and partner but all under different and non-coordinated departments	BioShield created BARDA, a single point of authority. Integration of national biodefense portfolio between HHS and DOD	**Need for continuously improved federal coordination, communication, and expectations.**
	N/A	Funding is inconsistent due to transfers and re-allocations	BioShield funds of $5.6 billion over 10 years	**BioShield funds need to be available for BioShield contracts.**
	Advocacy groups are lobbying forces linking scientific community to patients to government	Industry's fierce competition and lobbying due to monopsony	N/A	**Third parties, such as military, indirectly linked to partnership and voicing insights from users can link government and industry.**
Military	Lead users = patients represented by advocacy groups	N/A	Military is lead users that can provide knowledge, clinical base and collaboration for potential product and platform	**Lead users provide insights into market needs, clinical patient base, knowledge, development and manufacturing options.**
	N/A	Governance structure	Governance structure	**Importance of matching appropriate governance structure to project.**
	Academia, industry, government and advocacy groups partnership	N/A	Potential for sharing basic research and scientific knowledge, and technology transfer	**Technology, manufacturing transfer between academia, military, industry and government.**
	Applicability of non-orphan indication to orphan indication	N/A	Existing collaboration with biodefense industry	**Collaboration and investment in product but also platform.**

Some of the recommendations made in this dissertation reflect the recommended strategies outlined in the HHS report (HHS 2010b). HHS approach includes optimization of the regulatory process, such as closer guidance from the FDA to the sponsors, review of the laws and regulations impacting biodefense countermeasures development, and finally one of the most innovative strategies, provision of expertise and infrastructure for advanced development and scale-up manufacturing. In one instance, the report identifies the need to strengthen the regulatory process as the FDA oversees the entire evaluation process of product development from a regulatory standpoint, and, therefore, is critical to the success of the enterprise. The report also advocates FDA guidance on development pathways for sponsors, as well as FDA intensive involvement and coordination throughout the development process. In 2011, the FDA will actually undertake a new initiative called "Advancing Regulatory Science for Public Health" designed to focus on improving the development process more efficiently, including the identification and qualification of animal models and surrogate measures of product efficacy. The FDA, through a team of experts, also plans on working with sponsors to identify and help resolve scientific issues as early and efficiently as possible, and to facilitate the more rapid evaluation of high priority candidates. For each biodefense countermeasure, the FDA and government partners, such as HHS/BARDA, will work with sponsors to develop a "Regulatory Science Plan" to specify known scientific gaps or opportunities for improvement, and identify priority areas and the required strategies and resources, both before and after project initiation. Finally, the FDA will launch a collaborative project with other HHS members to better ensure that laws and regulations support preparedness

and response. Another critical observation from the report is the lack of domestic manufacturing capacity needed to rapidly produce and package countermeasures in the face of emergency. The report recognizes that progress can be impeded when relying solely on the product sponsor to take on the roles of developer, manufacturer, and regulator strategist. Because providing expertise and infrastructure for advanced development and scale-up manufacturing would significantly lower barriers to product development, the review recommends that HHS, either alone or with DOD, establishes Centers for Innovation in Advanced Development and Manufacturing. The centers will provide advanced development and manufacturing capability (such as surge vaccine production and manufacturing capacity in a serious emerging disease threat) and therefore supply a cost-effective, reliable and sustainable production of countermeasures. Additionally, they will link the industry to needed expertise and potential collaboration. The envisioned result is an integrated, domestic infrastructure based on strategic partnerships with industry and/or academia with unprecedented capabilities to develop and manufacture biodefense countermeasures. The centers will also provide training opportunities for current and future industry and government scientists engaged in advanced development and manufacturing of countermeasures.

The new HHS strategies are visionary but they also indicate that the current BioShield model is not sufficient in funds and resources to produce the necessary biodefense countermeasures. Should the government shoulder most of the costs associated with development and manufacturing? Perhaps a more balanced solution is to contract a third

party (private company, government-affiliated company, or military) for stand-by manufacturing to be used only in case of emergency. HHS proposed federal expertise and intensive FDA involvement would be essential in alleviating the burden of development for the industry. On the other hand, the burden of manufacturing could be shared between the industry (for basic dose requirement) and a third party on stand-by (for mass production during an emergency). This proposal is feasible when examining the timeline of full development for the 2009 H1N1 pandemic flu vaccine (WHO 2009): It took approximately five to six months for the first supplies of approved vaccine to become available once a new strain of influenza virus with pandemic potential was identified and isolated. This estimate included identification of the strain, manufacturing, clinical trials, and regulatory approval. Manufacturing took between two to three months. This timeline can be used to make a crude estimate for the "third party on stand-by" scenario. Of course, it would greatly vary from product to product and from situation to situation. However, this scenario becomes more promising when considering that the disease identification (assuming known strain) and the product development and/or approval would already be completed. It becomes even more promising if some variables are controlled, such as completing validated methods and processes, ensuring availability of stock material, equipment, and instruments, and completing technology transfer ahead of time. It could even be an acceptable business model if the third party was already actively producing a similar compound, manufacturing the biodefense product for broader applications or using its associated technological platform. This would imply that the manufacturing process, including compatible equipment and instruments, would

already be in place. In this scenario, the costs of large-scale manufacturing can therefore be put on hold (with stipulation that funding for this specific purpose cannot be reallocated) until mass production is needed in times of crisis or when the product expires. Additionally, lessons from the ODA and from the anthrax cases indicate that successful development of biodefense drugs can be increased with shared expertise, facilities and resources, whether with currently absent large pharma companies or with the currently involved military. Finally, the collaboration between private industry and the military has been fruitful in the past as demonstrated by the BioShield anthrax contracts and should be enhanced to promote the successful development of biodefense countermeasures.

CHAPTER 6: CONCLUSION

Project BioShield was enacted in 2004 to stimulate the development of biodefense countermeasures for delivery to the national stockpile. Although this legislation was visionary, it has yielded only a limited number of countermeasures and regulatory approval of not a single BioShield product. The main barriers hindering the development of biodefense countermeasures include: 1) unique science; 2) an uncertain regulatory pathway; 3) non-existent patient base; 4) a low rate of return and high opportunity costs; 5) inconsistent funding; 6) liability concerns; 7) and complex politics.

This dissertation analyzed the Orphan Drug Act and BioShield anthrax contracts to identify opportunities to remove those barriers:

1) The most common type of orphan drugs, oncology, have contributed to the success of ODA because of the products' potential broader and more lucrative applications. This can be applied to BioShield contracts through investment in biodefense products and related technological platforms or potential broader applications. Additionally, only BioShield antibodies are currently covered under the ODA. The benefits of ODA must automatically be extended to all BioShield products including vaccines;

2) Despite the absence of large pharma in the biodefense market, the anthrax contracts study demonstrates that small companies have the capacity to develop biodefense products, with the condition of sustained and committed government funding. Additionally, the ODA success was supported by advocacy groups, and similarly, progress of some BioShield contracts was supported by the military. Enhancing the military partnership could be critical to the success of BioShield;
3) Close FDA advice and counseling has fostered an increase in orphan designations, and could similarly promote further interest in more biodefense product development. However, this approach is limited because orphan designations are obtained through an application process, while BioShield contracts are awarded through open and full competition. This barrier can be alleviated by favoring the use of simplified acquisition procedures;
4) While for orphan drugs, use depends on individual willingness to pay, the BioShield market depends on the government willingness to pay based on justification for use of a biodefense product in an emergency or facing a credible threat. Because orphan drugs have a market with a demand while the biodefense market is naturally non-existent, the government market guarantee is crucial in maintaining the biodefense market. Over the years, biodefense and BioShield monies have been allocated out of their specific budget. If the Special Reserve Fund is renewed after its expiration in 2013, a stipulation should be made that no monies can be allocated out of the fund to preserve the promise of guarantee.

Finally, the most critical barriers hindering the efforts to develop biodefense countermeasures are regulatory and political. First, the regulatory pathway is still unproven. Furthermore, in addition to the government being the sole customer (composed of different federal departments and sub-departments) to the biodefense market, it is also the regulator, legislator and collaborator. This can create additional layers of barriers during the development and approval process including shifting priorities and needs, inconsistent funding, lack of coordination and communication, and heated competition caused by a monopsony. HHS has proposed innovative strategies to lower barriers to regulatory concerns, including providing expertise and capabilities support to the industry for development, manufacturing and regulatory approval. If timely and efficiently implemented, those strategies have the potential to significantly impact the biodefense market. These radical initiatives suggest however that without significant federal funding, involvement, support and coordination, the development of biodefense countermeasures might be stumped. Additionally, these initiatives also require the government to take on the role of developer and manufacturer, in addition to customer, regulator, legislator and collaborator. This dissertation proposes an alternative model where the resources and the burden of development and manufacturing are shared between the private industry, the government, and a third contractor party on standby such as a private, federal or military entity. The alternative model enhancement to the biodefense drug model suggested in this dissertation along with BioShield can create the necessary foundation to stimulate the development of biodefense countermeasures for preparedness against potential bioterrorist attacks

APPENDIX: CONFLICT OF INTEREST STATEMENT

The author was employed at Human Genome Sciences, Inc. from 2005 to 2010.

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