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PUBLIC HEALTH PREPAREDNESS

Developing and Acquiring Medical Countermeasures Against Chemical, Biological, Radiological, and Nuclear Agents

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April 13, 2011

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Highlights

Highlights of GAO-11-567T, a testimony before the Subcommittee on Emergency Preparedness, Response, and Communications, Committee on Homeland Security, House of Representatives

Why GAO Did This Study

The anthrax attacks of 2001 and a radiation leak after the recent natural disaster in Japan highlighted concerns that the United States is vulnerable to threats from chemical, biological, radiological, and nuclear (CBRN) agents, which can cause widespread illness and death. Medical countermeasures—such as drugs, vaccines, and diagnostic devices—can prevent or treat the health effects of exposure, but few are currently available for many of these CBRN agents.

GAO was asked to testify on the Department of Health and Human Services' (HHS) CBRN medical countermeasure development and acquisition activities. This statement focuses on (1) how HHS determines needed CBRN medical countermeasures and priorities for development and acquisition and (2) selected challenges to medical countermeasure development and acquisition. This statement of preliminary findings is based on ongoing work. To do this work, GAO examined relevant laws and presidential directives, analyzed federal agency documents and reports from advisory boards and expert groups, and interviewed officials from HHS and the Department of Homeland Security (DHS) about the processes for developing and acquiring CBRN medical countermeasures and the challenges related to those efforts. GAO shared the information in this statement with HHS. HHS provided technical comments, which GAO incorporated as appropriate.

View GAO-11-567T or key components. For more information, contact Cynthia A. Bascetta at (202) 512-7114 or bascettac@gao.gov.

What GAO Found

HHS coordinates and leads federal efforts to determine CBRN medical countermeasure priorities and develop and acquire CBRN medical countermeasures, primarily through an interagency body that includes other federal agencies with related responsibilities, such as DHS and the Department of Defense. HHS's medical countermeasure acquisition strategy is based on a four-step process: (1) identify and assess the threat of CBRN agents, (2) assess medical and public health consequences of attacks with these agents, (3) establish medical countermeasure requirements, and (4) identify and prioritize near-, mid-, and long-term development and acquisition. Through these processes, HHS determines which countermeasures to buy for specific CBRN agents, including the desired characteristics of these countermeasures—such as how many doses a vaccine requires to confer immunity—the needed quantity of certain medical countermeasures, and the acquisition priorities. While a few CBRN countermeasures can be immediately acquired, most have not yet been developed. Therefore, HHS and the interagency body support and oversee several stages of research and development to try to obtain usable countermeasures. These include basic cellular and biological research to understand the effects of these agents on humans; applied research to validate approaches, such as testing the effectiveness of treatment in animals; early development to assess the safety of potential countermeasures; and advanced development, in which the products are more fully evaluated for safety and effectiveness, including their formulation and manufacturing processes.

The federal government faces a variety of challenges in developing and acquiring medical countermeasures, such as the high failure rate in research and development and difficulties meeting regulatory requirements. For example, the failure rate for development and licensure of most drugs, vaccines, and diagnostic devices can be more than 80 percent, depending on the stage of scientific research and development. Given this risk, as well as a lack of a commercial market for most medical countermeasures, attracting large, experienced pharmaceutical firms to research and develop them is challenging. Smaller biotechnology companies are more likely to be developing medical countermeasures, but HHS must provide more guidance to these less experienced small companies than might be typical with larger companies. In addition, several challenges exist related to regulatory processes for evaluating promising medical countermeasures. These challenges include (1) proving a countermeasure's effectiveness using animals as proxies for humans, because humans cannot ethically be used in studies involving CBRN agents; (2) determining appropriate doses of countermeasures for children, who may be more vulnerable to exposure to CBRN agents; and (3) evaluating the safety and effectiveness of medical countermeasures for use in a public health emergency if they have not yet been approved or licensed. Finally, HHS faces the logistical challenge of ongoing replenishment of expiring medical countermeasures in the U.S. Strategic National Stockpile, the national repository of medications, medical supplies, and equipment for public health emergencies.

Chairman Bilirakis, Ranking Member Richardson, and Members of the Subcommittee:

I am pleased to be here today to discuss the Department of Health and Human Services' (HHS) chemical, biological, radiological, and nuclear (CBRN) medical countermeasure development and acquisition activities and associated challenges.[1] The anthrax attacks of 2001 raised concerns that the United States is vulnerable to intentional threats from CBRN agents. In addition, the recent earthquake and resulting tsunami in Japan that caused a nuclear reactor to rupture highlighted a population's vulnerability to unintentional CBRN exposure, such as to radiation. CBRN agents have the potential to cause widespread illness and death, which can be partially mitigated through the use of medical countermeasures. Medical countermeasures for CBRN agents include drugs, vaccines, and devices to diagnose, treat, prevent, or mitigate potential effects of exposure. Members of Congress, federal commissions, and other experts have noted the need for the United States to acquire available medical countermeasures and develop new ones to protect the public from attacks with CBRN agents. While rapid diagnosis, treatment, and prevention may minimize the public health impact of a release of these agents, there are currently few countermeasures available for many CBRN agents, and research and development to create usable countermeasures is a lengthy and complex process.

You asked us to provide information about HHS's CBRN medical countermeasure development and acquisition activities. My statement today addresses (1) how HHS determines needed CBRN medical countermeasures and priorities for development and acquisition and (2) selected challenges to federal CBRN medical countermeasure development and acquisition.

To develop preliminary findings based on our ongoing work on HHS's CBRN medical countermeasure development and acquisition activities and selected challenges of these activities, we reviewed relevant laws and agency documents and interviewed federal officials. Specifically, to understand how HHS determines needed CBRN medical countermeasures and priorities for developing and acquiring them, we examined relevant laws and reviewed presidential directives that guide HHS's CBRN medical countermeasure development and acquisition activities. We obtained and

[1]See app. I for a list of abbreviations used in this statement.

analyzed HHS planning documents for medical countermeasure development and acquisition, such as public health and medical consequence modeling reports and strategy and implementation plans for medical countermeasure development and acquisition priorities. We interviewed officials from the Department of Homeland Security (DHS) about their activities related to CBRN agents and medical countermeasures. We also interviewed officials from HHS offices and agencies, including the Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response (ASPR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), to obtain information on their activities related to medical countermeasure development and acquisition. These officials participate in the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), HHS's interagency decision-making body responsible for providing recommendations to the Secretary of HHS regarding CBRN medical countermeasure development and acquisition. To identify selected challenges that the federal government faces in developing and acquiring CBRN medical countermeasures, we reviewed reports from federal agencies, advisory boards, and nongovernmental organizations and interviewed federal officials from the agencies identified above and other experts. We included selected challenges that were discussed in multiple reports published by federal agencies or other expert groups, such as the Institute of Medicine, or those mentioned to us by officials from multiple federal agencies or organizations. We did not include any challenges that related to interagency coordination and agency investments in medical countermeasure development and acquisition because we are currently examining these issues for ongoing audit work. In addition, because it was not the focus of this hearing, we excluded HHS processes for and challenges in distributing CBRN medical countermeasures from the scope of this statement. We shared the information in this statement with HHS. HHS provided technical comments, which we incorporated as appropriate.

We are conducting this performance audit in accordance with generally accepted government auditing standards. This statement is based on work conducted from March 2011 to April 2011. The performance audit standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Several federal departments and agencies have responsibilities for assessing the threat of CBRN agents and determining requirements and priorities for developing and acquiring medical countermeasures for these agents, as part of their mission and, in some cases, as specifically required by law.

DHS leads federal interagency coordination and planning for emergency response to catastrophic CBRN incidents. Under the Project BioShield Act of 2004, DHS is required, in consultation with HHS, to assess the threat of CBRN agents.[2]

HHS leads the federal medical and public health response to potential CBRN incidents.

- HHS established PHEMCE in 2006. PHEMCE is a federal interagency decision-making body responsible for providing recommendations to the Secretary of HHS on (1) prioritized requirements for CBRN medical countermeasures, (2) coordination of medical countermeasure development and acquisition activities to address the requirements, and (3) strategies for distributing medical countermeasures held in the U.S. Strategic National Stockpile (SNS), the national repository of medications, medical supplies, and equipment for use in a public health emergency. As required by the Pandemic and All-Hazards Preparedness Act of 2006, PHEMCE also conducts annual reviews of the SNS, the results of which are used to make necessary additions or modifications to its contents.[3] PHEMCE is composed primarily of officials from HHS's ASPR, BARDA, CDC, FDA, and NIH, which also have specific agency responsibilities for countermeasure development and acquisition. In addition, PHEMCE includes officials from DHS, the Department of Defense (DOD), the Department of Veterans Affairs, the Department of Agriculture, and the Executive Office of the President.

- Within HHS, ASPR is responsible for leading federal government efforts to research, develop, evaluate, and acquire public health emergency medical countermeasures to prevent, treat, or mitigate the potential health effects from exposure to CBRN agents. Under the Project BioShield Act, HHS is responsible for arranging for the acquisition of certain medical countermeasures, some of which may not yet be FDA-approved or

[2]42 U.S.C. § 247d-6b(c)(2)(A).

[3]42 U.S.C. § 247d-6b(a)(1).

licensed.[4] These countermeasures also include those for children and other vulnerable populations, such as those for the elderly and immunocompromised individuals. The Project BioShield Act authorized the Special Reserve Fund for acquisition of these countermeasures.[5]

- Within ASPR, BARDA—established by the Pandemic and All-Hazards Preparedness Act of 2006—is responsible for overseeing and funding advanced development and acquisition of CBRN medical countermeasures.[6]

- CDC is responsible for maintaining the SNS. CDC also supports state and local public health departments in their efforts to detect and respond to public health emergencies such as CBRN incidents, including providing guidance and recommendations for the mass distribution and use of medical countermeasures.

- FDA is responsible for assessing the safety and effectiveness of CBRN medical countermeasures and regulates their development, approval and licensure, and postmarket surveillance.[7] FDA also provides technical support for the development of tools to support medical countermeasure development. Under the Project BioShield Act, as delegated by the HHS Secretary, FDA may temporarily authorize the emergency use of

[4]42 U.S.C. § 247b(c)(7)(C)(i).

[5]42 U.S.C. § 247d-6b(c)(1)(A). The Department of Homeland Security Appropriations Act of 2004 appropriated over $5.5 billion to the Special Reserve Fund to be available for obligation from fiscal year 2004 through fiscal year 2013. Pub. L. No. 108-90, 117 Stat. 1137, 1148 (2003). The Project BioShield Act also authorizes the federal government to use specific contracting authorities to procure certain medical countermeasures for these agents and requires HHS to report on these contracting authorities and procurements using the Special Reserve Fund, among other information. 42 U.S.C. §§ 247d-6b, 247d-6c.

[6]42 U.S.C. § 247d-7e. The act also gave BARDA the authority to make advance and milestone-based payments to vendors prior to product delivery to the SNS. 42 U.S.C. § 247d-7e(c)(5)(C), (D).

[7]In FDA regulations, drugs are "approved," vaccines and other biologics are "licensed," and devices may either be "approved" or "cleared." For this statement, we use the term "approve" to refer to both approval and clearance.

unapproved or unlicensed medical products in certain circumstances through emergency use authorizations (EUA).[8]

- The National Institutes of Health (NIH) is responsible for conducting and coordinating basic and applied research to develop new or enhanced medical countermeasures and related medical tools for CBRN agents.

- The National Biodefense Science Board (NBSB), established by the Pandemic and All-Hazards Preparedness Act, provides the HHS Secretary with expert advice and guidance on scientific and technical matters related to current and future CBRN agents, including those that occur naturally.[9]

DOD has exclusive responsibility for research, development, acquisition, and deployment of medical countermeasures to prevent or mitigate the health effects of CBRN agents and naturally occurring diseases on Armed Forces personnel. Under the PHEMCE structure, DOD also coordinates with HHS on the Integrated Portfolio to identify common medical countermeasure priorities.[10]

[8]21 U.S.C. § 360bbb-3. FDA can issue EUAs only after the HHS Secretary declares a public health emergency and under certain circumstances. For example, FDA can issue EUAs in declared emergencies only if the agent specified in the emergency declaration can cause a serious or life-threatening disease or condition; the known and potential benefits outweigh the known and potential risks of the countermeasure to diagnose, prevent, or treat the condition; and there is no adequate, approved, and available alternative to the product, among other requirements. FDA has issued 19 EUAs since 2004. In 2005, FDA issued an EUA for an anthrax vaccine to allow vaccination of DOD personnel. FDA has also issued several EUAs for medical countermeasures to diagnose and treat pandemic strains of influenza. The only currently active EUA is for anthrax antibiotics in home kits for postal workers to be used in the event of an anthrax attack.

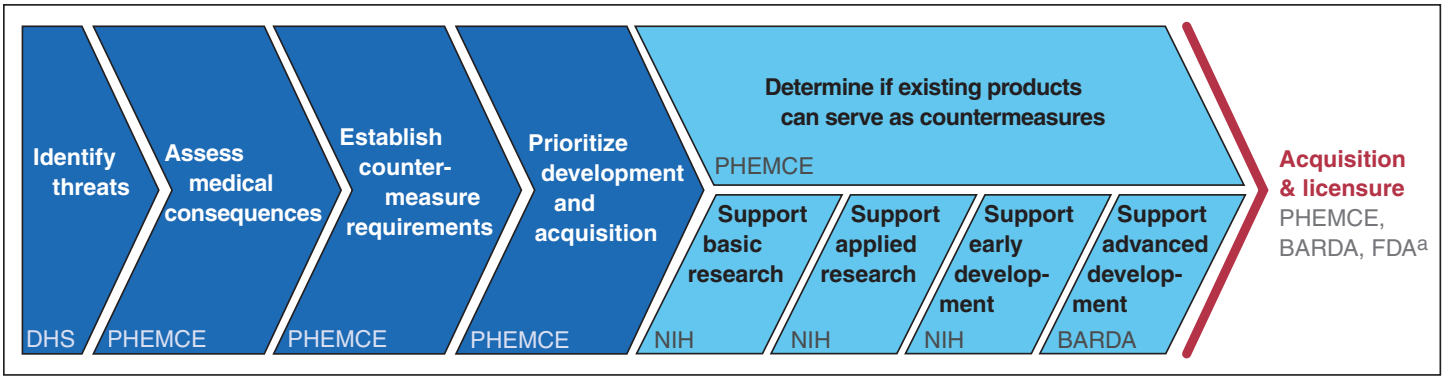
[9]42 U.S.C. § 247d-7f.

[10]The Integrated Portfolio is intended to reduce duplication of effort and provide a mechanism for HHS and DOD to share information and resources for common CBRN medical countermeasure priorities.

HHS, Through PHEMCE, Uses a Four-Step Process to Determine Acquisition Priorities for Medical Countermeasures and Oversees Their Development

HHS coordinates and leads federal efforts to determine CBRN medical countermeasure priorities and develop and acquire CBRN medical countermeasures, primarily through PHEMCE. HHS's medical countermeasure acquisition strategy is based on a four-step process: (1) identify and assess the threat of CBRN agents, (2) assess medical and public health consequences of attacks with these agents, (3) establish medical countermeasure requirements, and (4) identify and prioritize near-, mid-, and long-term development and acquisition programs.[11] Because desired CBRN medical countermeasures may not be immediately available for acquisition, HHS oversees and supports the various stages of research and development of these countermeasures, also under PHEMCE. (See fig. 1.)

Figure 1: Medical Countermeasures: Process to Prioritize Development and Acquisition



Source: GAO analysis of HHS information.

[a]FDA works with researchers throughout the development stages, to review safety and effectiveness test results, ensure that research meets FDA's regulatory requirements, and approve successful products for licensure.

[11]PHEMCE's near-term development and acquisition period is fiscal years 2007 and 2008; the midterm period is fiscal year 2009 through fiscal year 2013, and the long-term period is beyond fiscal year 2013. PHEMCE established these development and acquisition periods to correspond with appropriations for the Special Reserve Fund. The Department of Homeland Security Appropriations Act appropriated over $5.5 billion for the Special Reserve Fund to be available for obligation through fiscal year 2013 but provided that no more than $3.4 billion may be obligated through fiscal year 2008.

With input from HHS, DHS leads the first step in the process to assess, on an ongoing basis, the threat of CBRN agents and determine which of these agents pose a material threat to national security, as required by the Project BioShield Act.[12] The material threat assessments (MTA) that DHS issues examine the threat posed by given CBRN agents or classes of agents for plausible, high-consequence scenarios and provide estimates of the number of people exposed to different dose levels of an agent in the scenarios. Since 2004, DHS has determined that 13 of these CBRN agents pose a material threat, based on the MTAs.[13]

In the second step, HHS and its PHEMCE partners use the data from the MTA scenarios to assess the public health and medical consequences of an attack using these agents.[14] Public health consequence modeling estimates the number of individuals who may become ill, be hospitalized, or die from exposure to and infection with CBRN agents, with or without medical intervention. To develop these estimates from the MTA exposure data, HHS consults with experts and uses available scientific data, such as data on how much of an agent is needed to cause infection and how long it takes to develop symptoms of disease after exposure. In addition, HHS assesses the status of current countermeasure development and availability, including applicable countermeasures that DOD may be developing. Through consequence modeling, HHS determines the public health impact on the affected population in terms of the potential health effects throughout the course of disease based on different time frames for medical countermeasure delivery and treatment. According to HHS officials, consequence modeling allows PHEMCE to consider public health preparedness needs, such as whether a particular countermeasure is plausible or feasible for a certain CBRN agent and the amount that would be needed.

[12]Pub. L. No. 108-276, § 3(a), 118 Stat. 835, 842 (2004) (codified as amended at 42 U.S.C. § 247d-6b(c)(2)(A)(B)).

[13]The 13 agents that DHS determined pose a material threat to national security and public health are *Bacillus anthracis* (anthrax), *Burkholderia mallei* (glanders), *Burkholderia pseudomallei* (melioidosis), *Clostridium botulinum* (botulism toxin), Ebola virus (hemorrhagic fever), *Francisella tularensis* (tularemia), Junin virus (hemorrhagic fever), Marburg virus (hemorrhagic fever), multidrug-resistant *Bacillus anthracis* (MDR anthrax), *Rickettsia prowazekii* (typhus), *Variola major* (smallpox), *Yersinia pestis* (plague), and radiological and nuclear materials.

[14]To date, DHS has not issued determinations that any of the assessed chemical agents pose a material threat to the United States. Nevertheless, HHS has assessed the public health consequences of chemical agents for which DHS has developed MTAs.

In the third step, PHEMCE uses the consequence modeling results to determine requirements for needed medical countermeasures, including the needed quantity and the desired characteristics, such as how they would be used and stored. HHS officials told us that these requirements would include the preferred method of administration, such as oral administration of a medicine that can be stored at room temperature. PHEMCE partners consult with experts and incorporate intelligence information and information on state and local response capabilities to determine ideal countermeasure characteristics. If countermeasures that meet these characteristics are not immediately available, HHS may acquire countermeasures that are currently available and work with manufacturers over time to develop countermeasures that better meet the ideal characteristics.[15]

In the fourth step, the established medical countermeasure requirements help HHS assess and prioritize its countermeasure investments, and, according to HHS officials, form the basis for development and acquisition solicitations and contracts. Based on the requirements, in 2007, PHEMCE set its medical countermeasure acquisition priorities to focus on spending the remainder of the Project BioShield Special Reserve Fund for certain CBRN agents that DHS determined posed a material threat to national security. In addition, PHEMCE priorities focus on obtaining medical countermeasures for postexposure prevention or treatment of disease caused by those CBRN agents. HHS grouped these priorities in time frames for the near term (fiscal year 2007 through fiscal year 2008), midterm (fiscal year 2009 through fiscal year 2013), and long term (beyond fiscal year 2013). PHEMCE's stated priorities include acquiring diagnostics for each biological agent deemed a material threat, smallpox vaccine, medical countermeasures for Ebola and Marburg viruses, and medications to treat the acute and delayed effects of radiation. PHEMCE also uses the results of its annual SNS review to reassess prioritization of CBRN medical countermeasures, based on any SNS acquisitions made after the initial 2007 prioritizations.

[15]For example, HHS officials said that they would like to acquire an anthrax vaccine that confers immunity in a single dose, but because no such vaccine was available when HHS set the requirements, the department initially acquired a vaccine that could provide immunity in six doses. Through further research, HHS was able to determine that this vaccine could be administered in fewer doses.

BARDA oversees the acquisition and delivery of medical countermeasures into the SNS. If a medical countermeasure is not FDA-approved or licensed, its acquisition is funded by BARDA using the Project BioShield Special Reserve Fund. If a medical countermeasure is FDA-approved or licensed for use in treating the health effects of a CBRN agent, CDC purchases the countermeasure for the SNS. HHS officials told us that once FDA approves or licenses a countermeasure acquired with the Special Reserve Fund, BARDA is still responsible for overseeing its acquisition through the end of the Project BioShield contract. BARDA is also responsible for negotiating with the manufacturer to obtain additional quantities of the countermeasure in the event of a CBRN attack. CDC officials told us that they develop a 5-year project plan for each countermeasure in the SNS upon acquisition to evaluate specific needs over time—such as shelf life, replacement costs of expiring products, and storage and space requirements—and update the plan every year, or more frequently if conditions change.

HHS officials told us that of the few available medical countermeasures for CBRN agents, some are FDA-approved or licensed specifically for CBRN use. Other countermeasures that HHS has acquired for CBRN use have been approved or licensed for other uses only. For example, there are no currently available rapid diagnostic tools for any of the biological agents that DHS deemed material threats other than anthrax, nor are there any available medical countermeasures for postexposure prevention of disease for Ebola and Marburg viruses.

NIH and BARDA oversee and support CBRN medical countermeasure research and development, which is conducted in several stages.[16] (See fig. 1.)

- Early research: Early, or basic, research seeks to better understand CBRN agents and the response of the host organism to the agents through the study of the cellular and molecular biology of agents and hosts, their physiologic processes, and their genome sequences and structures. According to NIH officials, individual researchers typically initiate research in this stage. NIH assesses these research projects and their application for specific CBRN agents.

[16]FDA works with researchers throughout the development stages, to review safety and effectiveness test results, ensure that research meets FDA's regulatory requirements, and approve successful products for licensure.

- Applied research: Applied, or translational, research builds on basic research by validating and testing concepts in practical settings to identify potential products. NIH officials told us that the agency funds applied research to identify scientific or practical limitations that may affect the potential of a scientific concept to develop into a medical countermeasure product.

- Early development: NIH moves successful concepts from the applied research stage into the early development stage, in which it funds research to demonstrate basic safety, reproducibility, and ability to be used in humans. In its requests for research proposals for early development, NIH officials told us that the agency specifies its needs by product modes and categories, such as therapeutics, diagnostics, and vaccines; NIH can further specify the characteristics of a medical countermeasure, and companies agree to the terms of the contract up front.

- Advanced development: BARDA oversees and funds CBRN advanced research and development. In this stage, potential medical countermeasures are further evaluated in animal studies to demonstrate safety and effectiveness for preventing, diagnosing, or treating disease in humans. Successful products are then available for development and acquisition. In addition, in this stage, BARDA determines that manufacturing, scale-up production, and licensing of countermeasures can be achieved in a timely and reliable manner. BARDA also awards contracts using the Project BioShield Special Reserve Fund to acquire medical countermeasures for the SNS that are reasonably expected to qualify for FDA approval or licensure within 8 years.

Challenges to Development and Acquisition of Medical Countermeasures Include High Failure Rates in Research and Difficulties Meeting Regulatory Requirements

The federal government faces a variety of challenges in developing and acquiring medical countermeasures, such as the high failure rate in research and development and difficulties meeting regulatory requirements. One scientific challenge is that, as with other medical products, the failure rate for development of certain CBRN medical countermeasures can be high, depending on the stage of scientific research and development. HHS estimates that the failure rate for development and licensure of most drugs, vaccines, and diagnostic devices in the early development stage can be more than 80 percent, with an increasing probability of success as the product moves further through development. Because most CBRN research does not result in viable medical countermeasures, HHS officials told us that they try to fund a larger set of candidates in earlier stages of research in order to increase the likelihood that at least one candidate countermeasure may be successful. HHS officials noted that they would ideally prefer to have at

least two successfully developed medical countermeasures from different manufacturers available for a particular CBRN agent for several reasons, such as if certain segments of the population are resistant to one of the countermeasures or if one of the companies experiences manufacturing problems.

Given the high risk of failure in research, as well as a lack of a commercial market for most CBRN countermeasures, attracting companies experienced in meeting the complex requirements necessary to develop a new product is also challenging. The private sector—especially large pharmaceutical companies—has little incentive to invest millions of dollars to develop a potential new medical countermeasure because the lack of a commercial market makes a return on investment less likely or less lucrative. The Project BioShield Act facilitates the creation of a government market by authorizing the government to commit to make the Special Reserve Fund available to acquire certain medical countermeasures, including those that are not yet licensed or approved, provided they meet certain conditions.[17] In addition, the Pandemic and All-Hazards Preparedness Act established BARDA to support advanced research and development by, for example, awarding contracts and grants for countermeasure advanced research and development.[18] BARDA provides funding for advanced research and development for those countermeasures that are not eligible for the Special Reserve Fund. Nevertheless, despite the Special Reserve Fund and BARDA support, HHS and others have noted that engaging large pharmaceutical companies remains a challenge. In addition, smaller biotechnology companies conducting much of the research and development for medical countermeasures generally have less experience with drug development. As a result, FDA officials told us that they have to provide more regulatory and scientific guidance to these companies than they might provide to larger pharmaceutical companies, which generally have more experience with bringing products through the regulatory process.

There are also several challenges related to the regulatory processes for evaluating the development of promising medical countermeasures. For example, researchers face challenges proving the effectiveness of potential countermeasures because they cannot ethically or feasibly test the effectiveness of countermeasures on humans due to the dangers posed

[17]42 U.S.C. § 247d-6b(c)(4)(A).

[18]42 U.S.C. § 247d-7e(c)(4)(B).

by CBRN agents. However, because FDA requires evidence of a countermeasure's effectiveness for approval or licensure, researchers can submit evidence of effectiveness obtained from appropriate studies in animals in accordance with FDA's Animal Rule. The Animal Rule states that in selected circumstances, when it is neither ethical nor feasible to conduct human efficacy studies, FDA may grant marketing approval based on adequate and well-controlled animal studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans.[19] Under this rule, researchers can demonstrate effectiveness of medical countermeasures if the way a disease occurs in the animal being studied adequately mimics the way the disease occurs in humans. However, animals that manifest the disease in the same way as humans may not always exist for a given CBRN agent. For example, according to FDA officials, smallpox occurs only in humans, and related viruses that occur in animals, such as monkey pox, may not be similar enough to mimic smallpox in humans. Because of the complexities of using animal studies as models for human reactions to agents and potential countermeasures, FDA would prefer to meet with researchers earlier and more frequently, and FDA takes longer to evaluate product applications for CBRN medical countermeasures than to evaluate other medical products. In addition, the NBSB and others have reported that researchers face difficulty in applying FDA's draft guidance on the Animal Rule, which is currently under revision. According to the guidance, the agent tested in the animal must be identical to the agent that causes human disease. However, as discussed above, some animal studies may not meet that criterion and therefore cannot be used to demonstrate a countermeasure's effectiveness. To date, FDA has not approved any newly developed CBRN medical countermeasures based on animal model testing.[20]

Determining appropriate doses of CBRN countermeasures for children, who may be more vulnerable to the adverse effects of a CBRN agent, also involves regulatory challenges.[21] Most approved or licensed CBRN medical

[19]21 C.F.R. §§ 314.600-.650; 601.90-.95.

[20]Under the Animal Rule, FDA has approved existing products for CBRN use, such as drugs to treat the effects of nerve gas and cyanide exposure.

[21]See National Commission on Children and Disasters, *2010 Report to the President and Congress* (Rockville, Md.: October 2010). According to the report, in a CBRN incident children may be more vulnerable to exposure than adults because children inhale more air and consume more water in comparison to their body weight than adults.

countermeasures have been approved for use in adults only and lack pediatric dosing information. In addition, several candidate medical countermeasures currently in development lack or have limited pediatric dosing information. Regulations restrict children's participation in clinical trials when they do not benefit from them;[22] therefore, developing pediatric dosing information relies on existing adult data or data from animal studies.

There are also challenges in the processes for evaluating the emergency use of a promising medical countermeasure that has not been FDA-approved or licensed for treatment or postexposure prevention of disease for a given CBRN agent. In order for the government to use an unapproved countermeasure to respond to a CBRN event, FDA must issue an EUA. FDA can issue EUAs only after the HHS Secretary declares a public health emergency. In order for FDA to issue an EUA, CDC or another government or private entity has to submit detailed information for FDA to evaluate, such as available safety and effectiveness information, a discussion of risks and benefits of using the unapproved countermeasure, draft fact sheets for health care providers and patients, and instructions for using the countermeasure. While CDC or other entities may submit all available data for FDA review in advance, such as when CDC acquires a countermeasure for the SNS, the agency must formally submit the EUA request at the time of the declared emergency. In the event of an attack with a CBRN agent that can cause disease within hours or days after exposure, CDC and FDA would have to process the final documents quickly in order for FDA to issue EUAs for appropriate medical countermeasures. Further, the Project BioShield Act precludes the use of data collected during the emergency use of an unapproved product to constitute a clinical investigation to support later product approval.[23]

Finally, CDC faces the logistical challenge of ongoing replenishment of expiring medical countermeasures in the SNS. CDC can work with FDA to extend the expiration date of certain drugs in the stockpile, and thereby defer the cost of replacing the countermeasure and extend its availability for use in a potential CBRN event. In such cases, however, FDA has to conduct studies to ensure stability and quality of each drug. In addition, CDC faces the cost of relabeling the products to reflect the new expiration date. If the shelf life of an expiring countermeasure cannot be extended,

[22]21 C.F.R. §§ 50.50-.56.

[23]21 U.S.C. § 360bbb-3(k).

CDC must replace it. For some countermeasures in the SNS, CDC may not face this challenge. For example, CDC officials told us that anthrax vaccine is moved out of the SNS before expiration because CDC rotates it out to DOD facilities for routine use.[24] In addition, other countermeasures may be held for the SNS by private vendors and can be used commercially, provided that the vendors hold a certain amount for use in the event of a public health emergency.

Chairman Bilirakis, this concludes my prepared statement. I would be happy to answer any questions that you, Ranking Member Richardson, or other Members of the Subcommittee may have.

GAO Contact and Staff Acknowledgments

For further information about this statement, please contact Cynthia A. Bascetta at (202) 512-7114 or bascettac@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this statement. Key contributors to this statement were Marcia Crosse, Director; Sheila K. Avruch, Assistant Director; Shana R. Deitch; Tracey King; Corissa Kiyan; Carolina Morgan; and Roseanne Price.

[24]CDC and DOD have an agreement to share anthrax vaccine, which CDC holds in the SNS for DOD use.

Appendix I: Abbreviations

ASPR	Office of the Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
CBRN	chemical, biological, radiological, and nuclear
CDC	Centers for Disease Control and Prevention
DHS	Department of Homeland Security
DOD	Department of Defense
EUA	emergency use authorization
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
MTA	material threat assessment
NBSB	National Biodefense Science Board
NIH	National Institutes of Health
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
SNS	U.S. Strategic National Stockpile

GAO's Mission

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