

Anthrax Countermeasures: Current Status and Future Needs

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The U.S. government does not yet have the range of medical countermeasures needed to protect its citizens from anthrax and other potential bioweapons. In the event of an anthrax attack, treatment interventions in addition to antibiotics would be needed so that very ill patients can be treated and clean-up crews can be better protected, especially if an engineered strain is used. This article describes specific anthrax countermeasures that are in development, barriers to development, and potential mechanisms the government could use to accelerate the movement of these countermeasures through the pipeline. A key challenge will be to encourage the transition of promising leads from basic research to the product development stage, when they may qualify for BioShield funds.

IN THE THREE AND ONE-HALF YEARS since the October 2001 anthrax attacks, the federal government has taken steps to stockpile medical countermeasures (i.e., antibiotics and vaccine) to bioweapons for its citizens. The Strategic National Stockpile now contains large stores of antibiotics for anthrax, plague, and tularemia, as well as enough smallpox vaccine for the entire U.S. population. Yet, licensed drugs and vaccines are still lacking for many likely bioweapons. This is partly because of obstacles in the drug development and procurement process, but also because of the difficulty in linking academic research gains to product development in private industry.

This article examines the current federal incentives for developing medical countermeasures for civilian use, how companies and organizations are responding to those incentives, and strategies that have been suggested to spur countermeasure development for known biological threats. The efforts to produce additional countermeasures for anthrax, in particular, are highlighted: anthrax* is a proven biological weapon, and the nation's vulnerability to another attack remains high. This article describes specific anthrax countermeasures in develop-

ment, barriers to that development, and mechanisms the government potentially could use to accelerate the movement of these countermeasures through the pipeline.

THE NEED FOR NEW ANTHRAX COUNTERMEASURES

Anthrax disease results from a bacterial infection with *Bacillus anthracis*. The disease can take several forms: it can be cutaneous (in the skin), gastrointestinal, or inhalational. Inhalational anthrax, which afflicted 11 people in the October 2001 anthrax attacks, is associated with high mortality if it is not treated in the earliest stages. Inhalational anthrax follows the inhalation of *B. anthracis* spores, which then germinate and can cause disease. As a weapon, anthrax is lethal, potent, and highly resistant to sunlight and changes in temperature; because of its stability in the environment, decontamination requires intensive, expensive measures.^{1,2}

Currently, there are only two countermeasures available for anthrax: antibiotics and vaccine. When used together, they may have complementary effects, but both

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*Technically, *Bacillus anthracis* is the causative agent of anthrax disease. For the purposes of this article, however, the word "anthrax" will be used to refer to the disease *B. anthracis* causes, as well as *Bacillus anthracis* itself.

countermeasures have limitations. To prepare for another anthrax attack, additional anthrax countermeasures may need to be developed and stockpiled.

Antibiotics

Antibiotics may be used to treat people who are sick with anthrax, as well as to prevent disease in people who have been exposed to anthrax spores but are not yet sick. Because inhalational anthrax may have a long incubation period, ranging from 2 to 46 days (11-day median),³ many people could start taking antibiotics in order to prevent the disease if they knew they had been exposed. Today, there are enough licensed antibiotics in the U.S. Strategic National Stockpile (SNS) to treat approximately 20 million people for 60 days (the recommended duration of antibiotic prophylaxis).^{4,5}

However, antibiotics alone are unlikely to save the lives of people who don't begin treatment before the onset of advanced illness. *Bacillus anthracis* releases toxins that lead to hemorrhage (bleeding), edema (swelling), and necrosis (localized death of living tissue). These toxins persist in an infected person even after the bacteria are killed by antibiotics. The effect of the toxins of *B. anthracis* may be one of the reasons inhalational anthrax can cause death despite intensive medical care and a cocktail of antibiotics, as occurred with five of the victims who died in 2001.

In addition, if the anthrax strain used in 2001 had been engineered to be antibiotic-resistant, antibiotics currently in the SNS might have been completely ineffective. The former Soviet bioweapons program developed antibiotic-resistant forms of anthrax,⁶ and methods to create antibiotic-resistant strains using genetic engineering or bacterial selection are available in the open scientific literature and do not require much sophisticated knowledge in the biological sciences.^{7,8}

Another potential problem with relying solely on antibiotics is "nonadherence," a pervasive problem associated with the long-term use of medication. People who are exposed to anthrax spores, or who develop clinical anthrax infection, will be advised to take antibiotics for approximately 60 days. About 2,000 Washington, DC, postal workers were advised to complete 60 days of postexposure prophylaxis with antibiotics, but only 40% adhered to the recommended course.⁹ The adherence rate was 21% for postal workers potentially exposed to anthrax spores in the Morgan postal facility in New York City.¹⁰ Incomplete adherence to treatment after a large-scale attack could lead to "excess deaths"—that is, people who could have been saved by taking the full course of antibiotics—a conclusion supported by mathematical modeling efforts commissioned by the Department of Health and Human Services (DHHS)

(M. Boechler, R. Brookmeyer, L. Wein, written communication, 2004).¹¹

Vaccines

Besides antibiotics, the only other licensed countermeasure for the prevention of anthrax disease is Anthrax Vaccine Adsorbed (AVA or Biothrax®). Antibiotics do not stimulate immunity to anthrax, but vaccination for anthrax disease could provide long-term protection. AVA can prevent anthrax disease only if it is administered well before a person is exposed to anthrax spores. AVA could complement the use of antibiotics, however, if anthrax spores persist in a person's lungs and germinate after antibiotics are discontinued.¹² The vaccine also may help to protect people who do not fully comply with the recommended 60-day course of antibiotics.¹¹

AVA could have other uses after an attack. If a large geographical area were contaminated with anthrax spores, vaccination might be recommended for remediation workers who are to decontaminate the area. Vaccination also could be recommended for inhabitants who continue to live in a partially contaminated area, if full decontamination could not be achieved.

In September 2004, the Centers for Disease Control and Prevention (CDC) revised their recommendations on preventing anthrax disease to reflect the complementary roles of vaccine and antibiotics.¹³ The CDC recommendations now include 60 days of oral antibiotics, along with a three-dose AVA vaccination regimen (0, 2 weeks, 4 weeks). The difficulties of providing more than one vaccine dose to a large population, however, point to the need for a new anthrax vaccine that could be efficiently and rapidly delivered in a mass-vaccination campaign—a one-dose vaccine, preferably delivered through a transcutaneous, nasal, or oral route.

While vaccination with AVA may complement the use of antibiotics, it is not available in sufficient quantities to be useful in a large-scale attack. There are only 159 vials of licensed anthrax vaccine available for civilian use in the Strategic National Stockpile (SNS), which is enough to treat approximately 530 people.¹⁴ On May 6, 2005, DHHS awarded a BioShield contract to BioPort for an additional 5 million doses of the AVA vaccine, at a cost of \$122.7 million.¹⁵ AVA is not licensed for postexposure prophylaxis for prevention of inhalational anthrax or for use in a shortened 3-dose regimen, so a mass vaccination program would need to be conducted under an Investigational New Drug (IND) application.¹⁶ Typically, IND status is granted by the Food and Drug Administration (FDA) if it authorizes clinical trials of a new drug or a new use of a drug; in the case of AVA anthrax vaccine, everyone who receives it would be required to sign an in-

formed consent document and would need to be monitored for the vaccine's safety and efficacy.

THE CURRENT MEDICAL COUNTERMEASURE DEVELOPMENT PROCESS

The U.S. government plays a major role in developing countermeasures, particularly in funding and regulation, but most of the technical expertise for this process resides in academia, biotechnology companies, and pharmaceutical companies. In the U.S., the National Institutes of Health (NIH) is the largest supporter of basic research through its funding of academic scientists. This is where the normal drug development process starts (for a depiction of the timeline, see Figure 1).

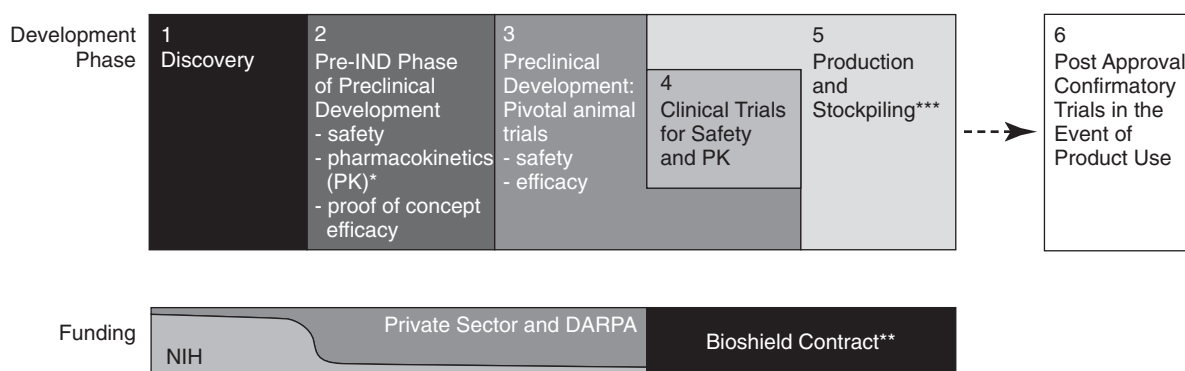
Years of discovery and effort will sometimes lead to the identification of a "target" within a human or a pathogen. A good drug will react or bind to these targets, preventing or curing disease. Once a good target is identified through basic research, it is typically the private sector biotechnology and pharmaceutical companies that develop promising leads into effective medicines and vaccines that can be licensed by the FDA. Once a product is licensed, it can be marketed by the manufacturer.

Scientists at biotechnology or pharmaceutical companies sift through thousands or even millions of potential "leads" to find a drug-like compound that binds to the target and has the desired effect. Once a lead is identified, chemists optimize it, and the compound eventually proceeds to evaluation in animal studies (also called preclinical

evaluation). If it is found to be safe and effective in animal models, the manufacturer may apply for Investigational New Drug status from the FDA. If the FDA grants an IND, the compound will proceed to three phases of clinical trials in human volunteers to test for safety and efficacy.

The development process for medical countermeasures against biological weapons differs from the usual drug development process at this step, because the efficacy of a countermeasure may not be able to be tested in humans. Usually, a medicine is challenged with the disease, either in a field trial or in a controlled clinical setting. This is not possible to do with inhalational anthrax: people rarely come down with the disease naturally, and it is not ethical to expose healthy human volunteers.

To address the problem of countermeasure efficacy testing in humans, the FDA created the Animal Efficacy Rule.¹⁶ The rule states that for FDA licensure, a countermeasure must protect animals from deliberate infection, and it must be safe in humans. The FDA prefers that two animal species be used in testing, but the agency can be consulted on the scientific appropriateness of other approaches. If the countermeasure is found to be *safe* in humans and *effective* in animals, the manufacturer may apply for a New Drug Application (NDA). If the NDA is approved by the FDA, the product may then be marketed in the U.S. In a typical drug development process, large-scale manufacturing begins only after FDA approval. For biodefense products, large quantities may be developed and placed in the Strategic National Stockpile prior to FDA approval, to be used if an Emergency Use Authorization is issued.¹⁷



* Pharmacokinetics (PK) involves characterizing the drug candidate for bodily absorption, distribution, metabolism and excretion.

** Early (Phase 1a) trials for safety and pharmacokinetics (PK) are desirable but not necessary, before Bioshield contract.

*** Once produced, the product may be granted an "EUA" (emergency use authorization) before FDA approval.

FIGURE 1. COUNTERMEASURE DEVELOPMENT PROCESS UNDER THE ANIMAL EFFICACY RULE

The process of going from a potential drug to manufacture is financially and technically risky. One study estimated that it takes from 5 to 15 years and over \$800 million to develop a drug or vaccine.¹⁸ Roughly half of the cost is attributed to the preclinical and clinical safety and efficacy testing (steps 3 and 4 in Figure 1).¹⁹ Investing this time and effort does not guarantee success, nor is it just a function of a paying market for the product. For example, genital herpes, which infects one out of four Americans,²⁰ may lead to a lifelong illness without a cure, though a cure for herpes would likely be very profitable to the company that makes it. The technical difficulties of producing an effective drug may result in a lack of therapies or vaccines for many illnesses, even though much effort and money have gone into the attempt. Only about one in five candidate drugs that are granted an IND are ever licensed.¹⁹

CURRENT FEDERAL INCENTIVES AND PROGRAMS FOR DEVELOPING MEDICAL COUNTERMEASURES

The federal government has recognized the lack of effective medical countermeasures for biological weapons and has responded by creating Project BioShield and by allocating additional monies for the National Institute of Allergy and Infectious Diseases (NIAID).

BioShield

On January 28, 2003, President Bush announced the creation of Project BioShield in his State of the Union address.²¹ The Project BioShield Act was signed into law on July 21, 2004.²² BioShield serves as a procurement mechanism, allowing the government to finance the stockpiling of countermeasures for biological, chemical, nuclear, and radiological weapons. Congress advance-appropriated \$5.6 billion to fund the entire 10-year term of the program.²³

Before a contract can be awarded, the Department of Homeland Security (DHS) must make a “material threat determination,” DHHS must evaluate the medical and public health consequences of the threat, and DHHS also must determine what medical countermeasures would be required to mitigate the threat. Only after interagency consultations and presidential approval may a contract be awarded. In addition, the government needs reasonable assurance that the specific countermeasure will be available in “sufficient quantities” and will be “licensable” by the FDA. The BioShield contract may specify that countermeasures that are not licensed at the time of delivery can be purchased at a discount, with a bonus payable to the manufacturer upon FDA licensure.

BioShield has an emergency-use authorization provision. The Secretary of DHHS, after consulting with the Directors of CDC and NIH, has the power to temporarily allow the use of countermeasures that lack FDA approval (or are approved only for other purposes) in the event of a biological, chemical, nuclear, or radiological event.

BioShield’s last major provision allows DHHS and NIH to relax their procedures under the Federal Acquisition Regulations for bioterrorism-related procurement and peer review. Procurement contracts up to \$25 million may be awarded under simplified acquisition procedures. Instead of following the usual peer-review process, BioShield allows an expedited award process for grants, contracts, and cooperative agreements up to \$1.5 million for countermeasure-related research and development.

In November 2004, the first BioShield contract for anthrax countermeasures was awarded to VaxGen, Inc., of Brisbane, California, for 75 million doses of a new “second generation” anthrax vaccine at a price of \$877.5 million.²⁴ This vaccine is a recombinant protective antigen vaccine (rPA), and it works by stimulating the immune system to produce antibodies against protective antigen, a component of *Bacillus anthracis*. rPA vaccine has an estimated shelf life of only 3 years, highlighting the importance of developing a “third-generation” anthrax vaccine with a longer shelf life.²⁵ On August 18, 2004, a request for proposals (RFP) was issued for the “Acquisition of Therapeutic Products for Treatment of Inhalational Anthrax Disease for the Strategic National Stockpile,” but no contract has yet been awarded.²⁶

NIH and NIAID

In FY2004, approximately \$3.8 billion was allocated to U.S. homeland security funding in the DHHS budget. Of this amount, nearly \$1.6 billion was allocated to NIAID to “accelerate development of new and improved vaccines, diagnostic tools, and therapies against potential agents of bioterrorism.”²⁷

Most of NIAID’s biodefense funding is directed at early basic research, discovery, and preclinical development (stages 1–3 of Figure 1). Among NIAID’s high-priority biodefense products, only a second-generation anthrax vaccine (rPA) is listed for anthrax.²⁸ While promising new directions for “next generation” anthrax countermeasures development have emerged from basic research on *Bacillus anthracis*, it is unclear how a promising lead from basic research should transition to the product development stage, when it can qualify for BioShield funds. The progression of technology transfer from basic research to production has been called a “valley of death”²⁹ for promising technologies, and, according to Dr. Anthony S. Fauci, Director of NIAID, “Until now, the path to product development has not been cen-

TABLE 1. EXAMPLES OF ANTHRAX THERAPEUTICS IN THE PIPELINE^{a,b}

<i>Anthrax countermeasure product</i>	<i>Mechanism</i>	<i>Development stage</i>	<i>Approximate investment to date (US\$)</i>	<i>Funding source</i>	<i>Company</i>	<i>Year founded</i>	<i>Licensed products</i>
Abthrax	Monoclonal Ab against PA	Phase 1 clinical trials completed; phase 2 clinical trials underway	10 million	Private investment	Human Genome Sciences, Inc.	1992	0
Anthim	Monoclonal Ab against PA	Advanced preclinical trials underway, including nonhuman primate trial	12 million	DOD/DARPA & private investment	Elusys	1998	0
Valortim	Human monoclonal Ab against PA	Preclinical trials underway	Not publicly available	Not publicly available ^c	Medarex and PharmAthene	1987 and 2001	0,0
Anthraxumab & unnamed product	Human monoclonal Ab against EF & human monoclonal Ab against LF	Preclinical trials underway	7.5 million	Dutch & Italian Ministries of Defense	IQ Therapeutics ^d	1993	0
Anthrax hyperimmune globulin	Human polyclonal antibodies	Preclinical trials underway	3.5 million+ (not publicly available)	CDC & other (not publicly available)	Cangene	1984	2

Unnamed product	Human polyclonal antibodies produced in cows ^e	Early preclinical development	25 million	Kirin Brewing Company; DOD's Joint Vaccine Acquisition Program; NIAID	Hemataech	1998	0
PlyG	Bacteriophage enzyme specific to anthrax	Early preclinical development	4 million	DARPA	Enzybiotics	2002	0
Adefovir	Nucleotide reverse transcriptase inhibitor that may block EF	Discovery phase (licensed for the treatment of chronic hepatitis B infection)	443,167 ^f		Gilead	1987	7

^aThe examples listed come from press releases from the manufacturers and the DHHS and do not include information that is not available to the public. Thus, the examples cited may not be a comprehensive list. The authors urge caution in interpreting this information, as press releases are not peer-reviewed, and the authors are unable to verify whether the information cited in press releases is accurate and complete.

^bMost of the products are antibodies (monoclonal or polyclonal), which bind the pathogenic components of anthrax bacteria (such as the protective antigen or toxins) and render them inactive. Other products have novel mechanisms of action.

^cIn October 2004, a press release stated that Medarex received one NIAID grant totaling approximately \$2.4 million to support preclinical research and development of its candidate, and, if all milestones are met, will be eligible for an additional \$4.8 million grant to support manufacturing and phase I safety clinical testing.

^dThe candidates were developed with assistance from Dstl Porton Down (UK), the Medical Biotechnology Center, and the U.S. Naval Medical Research Center (U.S.).

^eThis candidate is produced by immunizing "humanized" cows with anthrax. The cows have been genetically modified to produce human antibodies.

^fThe company has stated that it has no interest in pursuing the licensure of adefovir for any indication other than chronic hepatitis B infection. Studies on anthrax were being undertaken by Wen-Jei Tang, PhD, University of Chicago, with preexisting NIH General Medical Sciences academic grants; on May 10, 2005, NIAID announced a \$443,167 grant award for Dr. Tang's research, using authorities provided by BioShield allowing an expedited award process for grants, contracts, and cooperative agreements, up to \$1.5 million, for countermeasure-related research and development.⁴²

tral to [NIH/NIAID's] research strategy."³⁰ However, as Dr. Fauci stated, "The need for medical countermeasures for biodefense is exigent and real, and we have a responsibility to the American people to make these products available now."³¹ A process for shepherding promising ideas all the way through the development process still needs to be worked out.

NIAID pledged up to \$10 million in FY2005 "to support research projects focused on the design and/or pre-clinical development of therapeutics for CDC Category A agents." Category A agents are: anthrax, botulinum toxin, plague, smallpox, tularemia, and hemorrhagic fever viruses (such as Ebola). Up to \$1.5 million will be awarded for a project period of up to 18 months.³² Biodefense grantees are required to set strategic goals and milestones—a change from the traditional rules, priorities, and pace of NIH grants.[†]

NIAID also has expanded their Vaccine Treatment and Evaluation Units (VTEUs) for clinical testing by approximately 60% in the past year. The VTEUs are a network of university research hospitals across the U.S. that conduct clinical trials to test and evaluate candidate vaccines for infectious diseases. The VTEUs are not testing rPA vaccines being developed under NIH contracts, although one VTEU has conducted a phase I trial of a Department of Defense (noncommercial) vaccine for anthrax.³³ This new vaccine also is based on a laboratory-produced recombinant protective antigen (rPA). Government contractors will be able to produce pilot lots of experimental vaccines for use in clinical trials in Frederick, Maryland, for NIAID's Vaccine Research Center (the building is now under renovation, with an expected occupancy by the end of 2005³⁴).

SBIR

The Small Business Innovative Research (SBIR)³⁵ program "provides support for research and development of new or improved technologies and methodologies that have the potential to succeed as commercial products."³⁶ DHHS is required to reserve 2.5% of their extramural research or R&D budget for an SBIR program. However, the program has been criticized because venture capital-backed companies are ineligible,³⁷ the application process is complicated and time-consuming, and the amount of money granted is not commensurate with the development expenses of pharmaceuticals and other countermeasures.

[†]Biodefense researchers must submit quarterly progress reports according to milestones established at the beginning of the grant contract. There is an evaluation on a yearly basis, and biodefense researchers may lose the funds if the milestones have not been reached.

REACTION TO FEDERAL INCENTIVES

The Pharmaceutical Research and Manufacturers of America (PhRMA), representing the country's leading pharmaceutical research and biotechnology companies, had this comment on federal incentives for bioweapons countermeasures:

Senate passage of the BioShield bill is an important step forward in protecting Americans from bioterrorism. At the same time, it is necessary to recognize the scientific and other challenges, shared by the public and private sectors, and inherent in the research and development of bioterrorism countermeasures. We have urged, and still hope for, the enactment of additional measures, such as meaningful product liability protection for products specifically designed to be used (or used in new ways) to combat bioterrorism threats, as well as procurement provisions that more closely resemble the competitive private market in which the biotechnology and pharmaceutical industries ordinarily operate.³⁸

BioShield contains no liability protections for manufacturers, even though the risk may be higher than in other products. For example, biodefense countermeasures may secure FDA approval under the Animal Efficacy Rule. While safety testing of the countermeasures will be done in humans, efficacy tests will not, thus increasing the possibility of the countermeasure not performing as predicted. For example, vaccines have been shown to have variable efficacy in different species.³⁹

In addition to concerns about liability and development costs, large pharmaceutical companies have obligations to their boards of directors and shareholders. Current Securities and Exchange Commission accounting guidelines state that the companies cannot count payments for products as revenue unless the countermeasures are used;⁴⁰ thus, not recognizing revenue from government contracts may potentially hurt reported profits and earnings per share and, as a result, stock prices as well.

There are some reasons that large pharmaceutical companies with a great deal of experience and manufacturing resources might become interested in producing countermeasures: new vaccines are in general more profitable than old ones.⁴¹ Also, biologicals have a limited shelf life and will need to be replaced in the stockpile after several years, which could be an incentive for manufacturers to win contracts for several cycles.

Currently, however, small companies dominate the biodefense countermeasure market. For example, Vical, Inc., which has partnered with large companies like Merck and Aventis for some products, is working alone to develop a DNA vaccine for anthrax. Table 1 lists other companies that have anthrax countermeasures in development. Few of the companies listed have experience in

developing a product to FDA licensure. The examples in Table 1 come from publicly available DHHS and manufacturer press releases. We urge caution in interpreting this information, as the list may not be comprehensive and press releases are not peer reviewed.

Based on the available information, development of most of the products in Table 1 started prior to 2001, and most were funded by the Defense Advanced Research Projects Agency (DARPA).⁴³ As expected from the concentration of funding on early stages of countermeasure development, the increase in NIH funding for biodefense research does not seem to have affected the pace or scale of the development for these products. It is possible that the prospect of acquiring a BioShield contract facilitated the acquisition of private funding.

Small companies, which usually rely on limited venture capital funding, may have particular financial challenges in producing biodefense countermeasures. For example, to qualify for government contracts (such as BioShield), there may be rigorous security compliance requirements such as fenced-in, monitored facilities and secure computer networks. These features must be in place prior to securing a government contract, and expenditures for them are thus “at-risk” financial resources. In addition, the shortage of high-containment laboratory facilities capable of running animal efficacy tests lengthens the countermeasure development process, increasing financial risk.⁴⁴

DISCUSSION

The government does not yet have the range of anthrax countermeasures it needs for its citizens, nor does it have countermeasures for other potential bioweapons agents. In the event of an anthrax attack, more treatment options would be needed, so that very ill patients can be treated, clean-up crews can be protected, and people infected with engineered strains of the virus can be treated. The government needs to develop mechanisms so that a promising lead from basic research can make the transition to the product development stage, when it can qualify for BioShield funds (see Figure 1). Promising ideas need to be nurtured to fruition.

Several options are available for the government to improve the countermeasure development and acquisition process. Possibilities range from increasing direct government involvement in the drug development process to increasing financial incentives for pharmaceutical companies and biotechnology companies to produce countermeasures. While some believe that FDA regulations need to be eased in order to secure approval for countermeasure products, the FDA’s Animal Efficacy Rule may be a realistic balance of safety and speed. Dr. James H. Davis, Senior Vice-President and General Counsel of

Human Genome Sciences, remarked, “The FDA has been tremendous [and] has been doing everything possible to ease the path of these products.”⁴⁵

Guidance

The U.S. government could provide manufacturers with a guidance document that would define goals, priorities, and the market size for prospective countermeasures. DHS and DHHS could produce this document with guidance from the Weapons of Mass Destruction Countermeasures Subcommittee, which includes government officials from the Department of Defense, DHS, DHHS, and others. Countermeasures could be prioritized based on the immediacy of the threat; the type and size of the target population; whether a vaccine, prophylactic product, or drug would be the most appropriate countermeasure; whether the drug could be deployed on a mass scale; and whether the science base for the countermeasure is sufficiently developed to allow its manufacture.

The government also could clarify the selection process for BioShield funds. For example, if several companies are developing products with similar mechanisms of action, such as monoclonal antibodies, how will the government decide which product will merit a contract? Should it be the product in the most advanced stage of development? Or should it be the product that has the best potential or the longest estimated shelf life? Will companies continue to finance the development of a product after a contract has been awarded to a competitor? These questions have not yet been resolved.

The time cycles needed to secure BioShield investments are uncertain, and a company cannot afford to halt product development if a particular funding stream does not materialize. For example, Human Genome Sciences, Inc., reports that it is ready to scale-up manufacture of an anthrax countermeasure (a monoclonal antibody to rPA), but it will not do so unless it receives a federal contract. The company stated that it cannot justify additional expenses without a guaranteed market from the federal government.^{46,47}

Direct Involvement

It is debatable whether private investment should guide U.S. national security decisions. It has been suggested that the government should take a direct role in the countermeasure development process and assume more of the risk of development. This may be particularly important for bridging the gap between basic research, funded by NIH, and the point at which a potential countermeasure would qualify for BioShield funds.

The U.S. government could directly fund drug development via a DARPA-like approach, in which contracts with companies are extended only if specific milestones are met.^{48,49} Contracts could specify a lower cost for counter-

measure procurement in return for the government's taking on the costs of development risks. Promising leads from basic science could be funded to the point of IND filing and could be further developed later if the need arises—a process known as “strategic mothballing.” The U.S. government also could increase the scope of federal programs designed to encourage technology commercialization.⁵⁰

The NIH mission does not include developing products, but there is precedent for doing so when it is a high priority. For example, NIH awarded contracts to Acambis and Bavarian Nordic to develop MVA smallpox vaccine, and Avecia and VaxGen were awarded contracts to develop rPA anthrax vaccine. The NIH also has committed to the purchase of 8,000 doses of two pilot lots of avian influenza vaccine (H5N1) from Aventis Pasteur SA and Chiron for clinical trials that might enable the future licensing of the vaccines.⁵¹

The government also could propose a price for a given countermeasure, be it a therapeutic product, a vaccine, or a diagnostic test. A contract would be guaranteed on delivery of the requested product if all specifications were met. The government might then be obliged to purchase duplicate or even triplicate products if more than one company developed the specified product.

BioShield II

BioShield II, a bill that builds on BioShield, will likely be acted on this year in the 109th Congress. On January 24, 2005, Senator Judd Gregg (R-NH) introduced a bill titled “S3. Protecting America in the War on Terror Act of 2005.”⁵² It is intended to encourage the development of biodefense countermeasures as well as products to counter emerging infectious diseases. On April 28, 2005, Senators Joe Lieberman (D-CT), Orrin Hatch (R-UT), and Sam Brownback (R-KS) introduced the Project BioShield II Act of 2005 (S. 975), which is intended to create incentives for the pharmaceutical industry to use its own capital for biodefense countermeasure development.⁵³

A number of incentives to potential manufacturers of countermeasures will be considered, such as liability protections, patent extensions, and tax credits. Liability protection could protect companies from litigation in the event of unexpected adverse reactions after countermeasure use. Other options to protect companies were proposed at a hearing on October 6, 2004.⁵⁴ One option is to use Public Law 85–804,⁵⁵ which gives heads of designated U.S. government departments or agencies, including DHHS, the discretionary authority to grant contractors indemnity. It is also possible to extend the protections granted under the SAFETY (Support Anti-Terrorism by Fostering Effective Technology) Act to pharmaceuticals,⁵⁶ or to create a program similar to the National Vaccine Injury Compensation Program for biodefense countermeasures.

A key consideration involves the ability of the government to purchase products from a manufacturer other than the patent holder. In 2001, the U.S. government threatened to purchase a generic version of Cipro[®] to ensure a supply at a lower cost, even though Bayer held the patent.⁵⁷ In the end, Bayer cut its prices, other antibiotics for treating anthrax disease were identified, and a generic source of Cipro[®] was not pursued. However, the event was seen as detrimental to engaging pharmaceutical companies in producing biodefense countermeasures.

A potentially contentious issue will be if the definition of “qualified countermeasures” is expanded so that BioShield funds can be used for bioterrorism detection technologies and other research tools, in addition to biodefense vaccines, anti-infectives, and anti-toxins. Without additional funding for the BioShield special reserve fund, broadening the definition of qualified countermeasures could translate to less money being available for biodefense medical countermeasures.

CONCLUSION

Developing more and better countermeasures is expensive and technically difficult, especially because most countermeasures have a limited shelf life. Companies developing products of interest cannot wait—they must get funding or they may vanish, along with their products. For bioterrorism countermeasures, the government may be the only customer for these products. This underscores the need for the government to have a strategy for taking promising developments in basic research and shepherding them through development, ensuring proper inclusion in the stockpile, and replenishing the stockpile with more, better, and safer countermeasures.

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