

## POLICY REVIEW

# Biodefense countermeasures: the impact of Title IV of the US Pandemic and All-Hazards Preparedness Act

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The 2006 US Pandemic and All-Hazards Preparedness Act gave the Department of Health and Human Services (HHS) new authority to fund the development and procurement of medical countermeasures against chemical, biological, radiological, and nuclear (CBRN) threats. The legislation builds on the authority the HHS gained in 2004 under Project BioShield, which established a fund to procure medical countermeasures. This article reviews the new HHS authorities and the improvements on BioShield, and it describes some of the challenges HHS will face in exercising the new authorities to fund the development and procurement of medical countermeasures against CBRN threats.

## Introduction

Improvements were necessary: the original Project BioShield<sup>1</sup> proved to be insufficient to meet the needs of the government for acquiring medical countermeasures for the Strategic National Stockpile. BioShield could not be used to fund advanced development of medical countermeasures because of strict provisions in the legislation, so technologies and products that might be of interest to the government could not be shepherded through development to maturity, when they could be stockpiled. Biopharmaceutical companies were also less likely or able to fund the advanced development of potential countermeasures themselves, unwilling to take the considerable financial risk that their products would fail in development or not be procured by BioShield even if the products were successful. Some companies, mostly smaller biotechnology companies, pursued products with hopes of a BioShield procurement contract in spite of the risks. In general, however, large biopharmaceutical companies were uninterested in entering an uncertain, risky market where the US government would be their sole customer.

The Pandemic and All-Hazards Preparedness Act<sup>2</sup> sought to correct the shortcomings in Project BioShield by allowing for funding of advanced development of products under a new contracting mechanism called the Biomedical Advanced Research and Development Authority (BARDA). The legislation also modified Project BioShield so that milestone payments could be made to companies, without the need for companies to repay the funding to the government if the product fails or the contract is canceled.

## Project BioShield

After the anthrax attacks in 2001, there was broad 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,<sup>3</sup> and the Project BioShield Act was signed into law on 21 July 2004.<sup>4</sup> The Act created a Special Reserve Fund for use in procuring countermeasures for the stockpile. Congress advance-appropriated \$5.6 billion to the fund for use over 10 years (Fiscal Year (FY) 2004–2013; the US government's fiscal year (FY) starts on 1 October of the previous year and extends to 30 September of the next year. For example, FY 2007 starts on 1 October 2006 and extends to 30 September 2007). In addition to the fund, BioShield increased the authority and flexibility of the National Institutes of Health (NIH) to develop the so-called 'qualified countermeasures' (a drug, biological product, or device that the HHS Secretary determines as a priority) for CBRN threats, and it permitted the use of medical treatments not approved by the US Food and Drug Administration (FDA) during an emergency.<sup>5</sup>

BioShield set strict limits for how the government may procure medical countermeasures. Before a contract is awarded, the Department of Homeland Security (DHS) must make a 'material threat determination,' to determine that there is a significant threat to the US that warrants a countermeasure. HHS must then evaluate the medical and public health consequences of the specific threat, and determine what medical countermeasures would be required



to mitigate the threat. Only after interagency consultations and presidential approval may HHS award a BioShield contract. To be eligible for an award, the government must determine that the countermeasure will be available in 'sufficient quantities' and will be able to be licensed by the FDA within eight years.<sup>4</sup> If the countermeasure is not licensed at the time of delivery to the stockpile, the government may opt to purchase the countermeasure at a discounted price, with a bonus payable to the manufacturer upon FDA licensure. The government may also opt to make advance payments to the manufacturer before delivery, but if the contract is canceled, those advance payments must be repaid.

Project BioShield was intended to encourage industry to develop medical countermeasures for CBRN threats, primarily by creating a market for such products. Having a 10-year fund specifically for procurement of countermeasures was thought to be an incentive for industry, as it reduces the usual year-by-year change in governmental appropriations and political priorities.<sup>6</sup> However, even with this security, it was generally felt that Project BioShield did not go far enough to encourage industry participation in medical countermeasure development, as shown by the small handful of countermeasures it has procured for the stockpile.<sup>7</sup> There are three important reasons for this:

#### *BioShield does not support advanced development of medical countermeasures*

As BioShield is a late-stage procurement program for medical countermeasures to be deposited in the stockpile, the developer bore much of the financial and developmental risk. Early development could be funded through NIH or Small Business Innovation Research (SBIR) grants.<sup>8</sup> BioShield could procure licensed countermeasures or countermeasures that will likely be licensed within eight years; however, advanced development steps between these two funding mechanisms were not covered by government funding. This gap in funding has been referred to as the 'Valley of Death,' and it has been a significant disincentive for industry participation in the development of medical countermeasures against CBRN threats, particularly for small biotechnology companies, which could ill afford to pay for the gap in funding.<sup>5</sup> In addition to being a burden on companies, the Valley of Death was disadvantageous to the US government. As BioShield funding could not contribute to the preclinical stage of medical countermeasure development, the government was forced to rely on market forces to encourage the development of new products or technologies that might eventually be procured under BioShield.<sup>6</sup>

#### *BioShield did not attract significant attention from large pharmaceutical companies*

When Project BioShield was signed into law, the Pharmaceutical Research and Manufacturers of America (PhRMA) stated that they hoped for 'procurement provisions that more closely resemble the competitive private market in

which the biotechnology and pharmaceutical industries ordinarily operate,' which BioShield did not.<sup>9</sup> The funding of \$5.6 billion over 10 years was not seen as sufficient to entice involvement of the larger pharmaceutical companies, and selling a product for procurement to the US stockpile was just not seen as attractive to industry as a product that has recurring annual sales and a broader commercial market.<sup>6</sup> The pharmaceutical companies' experience in developing and manufacturing medicines and vaccines, and bringing them to market, was thus not available for biodefense countermeasures.

#### *BioShield contract uncertainties put developers at risk*

Countermeasure developers faced not only the technical risk that their products would fail in development, but also the market risk that their products would not be procured under BioShield, even if they were developed. While large biopharmaceutical companies have been uninterested in entering a market where the US government would be the sole customer, some smaller biotechnology companies pursued BioShield contracts, with varying success: the largest BioShield contract awarded, \$877 million contract to VaxGen for the delivery of 75 million doses of rPA (recombinant protective antigen) was canceled on 17 December 2006 for failure to meet a contract milestone.<sup>10</sup> In other cases, the HHS requests for proposals (RFPs) for BioShield contracts have been canceled or delayed. Companies have not been given a clear path to produce countermeasures, adding to the perception that developing countermeasures is a market risk.<sup>11,12</sup>

## **Pandemic and All-Hazards Preparedness Act provisions**

Title IV within the Pandemic and All-Hazards Preparedness Act legislation, signed on 19 December 2006, was intended to correct some of the shortcomings in BioShield. The Act gave the HHS the ability to support advanced-stage research and development (R&D) funding for medical countermeasures against CBRN threats, intending to bridge the Valley of Death for countermeasure developers. It also gave HHS authority to make milestone payments, among other contracting authorities, to facilitate medical countermeasure development by sharing the financial burden of development with the manufacturers.

Specifically, the Act includes the following provisions:<sup>2</sup>

#### *Establishes the Biomedical Advanced Research and Development Authority (BARDA)*

BARDA is intended to facilitate collaboration among the US government, relevant biopharmaceutical companies, and academic researchers for the purpose of developing medical countermeasures against CBRN threats. BARDA may bridge the Valley of Death in medical countermeasure development, because HHS can use its authorities to award contracts, prizes, and other means to support activities

performed *after* basic research and preclinical development, and *before* BioShield procurement.<sup>2</sup>

BARDA will be exempt from certain Freedom of Information Act (FOIA) disclosure requirements for information that 'reveals significant and not otherwise publicly known vulnerabilities of existing medical or public health defenses.' This exemption will be subject to review every five years, and sunsets (terminates) after seven years.

#### *Establishes the Biodefense Medical Countermeasure Development Fund*

There was \$1.07 billion authorized for advanced development funding, separate from the BioShield Special Reserve Fund. The authorization included funds already committed to advanced development programs, such as pandemic influenza preparedness and medical countermeasure development at NIH/National Institutes of Allergy and Infectious Diseases (NIAID). However, as of this writing, no funds have been appropriated for the BARDA development fund in FY2008. The President's FY2008 budget requests \$189 million for the BARDA fund, but it is not yet clear what will be appropriated by Congress.

#### *Establishes the National Biodefense Science Board*

Under the Act, the Board will 'provide expert advice and guidance to the Secretary on scientific, technical, and other matters... regarding current and future chemical, biological, nuclear, and radiological agents, whether naturally occurring, accidental, or deliberate. The board will consist of US government officials, 4 representatives of the biopharma and medical device industry, 4 academic representatives, and 5 others including at least one practicing healthcare professional and one representative of healthcare consumers.' The Act directs HHS to convene the first meeting of the Board in December 2007 (this meeting took place on the 17–18 December 2007; a report can be found here: <http://www.hhs.gov/aspr/omsph/nbsb/>). Working groups may also be convened under the Board, to give advice to BARDA about medical countermeasures. This may include identifying innovative research for development by BARDA, or identifying animal models or other research tools that could accelerate countermeasure development.

#### *Directs the FDA to provide technical assistance to the developers of medical countermeasures on manufacturing and regulatory processes*

These FDA experts will provide countermeasure manufacturers with off-site and on-site assistance.

#### *Gives HHS new authorities to expedite countermeasure development, including expanded authorities for BioShield*

The Act gives the Secretary of the HHS several new authorities to promote the development and procurement of medical countermeasures. These authorities include the ability to award procurement contracts, grants, and co-operative agreements; to select 'other transactions'

authority (in addition to the usual authorities allowed under the Federal Acquisitions Regulation<sup>13</sup>) as well as to expedite procurement authorities; to expedite to peer review; to offer personal service contracts; to waive advance payment and advertising requirements that govern US government contracts; to make awards to foreign nationals; and to establish research centers.

Most importantly, the Act specifies new BioShield contract authorities to make milestone payments (ranging from 5 to 50% of the total contract amount), which do not have to be repaid if the vendor fails to deliver finished product to the stockpile. In addition, HHS may enter into exclusive sales contracts, and may establish a 'warm-base manufacturing' capacity for a countermeasure, which means that there would be a limited amount of annual production of the countermeasure, which could be ramped up in a public health emergency. The Secretary of HHS was also granted some limited antitrust exemption authorities to facilitate communication to improve the development of medical countermeasures.

### **Challenges for implementation of the new authorities**

#### *Managing 'fixed' and 'flexible' countermeasures*

As the average drug or vaccine may take eight to 10 years to develop, and cost upward of \$800 million, developing and stockpiling medical countermeasures against each CBRN threat will require a great deal of time and money, and may not be possible.<sup>14,15</sup> For example, there are 28 biological agents in the 2006 DHS risk assessment that are thought to have potential use in terrorism.<sup>16</sup> If factors such as antibiotic resistance are considered in addition to these threats, the number of potential threats expands further. Natural biological agents will also certainly cause epidemics for which no countermeasure exists—as SARS did in 2003—and the current methods for producing medical countermeasures are insufficient to meet that need. In response to these concerns, there have been calls for an alternative medical countermeasure strategy to 'one bug, one drug' or 'fixed' defenses.<sup>17–19</sup>

The alternative is a 'flexible defense' for medical countermeasure development, which is now part of HHS's mission: BARDA is intended to promote 'innovation to reduce the time and cost of countermeasure ... development' as well as improve the development of research tools, rapid diagnostics, broad-spectrum antimicrobials, and vaccine technologies. The White House has also issued a directive (HSPD-18) for a 'broad-spectrum 'flexible' approach to address other current and future [CBRN] threats' in addition to defenses against a finite number of 'known or anticipated agents.'<sup>20</sup> This gives HHS a mandate to define operationally what a flexible defense will entail for medical countermeasures against CBRN threats.

HHS is not planning to abandon fixed defenses, which they 'determined to be effective and viable for some of the

highest priority threats such as smallpox and anthrax.<sup>21</sup> But beyond the specific countermeasures that are of the highest priority, HHS will be focusing efforts to develop and/or acquire 'broad-spectrum solutions using technologies that enable more flexible next generation interventional concepts.'<sup>22</sup>

Flexible defense has not yet been defined operationally, and the timelines for funding, developing, producing, and prioritizing a flexible defense strategy remain unclear.<sup>23</sup> Much research will be required to realize the goal of an effective antiviral arsenal, for example, and many relevant technologies are in their infancy. HHS statements recognize this and suggest that most flexible defense research will be pursued by NIH, whose 'long-term focus is on platform technologies and broad-spectrum medical countermeasures that will allow for the rapid introduction of additional response capabilities for emerging infectious agents.'<sup>24</sup> In addition to long timelines, HHS should consider how it will prioritize investment in these technologies. For example, it may be difficult to decide how funding for antiviral mechanisms may be more or less important than funding for new broad-spectrum antibiotics.

#### *Engaging the biopharmaceutical industry to make countermeasures*

Before BARDA, there were too many reasons for biopharmaceutical companies to not want to participate in developing and manufacturing CBRN countermeasures. In addition to the *structural* disincentives—such as the 'Valley of Death'—HHS actions have further discouraged industry participation. A BioShield contract was canceled;<sup>10</sup> RFPs have been canceled or delayed; and HHS has also been faulted for not providing a clear path to companies that would like to produce countermeasures.<sup>11,12</sup> It remains to be seen if BARDA authorities will change this environment. However, there is reason for optimism: there have been several recent contracts awarded. On 4 June 2007, HHS awarded a \$500 million contract to Bavarian Nordic A/S of Copenhagen, Denmark to deliver 20 million doses of a 'next generation' modified vaccinia Ankara (MVA) smallpox vaccine, indicated for people with weakened immune systems.<sup>24</sup> Bavarian Nordic will be the first BioShield contract to allow for advanced payment under BioShield as well as to provide milestone payments, authorized by the Pandemic and All-Hazards Preparedness Act.<sup>25</sup> There have also been several awards for anthrax countermeasures from BARDA and NIAID: Elusys Therapeutics Inc. has been awarded a \$12 million contract for Anthim, an anthrax therapeutic;<sup>26</sup> PharmAthene and Medarex were awarded \$13.9 million for development of Valortim, a monoclonal antibody targeting anthrax protective antigen;<sup>27</sup> Emergent BioSolutions was awarded contracts including up to \$11.5 million in milestone payments to advance a postexposure prophylaxis indication for BioThrax, the anthrax vaccine,<sup>28</sup> as well as a \$9.5 million for nonclinical and clinical studies of anthrax immune globulin.<sup>29</sup>

HHS has also made recent efforts to communicate more with the biopharmaceutical industry. They recently published a strategy document and implementation plan for medical countermeasure development,<sup>22,24,30</sup> they launched a stakeholders web portal, held a stakeholders workshop to get feedback on their plans in the summer of 2007, and held a 'BARDA Industry Day' for companies and stakeholders to demonstrate their technologies to HHS personnel.<sup>31</sup>

#### *Adequate funding and tolerance of risk for developing countermeasures*

Developing drugs or vaccines is not only expensive, but risky: more than 80% of pharmaceutical drugs in Phase I development will eventually fail.<sup>32</sup> Given these realities, it is likely that most CBRN countermeasures HHS will pursue will fail, and they will cost a great deal of money. Because this failure rate is well understood by industry, they require incentives to participate in making medical countermeasures for the US stockpile, such as rewards for milestones compared with only rewarding finished products. However, it is unclear whether the funders of the countermeasure effort—the US Congress—will understand that only a small portion of investments may succeed, and that each investment may be substantial. A concerted effort may be needed to make the Congressional and other governmental leaders understand the necessary risks associated with countermeasure development, as well as the necessary scale of investment in the nation's medical countermeasure enterprise.

#### **Conclusion**

The US government has taken steps to develop a system to procure medical countermeasures for CBRN threats, to protect its citizens in the event of a public health emergency. Without a commercial market to encourage the development of the vaccines, drugs, diagnostics, and technologies that are needed, the government has had to create a market, and encourage commercial developers of medical countermeasures to participate. Largely, it has done this through Project BioShield, and now through the BARDA, created through the Pandemic and All-Hazards Preparedness Act. It is too early to tell whether BARDA will be successful in its aims. However, the chance of its success will depend a great deal on whether these authorities are funded commensurate with their purpose, and in line with the commercial market.

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