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Research Commentary

Developing Medical Countermeasures: From BioShield to BARDA

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ABSTRACT The U.S. Congress passed the Project BioShield Act in 2004 to create market incentives for the private sector to develop medical countermeasures (MCMs) against high-priority chemical, biological, radiological, and nuclear threats. Two years later, Congress patched recognized gaps in the BioShield legislation by adopting the Pandemic and All-Hazards Preparedness Act of 2006, which established the Biomedical Advanced Research and Development Authority (BARDA) within the Department of Health and Human Services (DHHS). BARDA provides financial and managerial support for companies developing MCMs. This article examines U.S. government efforts in the MCM field and prospects for the future. Drug Dev Res 70:224–233, 2009. © 2009 Wiley-Liss, Inc.

Key words: medical countermeasures; biodefense; CBRN; BARDA; Project BioShield

INTRODUCTION

Shortly after the terrorist attacks of September 11, 2001, letters contaminated with anthrax bacterial spores were sent through the U.S. mail, killing 5 people and sickening 17 others. Since then, the federal government has stepped up its efforts to procure medical countermeasures (MCMs) to protect the U.S. civilian population against the effects of chemical, biological, radiological, and nuclear (CBRN) attacks, as well as pandemic diseases such as avian influenza. Licensed vaccines against anthrax and smallpox have been added to the Strategic National Stockpile, but effective countermeasures are still lacking for other agents of terrorism concern.

Although U.S. government spending on MCMs has increased sharply since 2001, it has been difficult to interest large pharmaceutical companies in developing such products. In general, Big Pharma prefers to invest in mainstream drugs for which there is a large, well-defined market and a clear path to regulatory approval by the Food and Drug Administration (FDA). These incentives are lacking for anti-infective drugs and are almost totally absent for CBRN countermeasures because the federal government is usually the only customer [Matheny et al., 2007]. To attract greater involvement by private industry, Congress has passed legislation creating new market incentives. This article describes efforts by the federal government to procure MCMs for civilian use, and the prospects for the future.

BIOSHIELD LEGISLATION

The Project BioShield Act, signed by George W. Bush on July 21, 2004, authorized the Department of Health and Human Services (DHHS) to purchase prophylactic and therapeutic MCMs against pathogens

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and toxins of bioterrorism concern, chemical warfare agents, and acute radiation syndrome caused by radioactive fallout from a nuclear weapon or a radiological "dirty bomb." Congress also established a $5.6 billion Special Reserve Fund to procure MCMs for the Strategic National Stockpile over a 10-year period (fiscal years 2004–2013) to avoid the uncertainty of the annual appropriations process.

The Project BioShield Act had a number of limitations, however. Under the terms of the original legislation, DHHS could agree to purchase a licensed or "licensable" drug or vaccine at the end of the research and development (R&D) process but could not provide the developer more than 10% of the value of the contract in advance payments prior to delivery. As a result, companies interested in developing an MCM had to bear most of the costs of advanced development, including expensive clinical trials, despite the risk that the product might fail to achieve licensure. Furthermore, the lack of federal funding for advanced development created a financial desert—colorfully termed the "valley of death"—between preclinical R&D (supported mainly by the National Institutes of Health [NIH]) and procurement under Project BioShield.

A second flaw in the BioShield legislation was that it contained the provision that MCMs purchased for the Strategic National Stockpile could have "no significant commercial market." Although the intent was to prevent large drug companies from profiting from the publicly funded development of MCMs by selling them for commercial uses, the end-result was to deter the development of broad-spectrum antimicrobial drugs that would be effective not only against agents of bioterrorism concern but also against major public-health threats, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant tuberculosis (MDR-TB) [Klotz, 2008].

A third problem with the BioShield legislation was that it did not provide companies with protection against liability claims in the event that an MCM administered during a public health emergency turned out to have unexpected adverse side effects. Although DHHS drew on existing indemnity provisions such as Public Law 85-804 for early procurement contracts, the uncertainty surrounding liability was a serious deterrent to industry participation. To address this problem, a tort-reform provision included in the Public Readiness and Emergency Preparedness (PREP) Act of 2005 conferred near-complete immunity on manufacturers with respect to emergency use of a biodefense drug or vaccine, with the exception of claims arising from willful misconduct. (Although the PREP Act does not currently include a compensation program, as soon as the law is invoked to waive liability, Congress must appropriate funds to compensate the injured parties.) Despite the legal immunity provided by the PREP Act, the high risks of MCM development and the small size of the market caused the major pharmaceutical companies to stay away.

To make matters worse, the first major contract under Project BioShield was a fiasco. After the 2001 anthrax mailings, the U.S. government sought to acquire a stockpile of anthrax vaccine that could be distributed to the public as a second line of defense (after antibiotics) in the event of another attack. In November 2004, DHHS awarded an $877 million contract to VaxGen, Inc., a small biotech company in Brisbane, California, for the purchase of 75 million doses of a second-generation anthrax vaccine called recombinant Protective Antigen (rPA). The contract committed VaxGen to deliver the first installment of 25 million doses in only 2 years, by November 2006 [Kaufman, 2004]. In setting this deadline, DHHS had no objective criteria by which to assess the technological maturity of VaxGen's product and did not take into account the complexity of vaccine development. In fact, the delivery schedule would have been nearly impossible even for a large, experienced company to meet. VaxGen later admitted that it knew the deadline was unrealistic and that the odds of success were only 10–15%, but it took the gamble in the hope of reaping a large profit [Rhodes, 2007].

When VaxGen encountered technical problems with the stability of its anthrax vaccine in May 2006, DHHS agreed to a 2-year extension for delivery of the initial lots. In November 2006, however, the FDA imposed a hold on VaxGen's Phase 2 clinical trial because the company did not have adequate data on the stability of the vaccine to resume human testing. After the company missed a key performance milestone, DHHS cancelled the contract on December 19, 2006. By that time, the government had lost confidence in VaxGen's ability to meet the terms of the contract by solving the stability problem in a reasonable amount of time [Merle, 2006]. According to an analysis by the Government Accountability Office, the watchdog arm of Congress, three major factors contributed to the failure. First, DHHS awarded the procurement contract to VaxGen when its product was at an early stage of development and critical manufacturing issues had not been resolved. Second, VaxGen took unrealistic risks in accepting the contract terms. Third, the two sides did not clarify critical requirements from the outset [Rhodes, 2007]. DHHS learned an important lesson from the VaxGen debacle. According to Gerald Parker, the Principal Deputy Assistant Secretary for Preparedness and Response, the department decided

to reduce risk by procuring MCMs at a more mature stage of development [Friedman, 2007].

Even before the collapse of the VaxGen contract, two competing bills had emerged in the U.S. Senate to address some recognized gaps in the BioShield program. Both pieces of legislation were drafted in early 2005, less than a year after the original Act had been adopted, because of the perception that more could be done to create market incentives for participation by private industry. The first bill, known as "Project BioShield II" and co-sponsored by Senators Joseph Lieberman (D-CT), Orrin Hatch (R-UT), and Sam Brownback (R-KS), proposed a major revamping of the BioShield program, including tax incentives to increase capital investment in MCMs and a "wild-card patent extension" provision that would give developers the right to extend the patent rights for up to 2 years on any commercial drug in their portfolio. This measure would have provided a major carrot for participation by large pharmaceutical companies, but opposition from generic drug manufacturers and consumer groups doomed the proposed legislation. Instead, Congress passed a more modest bill, co-sponsored by Senators Richard Burr (R-NC) and Edward Kennedy (D-MA), that patched some of the gaps in the Project BioShield legislation. Called the Pandemic and All-Hazards Preparedness Act (PAHPA), it was signed into law by President Bush on December 19, 2006.

One provision of the Act allows DHHS to make advanced payments to companies worth up to 50% of the value of a BioShield procurement contract prior to delivery of the licensed product, contingent on the successful completion of development milestones. The first contract to include pre-delivery payments was awarded on June 4, 2007, to Bavarian Nordic of Copenhagen, Denmark, for the manufacture and delivery of 20 million doses of a third-generation smallpox vaccine [Anonymous, 2007a]. Other private-sector incentives in the PAHPA legislation include a "limited antitrust exemption" that enables DHHS to act as matchmaker in selecting companies for the joint development of an MCM, such as a vaccine manufacturer and a firm specializing in adjuvants (compounds that enhance the immunogenicity and effectiveness of a vaccine).

COUNTERMEASURE DEVELOPMENT PROCESS

Developing MCMs for the civilian population has much in common with the process for commercial drugs and vaccines, but with some important differences. First, the Department of Homeland Security (DHS) conducts risk and threat assessments to determine whether a particular CBRN agent poses a "material threat" to U.S. national security. To date, DHS has issued Material Threat Determinations (MTDs) for nearly two dozen pathogens and toxins of bioterrorism concern, including the causative agents of botulism, plague, anthrax, multidrug-resistant anthrax, smallpox, tularemia, typhus, Q-fever, Rocky Mountain spotted fever, glanders, melioidosis, and several viral hemorrhagic fevers, as well as chemical nerve agents and ionizing radiation. In response to the MTDs, DHHS directs the development of countermeasures against the designated threat agents.

During the first phase of MCM development, basic research in academia and industry generates new insights into promising pharmacological targets in a pathogen or its human host. Much of this research is funded by the National Institute of Allergy and Infectious Diseases (NIAID), a component of the NIH. Program officers at NIAID identify areas where basic research is needed, issue Requests for Proposals (RFPs) on topics of interest, and award research grants to academic or government laboratories. Ever since the anthrax letter attacks, NIAID funding for biodefense research has soared, from $53 million in FY 2001 to $1.63 billion in FY 2008 [Franco, 2008]. The Department of Defense (DoD) also funds basic research and advanced development of MCMs for military use, some of which are relevant to civilian applications.

The drug discovery process is long and arduous, involving the combinatorial synthesis and high-throughput screening of libraries containing many thousands of compounds. Several years of laboratory research may be required to identify a "lead" molecule that interacts with a cellular target to prevent or cure an infectious disease. Once a lead has been identified, scientists modify its chemical structure in an effort to enhance desired pharmacological activity and eliminate unwanted effects. Promising lead compounds that emerge from basic research are made available to private industry by publication in the scientific literature or through patenting and technology-transfer arrangements. During pre-clinical development, the safety and efficacy of a drug candidate for the treatment of a particular disease are evaluated in studies in experimental animals. If the compound proves to be safe and effective in animals, the company applies to the FDA for Investigational New Drug (IND) status.

After receiving IND status, a drug candidate moves into three phases of clinical trials, which are performed in increasingly larger groups of human volunteers. Phase 1 trials are conducted with a small group of healthy volunteers to evaluate drug safety and arrive at a clinically effective dosage. Phase 2 trials involve a larger number of volunteers who are representative of the type of patient the drug is expected to benefit, and are designed to gather

additional safety data and determine efficacy. When the Phase 1 and 2 trials suggest that a drug candidate is both safe and effective, the company may proceed to Phase 3 trials, which involve thousands of subjects and yield safety and efficacy data of greater statistical significance. If a lead compound makes it through the three phases of clinical testing successfully, the developer applies to the FDA for a New Drug Application (NDA). Drug candidates that appear to offer significant improvement over existing products may receive a "priority review" that shortens the approval process from 18 months to six, but costs an additional $1 million per product [Matheny et al., 2007]. After FDA licensure, a drug or vaccine may be manufactured and marketed in the United States.

Throughout the drug development pipeline, from basic research to licensed product, the attrition rate is extremely high. For every 5,000 lead compounds synthesized in a research laboratory, only one makes it to final licensure. In addition, of the drug candidates that enter Phase 1 clinical trials, often after a decade of pre-clinical research and evaluation, only 20% reach the commercial market [Kola and Landis, 2004]. Because of this high level of technical risk, developing a new drug or vaccine typically takes between 8 and 10 years, followed by a year or more of regulatory review, and costs more than $800 million. Clinical trials are the most expensive part of the process [Borio and Gronvall, 2005].

On top of the normal risks of pharmaceutical research and development, MCMs involve additional complications. In clinical trials of a typical commercial drug or vaccine, efficacy can be tested against a naturally occurring disease in a field trial or a controlled hospital setting, yet such experiments are not possible with most diseases of biodefense concern, such as smallpox or inhalational anthrax. Not only is the natural incidence of the disease extremely rare, if it occurs at all, but deliberate exposure of human volunteers to the causative agent is clearly unethical. To address this problem, the FDA has established two alternate pathways for MCMs that cannot be tested in humans: the Animal Efficacy Rule and the Emergency Use Authorization.

Under the Animal Efficacy Rule, a biodefense drug or vaccine may be licensed for human use if it has been shown to be safe in human volunteers and effective in experimental animals exposed to the infectious or toxic agent. A particularly challenging aspect of the animal rule is that it requires elucidating the drug's mechanism of action. Although the FDA prefers the use of two different animal species for efficacy testing, alternative protocols may be approved on a case-by-case basis. Unfortunately, animal models have yet to be developed and validated for many infectious diseases of bioterrorism concern, and even when such models exist, they provide at best a rough approximation of a drug or vaccine's efficacy in humans. To date, the FDA has licensed only a few MCMs under the Animal Efficacy Rule. The first, pyridostigmine bromide, was approved in 2003 as a pretreatment against the chemical nerve agent soman; it had previously been licensed for treating the neurological disease myasthenia gravis. The FDA also relied on animal efficacy studies to approve the use of hydroxycobalamin, a drug used to treat smoke inhalation, as a countermeasure against cyanide. Nevertheless, it remains to be seen if the FDA will license new drugs or vaccines under the Animal Efficacy Rule.

The Emergency Use Authorization (EUA), a provision of the Project BioShield Act of 2004, allows the U.S. government to approve the use of unlicensed drugs and vaccines in a public health emergency, such as a bioterrorist attack or an influenza pandemic. Although unlicensed MCMs may be procured for the Strategic National Stockpile, the final decision to authorize their use must be made after the Secretary of DHHS has declared a public health emergency and not before. In 2007, however, FDA issued guidance describing general criteria for determining the suitability of an unlicensed drug or vaccine for emergency use [FDA, 2007]. Furthermore, because the time available for submission and review of an EUA request could be severely limited, the FDA accepts pre-EUA applications for candidate products and allows industry representatives to meet with FDA officials to discuss the steps required for an EUA designation [Nightingale et al., 2007].

The EUA provision also empowers the FDA to approve the emergency "off-label" use of a commercially available anti-infective drug to treat exposure to a bioterrorist threat agent. For example, during the anthrax letter attacks in Autumn 2001, DHHS authorized the off-label use of the antibiotic ciprofloxacin (Cipro®), manufactured by Bayer Corporation, for the treatment of inhalational anthrax. (In August 2000, the FDA had approved the use of ciprofloxacin only for prophylaxis following anthrax exposure in addition to the other indications for which Cipro was already approved.) To pressure Bayer to lower the price of the drug, DHHS threatened the company with compulsory licensing to generic manufacturers if it did not comply. This tough bargaining position worked, but it had a chilling effect on the U.S. government's relations with the pharmaceutical industry. Because DHHS depends on the good will of drug manufacturers, the department is unlikely to repeat this tactic. Indeed, in

subsequent price negotiations with industry, DHHS has not abused its bargaining leverage

DHHS COUNTERMEASURE ACQUISITION STRATEGY

In 2006, DHHS established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) to provide an integrated approach to the research, development, and acquisition of drugs and vaccines for the civilian population against both naturally occurring and deliberately induced public health threats. This program coordinates the MCM activities of the three DHHS internal agencies—FDA, NIH, and the Centers for Disease Control and Prevention (CDC)—and, more peripherally, those of the Department of Defense, Homeland Security, and Veterans Affairs. On March 20, 2007, DHHS released the final version of the *PHEMCE Strategy for CBRN Threats*, setting out the basic principles and priorities of the enterprise [DHHS, 2007a]. The *PHEMCE Implementation Plan*, issued in April 2007, specifies near-term, mid-term, and long-term goals for MCM research, development, acquisition, storage, maintenance, deployment, and use for the 15-year period from 2007 to 2023 [DHHS, 2007b]. Key elements of the strategy and implementation plan are as follows:

1. The top priority of the strategy is to acquire MCMs for the prophylaxis and treatment of the U.S. civilian population. In the event of a global public health emergency, however, the federal government may use stockpiled MCMs (such as smallpox vaccine) to meet critical needs in other countries.
2. MCMs for the civilian population are intended primarily for post-incident use, except for rare cases in which pre-event vaccination or antibiotic prophylaxis may be warranted. In general, the preferred strategy is to wait until a CBRN terrorist incident has occurred, use diagnostic tests to identify the causative agent, and administer the appropriate countermeasures. For this reason, DHHS has concentrated on developing vaccines and drugs that are effective after exposure and have a long shelf-life.
3. MCMs are intended to treat the acute health effects of CBRN agents, that is, within hours to weeks after exposure. Because of the demanding timelines that could arise in a public health emergency, "Push Packs" containing drugs and vaccines have been pre-positioned around the United States for distribution to any point in the country within 12 h. The CDC is also working with states and localities to increase the speed at which MCMs would be dispensed to the affected populations in the event of a terrorist attack or a major epidemic.
4. MCMs are designed for use by the majority of the civilian population, but DHHS recognizes the need to develop alternatives for individuals who are at risk of complications from standard vaccines because they have an impaired immune system or a preexisting medical condition, such as HIV infection.
5. DHHS seeks a balance between current and next-generation MCMs. Available drugs and vaccines will be considered for procurement if they meet critical, near-term needs and can be deployed effectively under current preparedness plans. At the same time, DHHS seeks to synchronize MCM development with the life cycle of current stockpiles. As existing lots expire, improved next-generation products should be available to replace them.
6. The development of "fixed" defenses against agents of bioterrorism concern should be balanced against more flexible approaches. Because of the impracticality of developing and stockpiling MCMs against every validated threat agent, DHHS has begun to pursue alternatives to the traditional "one bug, one drug" approach. To this end, the PHEMCE Strategy calls for exploiting new technologies to develop "broad-spectrum solutions."

The need for flexible approaches is also a major theme of Homeland Security Presidential Directive (HSPD)-18: Medical Countermeasures against Weapons of Mass Destruction, a government-wide acquisition strategy that President Bush signed on January 31, 2007. HSPD-18 calls for a two–tiered approach that balances "the immediate need to provide a capability to mitigate the most catastrophic of the current CBRN threats with long-term requirements to develop more flexible, broader spectrum countermeasures to address future threats" [White House, 2007]. In the case of high-priority threat agents, such as anthrax and smallpox, the focused development of specific drugs and vaccines is still warranted. At the same time, however, uncertainties in the threat environment—including the possibility that pathogens could be deliberately engineered to make them resistant to standard vaccines or antibiotics—require that the MCM development process be as rapid and flexible as possible.

Examples of innovative approaches to MCM development include: (1) techniques for identifying early markers of infection prior to the appearance of acute symptoms; (2) broad-spectrum anti-infective drugs that are effective against wide range of natural, bioengineered, and emerging pathogens; (3) novel

"platform" technologies for the rapid, cost-effective development of diagnostics, therapeutics, and vaccines in response to new threats; (4) improved in vivo, in vitro, and in silico models of infectious disease and toxicity; and (5) approaches to the manufacture of medical countermeasures that lend themselves to surge production in an emergency. An example of the latter is the production of influenza vaccine in cell culture rather than fertilized chicken eggs.

Innovative platform technologies, such as RNA interference and the stimulation of innate immunity, are still at an early stage of development. Another promising field is the use of high-throughput DNA synthesizers for the de novo construction of entire viral genomes. This technology could provide a systematic way of developing attenuated (weakened) synthetic viruses for use as vaccines. Redesigning and synthesizing a virus that incorporates hundreds of small changes in its DNA sequence may cause it to replicate more slowly and diminish its virulence, while still inducing immunity. In principle, the large number of mutations would make it hard for the virus to revert spontaneously to the virulent form, although more research is needed to address safety issues [Barry, 2008]. Given the long timelines involved in MCM development, it is important that the federal government fund "enabling technologies" such as animal models, reagents, and other tools that developers can use [Gronvall et al., 2007a]. In addition, it will be necessary for the FDA to refine its licensing policies for flexible MCMs. The approval process for broad-spectrum anti-infectives and polyvalent vaccines is likely to be particularly complex because of the need to demonstrate efficacy against a range of different pathogens.

MANAGEMENT OF MEDICAL COUNTERMEASURE DEVELOPMENT

Title IV of PAHPA created a new federal agency called the Biomedical Advanced Research and Development Authority (BARDA), whose mission is to utilize all available tools, including public–private partnerships, to manage the successful development of medical countermeasures against CBRN threats, as well as pandemic influenza and other emerging infections. BARDA is also responsible for procurement under Project BioShield. Reporting to the DHHS Assistant Secretary for Prevention and Response, the agency began operation in April 2007 and currently employs about 230 people. On July 5, 2007, DHHS released the *Draft BARDA Strategic Plan for Medical Countermeasure Research, Development and Procurement* [DHHS, 2007c]. According to this roadmap, BARDA's main missions are to identify the most promising products in the pipeline, shepherd companies through the "valley of death" by making milestone-based performance payments during advanced development, identify which products are ripe for acquisition for the Strategic National Stockpile, and promote innovations to reduce the time and cost of advanced development. In addition to providing financial and managerial support for advanced development, BARDA assists companies to overcome the technical hurdles associated with FDA licensing and manufacturing scale-up [Gronvall et al., 2007b].

Under BARDA's "TechWatch" program, staff members monitor academic and industrial research for promising new products and technologies relevant to the MCM mission. One approach is to send out a Request for Information (RFI), which may be either broad or narrowly focused, to identify countermeasures that are already on the market or under development [Gottron, 2007]. In addition, BARDA has a website for outreach to academic and industrial laboratories (www.MedicalCountermeasures.gov) that provides links to regulatory guidance, Requests for Proposal, and other documents. This site enables companies to submit information on products in development and to request meetings with BARDA officials.

For each top-priority CBRN threat, BARDA aims to manage risk by supporting the concurrent development of two or more alternative products, thereby increasing the odds that at least one successful drug or vaccine will emerge at the end of the pipeline. If multiple candidates make it through advanced development, BARDA will "down-select" at the procurement stage. In addition, for the next set of biological threat agents, BARDA will abandon the "one bug, one drug" paradigm. Instead of developing separate antibiotics to counter the causative agents of anthrax, plague, and tularemia, the agency plans to develop a single broad-spectrum antibiotic to cover all three. BARDA is also interested in identifying commercial drugs that have been licensed for treating particular diseases but might be relevant for biodefense indications, although additional clinical testing would be required for FDA approval.

BARDA program managers oversee the advanced development of MCMs by means of a series of milestones and decision points called the Technology Readiness Level (TRL) scale. Adapted from a system invented by the National Aeronautics and Space Administration, the TRL scale extends from 1 to 13 and measures the technological maturity of a product in the development pipeline. To determine the TRL level of products under development, BARDA staff members place calls to contractors every 2 weeks and conduct site visits every three months. In general, TRLs 1 through 8 cover basic research and pre-clinical

testing, while TRLs 7 through 11 cover advanced development, where eligibility for BARDA support begins. Nevertheless, the hand-off from basic research to advanced development, and from advanced development to procurement under Project BioShield, is determined on a case-by-case basis.

The TRL tracking system enables BARDA to provide companies with interim project funding when specific milestones have been reached. These pre-delivery payments are a lifeline for small biotech firms that operate on limited budgets, and create an incentive for private investors to provide outside venture capital for MCM development. According to an assessment by the Congressional Research Service, the use of the TRL milestone system should allow drugs and vaccines to mature longer before competing for procurement under Project BioShield, thereby reducing the risk of failure [Gottron, 2007]. Indeed, John M. Clerici, co-chair of the public health preparedness practice at the law firm of McKenna, Long & Aldridge, contends that if BARDA had existed back in 2004, the VaxGen debacle could have been avoided. DHHS would not have had to gamble on buying the anthrax vaccine based on data from Phase 1 clinical trials, a point in the development pipeline at which the odds of failure are 80%. With BARDA in place, it is possible to delay a final procurement decision until after Phase 2 clinical trials, when the chances of failure fall below 50%, or even later. The milestone approach also makes it possible to terminate projects that fail to meet expectations at an earlier stage (Clerici JM, personal communication).

In addition to managing the advanced development of MCMs, BARDA has continued to award procurement contracts under the Project BioShield Special Reserve Fund. In September 2007, Emergent BioSolutions (Rockville, MD) received a contract worth $448 million to supply 18.75 million additional doses of its BioThrax Anthrax Vaccine Absorbed (AVA) through 2010 [DHHS, 2007d]. This contract will replenish the supply of licensed anthrax vaccine in the Strategic National Stockpile, much of which has expired, until a next-generation vaccine can be acquired. As part of the deal, Emergent BioSolutions must extend the shelf-life of AVA from 3 to 4 years, and seek FDA approval for use of the vaccine for post-exposure therapy. DHHS also plans to contract with Emergent and other manufacturers to maintain a "warm" production base so that the vaccine stocks can be replenished as needed [Matheny et al., 2007]. In February 2008, BARDA issued an RFP for the procurement of at least 25 million doses of a second-generation (rPA) anthrax vaccine. The two leading contenders for the contract are Emergent BioSolutions and PharmAthene Corporation of Annapolis, Maryland [Schmirring, 2008].

INTERAGENCY COORDINATION

In general, DHHS takes the lead on developing MCMs that are primarily for civilian use, while the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD) in the Department of Defense (DoD) is responsible for those with mainly military applications. DoD has a number of innovative programs in the MCM field. For example, the Defense Threat Reduction Agency has a Transformational Medical Technologies Initiative (TMTI) that focuses on developing broad-spectrum defenses against bacterial pathogens and hemorrhagic fever viruses. In addition, the Defense Advanced Research Projects Agency (DARPA) has an Accelerated Manufacture of Pharmaceuticals program that seeks to create a cost-effective manufacturing system capable of producing 3 million doses of high-quality vaccine or monoclonal antibody in only 12 weeks.

HSPD-18 directed the Secretaries of DHHS and DoD to coordinate their MCM development efforts in order to promote synergy, minimize redundancy, and employ common requirements. To the extent that MCMs developed for the military are relevant for civilian use, DHHS may decide to transition them into advanced development and procure them under Project BioShield. The two departments have also created interagency coordinating committees that meet at multiple levels, including working groups in which representatives from NIAID, DARPA, and BARDA set requirements and examine each other's development pipelines to minimize redundancy. Nevertheless, a current impediment to collaboration is the fact that DoD and DHHS have different systems for managing advanced development: Whereas BARDA has 13 TRLs, the Joint Program Executive Office for Chemical and Biological Defense has only 9, and it has also defined a separate set of Manufacturing Readiness Levels (MRLs). Creating a harmonized management system for use by the two departments would make it easier to transition technologies, while making the process more transparent for industry.

STEPS TO IMPROVE MARKET INCENTIVES

BARDA has taken a number of steps to improve market incentives for drug companies to participate in MCM development. First, the agency is trying to expand the size of the market by selling U.S.-made biodefense drugs and vaccines to allied countries. At the November 2007 meeting of the Global Health Security Initiative (GHSI), the health ministers from

the G-7 countries plus Mexico discussed how "to address CBRN threats through research and development for novel medical countermeasures, and to explore options for expanded access to needed countermeasures" [Global Health Security Action Group, 2007]. The participating countries also expressed interest in establishing global stockpiles of MCMs under the auspices of the World Health Organization (WHO). These efforts are still at an early stage, however, and have been complicated by the fact that the GHSI countries do not agree on the urgency of the CBRN terrorism threat and have different priorities for countermeasure procurement. Second, BARDA is interested in acquiring broad-spectrum anti-infective drugs that are suitable for treating more common infectious diseases, enabling small biotechnology firms to access commercial markets rather than being forced to rely exclusively on government contracts. For example, as a treatment for smallpox, the biotechnology company Chimerix received a $37 million contract to develop an oral formulation of the antiviral cidofovir called CMX001 that is less toxic than the existing version, which must be administered intravenously. CMX001 is currently undergoing Phase 2 clinical trials and efficacy testing in animal models of smallpox. At the same time, Chimerix is developing the same drug to treat natural infections with human cytomegalovirus. In this way, the company has turned a government contract for a biodefense countermeasure into a commercial opportunity, significantly improving its financial prospects (Clerici JM, personal communication).

A few large pharmaceutical and biotechnology concerns have teamed with smaller companies on MCM development. For example, Genzyme Corporation partnered with Osiris Therapeutics to develop a formulation of adult stem cells to treat the potentially lethal complications of acute radiation syndrome [Anonymous, 2007b]. In other cases, a small biotech firm has developed an MCM and partnered with a large pharmaceutical company on the "back end" (manufacturing and marketing), which entails far fewer risks. For example, the British biotechnology firm Acambis PLC formed a joint venture with U.S. drug giant Baxter to produce a second-generation smallpox vaccine (Clerici JM, personal communication). Similarly, the Danish firm Bavarian Nordic teamed with U.S. heavyweight GlaxoSmithKline to manufacture a third-generation smallpox vaccine [Bavarian Nordic, 2004].

Nevertheless, although large pharmaceutical concerns have shown interest in developing vaccines and antiviral drugs against pandemic influenza, for which Congress has appropriated $7.1 billion, the more modest incentives offered by PAHPA have been insufficient to lure them into the MCM development field. For giant corporations like Merck and Pfizer, the economic disincentives still predominate, including the small size of the countermeasure market, the largely untested mechanism for licensure under the Animal Efficacy Rule, and the opportunity costs of foregoing more lucrative products. Expected revenues from BioShield contracts are well below the $3 billion or more that a large pharmaceutical concern can expect to earn from a new commercial drug [Matheny et al., 2007]. Indeed, a single blockbuster drug, the cholesterol-lowering statin Lipitor®, earned Pfizer $10.86 billion in 2004 [Pfizer, 2004].

Because of these factors, U.S. government contracts to develop MCMs remain chiefly of interest to smaller biotech firms that are less risk-averse and have lower earnings expectations. According to the Biotechnology Industry Organization (BIO), additional incentives will be needed to spark the interest of Big Pharma, including a clear commitment by the federal government to purchase certain products in specified quantities, better coordination among the government agencies involved in the procurement and regulation of MCMs, and higher and more consistent federal funding for development and procurement, including a greater assumption of risk by the government for products that lack a commercial market [Young, 2006].

THE ROAD AHEAD

The PAHPA legislation was the latest effort by Congress to overcome the economic and regulatory hurdles that have deterred pharmaceutical and biotechnology companies, large and small, from investing in MCMs. Managing the development and procurement process is a complex task involving multiple moving parts, including relations with private industry, other federal agencies, state and local health departments, and Congress [DHHS, 2008a]. The initial response from industry has been positive because BARDA has made the acquisition process more flexible and transparent. Thanks to the introduction of milestone payments during advanced development, more companies can afford to participate and there has been greater interest from the investment community (Clerici JM, personal communication).

With effective leadership and a strategic vision, BARDA can make a difference in acquiring MCMs for the Strategic National Stockpile. On April 14, 2008, DHHS announced the selection of the agency's director, Robin Robinson, Ph.D., who has both government and industry experience and led the successful effort to develop, procure, and stockpile the first H5N1 influenza vaccine approved for human

use [DHHS, 2008b]. Despite BARDA's promise, however, it remains underfunded. Although the PAHPA legislation authorized $1.7 billion for a Biodefense Medical Countermeasure Development Fund in fiscal years (FY) 2006 to 2008, the full amount was never appropriated. In FY 2007, Congress transferred $99 million to BARDA's advanced development fund from the NIAID biodefense research program. To disburse this money, BARDA signed an agreement with NIAID under which the two agencies jointly issued four advanced-development contracts in September 2007, shortly before the end of the fiscal year. In FY 2008, Congress appropriated $123 million for BARDA, a 41% cut from the President's budget request. This total included $102 million for advanced development and $21 million for BioShield management [ASM, 2007]. The FY 2009 BARDA appropriation included $250 million for advanced development and $22 million to manage Project Bioshield.

BARDA will remain a work in progress for some time as it smoothes out the kinks in the acquisition management process and improves its outreach to industry. Many companies do not yet understand what the agency wants or how to get their products considered for advanced development. In addition, BARDA is still searching for an organizational identity. Will it focus narrowly on the advanced development of MCMs or engage in more ambitious and innovative pursuits? The PAHPA legislation gives BARDA the authority to award some contracts with a "high risk, high reward" structure, similar to that employed by DARPA. If the new director decides to emphasize that approach, BARDA could invest heavily in the development of flexible platform technologies. Another question mark is whether Congress, which tends to be risk-averse, will give BARDA the resources it needs to accomplish its mission.

Inevitably, given the complexity of MCM development, much will have to be learned by trial and error. According to Robert Kadlec, M.D., an Air Force physician and biodefense expert who helped to draft the PAHPA legislation, "Originally we thought that BioShield would be the answer, but its limitations led to the creation of BARDA. Now it seems likely that further mid-course corrections will be needed. The nature of most government programs is imperfect incrementalism" (Kadlec R, personal communication).

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