



March 2014

# NATIONAL PREPAREDNESS

HHS Has Funded  
Flexible  
Manufacturing  
Activities for Medical  
Countermeasures, but  
It Is Too Soon to  
Assess Their Effect

# GAO Highlights

Highlights of [GAO-14-329](#), a report to congressional committees

## Why GAO Did This Study

Public health emergencies, such as the 2001 anthrax attacks and the 2009 H1N1 influenza pandemic, raise concerns about the nation's vulnerability to threats from CBRN agents and new or reemerging infectious diseases, such as pandemic influenza. HHS is the federal agency primarily responsible for identifying medical countermeasures needed to address the potential health effects from exposure to CBRN agents and emerging infectious diseases. HHS conducted a review to assess how to better address these concerns. Its August 2010 review concluded that the advanced development and manufacture of CBRN medical countermeasures needed greater support. The review recommended that HHS develop centers to provide such support, in part by using flexible manufacturing technologies, such as disposable equipment, to aid in the development and rapid manufacture of products.

The Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 requires GAO to examine HHS's flexible manufacturing initiatives and the activities these initiatives will support. This report addresses (1) how much funding HHS has awarded for flexible manufacturing activities for medical countermeasures, and (2) the extent to which these activities will support the development and production of CBRN medical countermeasures. To address these objectives, GAO examined HHS documents and interviewed HHS officials, contractors, and stakeholders. In comments on a draft of the report, HHS agreed with its findings and provided additional information.

View [GAO-14-329](#). For more information, contact Marcia Crosse at (202) 512-7114 or [crosse@gao.gov](mailto:crosse@gao.gov).

March 2014

## NATIONAL PREPAREDNESS

### HHS Has Funded Flexible Manufacturing Activities for Medical Countermeasures, but It Is Too Soon to Assess Their Effect

## What GAO Found

In fiscal years 2012 and 2013, the Department of Health and Human Services (HHS) Biomedical Advanced Research and Development Authority (BARDA) awarded nearly \$440 million in contracts to establish three Centers for Innovation in Advanced Development and Manufacturing (CIADM) and a network of facilities to provide packaging support for medical countermeasure distribution, known as the Fill Finish Manufacturing Network (FFMN). The contracts require the CIADMs to develop three activities to support flexible manufacturing for medical countermeasure development and production: the manufacture of pandemic influenza vaccines during an emergency; core services to support the development and production of chemical, biological, radiological, and nuclear (CBRN) medical countermeasures; and workforce training. During the contract base periods, each CIADM is to retrofit existing or build new facilities able to produce 50 million doses of pandemic influenza vaccine within 4 months of receipt of the influenza virus strain and to establish the capacity to provide core services, such as assisting countermeasure developers by manufacturing products to be used for clinical trials. The CIADMs are also required to develop workforce training programs, which are intended to increase expertise in CBRN medical countermeasure development. The CIADM base contracts are intended to retrofit or build facilities to stand ready to provide these three activities and maintain this readiness through annual contract option periods. Once the facilities are prepared to provide these activities, BARDA may place task orders for provision of CIADM vaccine surge capacity, core services, or training, and BARDA, through the task orders, would provide additional payments to obtain these services. The FFMN is to supplement CIADMs' pandemic influenza surge capacity, packaging up to 117 million doses of pandemic influenza vaccine in 12 weeks, if needed, and can also provide core services as CIADM subcontractors.

HHS's CIADM core services activities are designed to support the development and production of certain CBRN medical countermeasures, but it is too early to tell how effective this approach will be. BARDA's establishment of the CIADMs implements a recommendation from HHS's review of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)—a federal interagency body that advises HHS on medical countermeasure priorities. The CIADMs are to support the development of biologics-based countermeasures only, which are products like vaccines that are derived from living sources such as cells, because BARDA considers these countermeasures to need the greatest support. BARDA has identified some of its current biologics-based countermeasure development contracts that could use core services' support and are priorities for PHEMCE. However, the CIADMs are still completing activities associated with their contract base period. Thus, BARDA has not issued any task orders for core services to date, but has created a CIADM steering committee and completed guidance to govern the task order process once the CIADMs are operational. Until the CIADM core services are used, it will be unclear how effectively they will support the development and production of CBRN medical countermeasures. Stakeholders we interviewed were uncertain about the demand for and availability of funding for core services. BARDA officials said that they anticipate having sufficient demand for the services and funding for task orders in fiscal years 2014 and 2015.

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## 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
CIADM	Centers for Innovation in Advanced Development and Manufacturing
DOD	Department of Defense
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
NIH	National Institutes of Health
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act of 2013
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
TAMUS	Texas A&M University System

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March 31, 2014

The Honorable Tom Harkin  
Chairman  
The Honorable Lamar Alexander  
Ranking Member  
Committee on Health, Education, Labor, and Pensions  
United States Senate

The Honorable Fred Upton  
Chairman  
The Honorable Henry A. Waxman  
Ranking Member  
Committee on Energy and Commerce  
House of Representatives

Public health emergencies in the new millennium—such as the 2001 anthrax attacks and the 2009 H1N1 influenza pandemic—continue to raise concerns about our nation’s vulnerability to threats from chemical, biological, radiological, and nuclear (CBRN) agents and new or reemerging infectious diseases. The Department of Health and Human Services (HHS) is the federal agency primarily responsible for identifying needed medical countermeasures to prevent or mitigate potential health effects from exposure to such threats. As part of that task, HHS works with other federal agencies to engage with industry to develop medical countermeasures through its Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). PHEMCE is a federal interagency body—composed of certain HHS agencies and offices, the Departments of Defense and Homeland Security, and others—established in 2006 and responsible for providing recommendations to the Secretary of Health and Human Services on medical countermeasure priorities and development and production needs.

There are some medical countermeasures—drugs, vaccines, and devices to diagnose, treat, prevent, or mitigate potential health effects of exposure—available for these agents and diseases. However, as with drugs and other pharmaceuticals in general, research and development to create usable countermeasures for CBRN agents and emerging infectious diseases is a lengthy, complex, and expensive process. The general lack of a commercial market for some medical countermeasures may reduce incentives for large pharmaceutical and medical device manufacturers to invest millions of dollars to develop such products,

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instead of others that may be more profitable. Hence, many medical countermeasure developers are small biotechnology companies with less experience than larger pharmaceutical companies in developing a product and bringing it to market.

In addition to the lack of incentives for larger pharmaceutical companies and the limited experience of smaller biotechnology companies, the 2009 H1N1 influenza pandemic raised particular concerns about the United States' ability to rapidly manufacture needed medical countermeasures for CBRN threats and new or reemerging infectious diseases.<sup>1</sup> As a result, in August 2010, HHS conducted a review of PHEMCE's activities to develop and produce needed medical countermeasures.<sup>2</sup> In its review, HHS concluded that the United States must have a nimble, flexible capability to rapidly produce medical countermeasures for CBRN threats or emerging infectious diseases in a public health emergency and that this capacity was lacking. The review also highlighted the need for more support for smaller biotechnology companies conducting advanced research and development of countermeasures, including assistance in moving countermeasures through clinical trials and developing and producing them to the point at which HHS would be able to procure them.<sup>3</sup> In the PHEMCE review, HHS also recommended that the department, either alone or in collaboration with the Department of Defense, establish centers to provide advanced development and manufacturing capability for medical countermeasures to address national security and to augment public health needs on a cost-effective, reliable, and sustainable basis. These centers are intended to support flexible manufacturing—that is, the use of disposable equipment and alternative technologies for product development and rapid manufacturing—to aid in the development and production of medical countermeasures. In its PHEMCE review, HHS stated that these centers would strengthen

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<sup>1</sup>See GAO, *Influenza Pandemic: Lessons from the H1N1 Pandemic Should Be Incorporated into Future Planning*, [GAO-11-632](#) (Washington, D.C.: June 27, 2011). For a list of our other reports regarding national preparedness for CBRN threats and new or reemerging infectious diseases, see the Related GAO Products later in this publication.

<sup>2</sup>Department of Health and Human Services, *The Public Health Emergency Countermeasures Enterprise Review: Transforming the Enterprise to Meet Long-Range National Needs*, (Washington, D.C.: August 2010). The Secretary of Health and Human Services called for this review in December 2009.

<sup>3</sup>Clinical trials are research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans.

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countermeasure development by linking countermeasure developers with needed expertise, using and improving flexible manufacturing technologies, augmenting manufacturing surge capacity against emerging infectious diseases or unknown threats, and helping train future countermeasure developers. In June 2012, HHS awarded three contracts to establish three Centers for Innovation in Advanced Development and Manufacturing (CIADM).

The Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) requires that we examine HHS's flexible manufacturing initiatives and the activities these initiatives are to support.<sup>4</sup> This report addresses (1) how much funding HHS has awarded for activities to support flexible manufacturing for medical countermeasures since fiscal year 2010, and (2) the extent to which these activities are to support the development and production of CBRN medical countermeasures.

To answer the first objective, we obtained and analyzed HHS financial data to calculate how much HHS awarded for flexible manufacturing capacity since fiscal year 2010, the date of publication of the PHEMCE review. We also analyzed the three contracts HHS awarded to establish the CIADMs to determine the amounts awarded under each contract and the activities each center will carry out. We interviewed officials from HHS's Office of the Assistant Secretary for Preparedness and Response (ASPR), ASPR's Biomedical Advanced Research and Development Authority (BARDA), and officials from each of the three CIADMs to determine the activities these funds are intended to support and the current status of the CIADMs. Finally, we interviewed two relevant stakeholder groups for their perspectives on planned center activities. Of these two stakeholder groups, we interviewed officials from one association that represents more than 1,000 domestic and international biotechnology companies and related organizations that develop medical countermeasures and other pharmaceuticals. We also interviewed officials from an academic research center that conducts research and analysis and provides policy recommendations to protect people's health from the consequences of public health emergencies.

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<sup>4</sup>42 U.S.C. 247d-7e(f).

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To answer the second objective, we examined HHS documents, such as the 2010 PHEMCE review, to identify barriers to advanced research and development. We also reviewed these documents for recommendations on overcoming those barriers, such as by supporting and developing flexible manufacturing capacity. We reviewed HHS's PHEMCE planning documents to identify PHEMCE's CBRN medical countermeasure priorities. We reviewed HHS's request for proposals for the CIADMs and the three CIADM contracts HHS subsequently awarded to identify the extent to which the CIADM's activities are to address PHEMCE's identified development and production barriers and CBRN countermeasure priorities. We interviewed the HHS and CIADM officials and relevant stakeholders identified above to assess how the CIADM's activities are to assist in supporting the development of CBRN countermeasures to fulfill PHEMCE's priorities.

We conducted this performance audit from September 2013 through March 2014 in accordance with generally accepted government auditing standards. Those 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.

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## Background

Since 2004, Congress has authorized over \$8 billion for medical countermeasure procurement. The Project BioShield Act of 2004 authorized the appropriation of \$5.6 billion to be available from fiscal year 2004 through fiscal year 2013 for the Project BioShield Special Reserve Fund,<sup>5</sup> and funds totaling this amount were appropriated.<sup>6</sup> The act facilitated the creation of a government countermeasure market by authorizing the government to commit to making the Special Reserve

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<sup>5</sup>6 U.S.C. § 321j.

<sup>6</sup>Pub. L. No. 108-90, 117 Stat. 1137, 1148 (2003).



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Fund available to purchase certain medical countermeasures,<sup>7</sup> including those countermeasures that may not yet be approved, cleared, or licensed by the Food and Drug Administration (FDA).<sup>8</sup> In 2013, PAHPRA authorized an additional \$2.8 billion to be available from fiscal year 2014 through fiscal year 2018 for these activities,<sup>9</sup> and \$255 million was appropriated in fiscal year 2014.<sup>10</sup> Congress has also made funding available through annual and supplemental appropriations to respond to influenza pandemics, including developing vaccines and other drugs.<sup>11</sup>

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## Federal Roles and Responsibilities Related to Medical Countermeasures

HHS is the primary federal department responsible for public health emergency planning. Within HHS, several offices have specific responsibilities for medical countermeasure development and procurement.

- HHS's ASPR leads PHEMCE and the federal medical and public health response to public health emergencies, including strategic planning and support for developing and securing medical

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<sup>7</sup>6 U.S.C. § 321j; 42 U.S.C. § 247d-6b(c). The Project BioShield Act also authorizes the federal government to use specific contracting authorities to procure certain medical countermeasures for CBRN agents. 42 U.S.C. § 247d-6b(c)(7). The act allowed for the use of the Special Reserve Fund only for medical countermeasure procurement; however, since 2006, various appropriations acts have transferred \$2.1 billion from the Special Reserve Fund, \$1.9 billion of which was transferred for advanced research and development.

<sup>8</sup>Under federal law and FDA regulations, vaccines and other biologics are “licensed,” drugs are “approved,” and devices may either be “approved” or “cleared.” See 42 U.S.C. § 262, 21 U.S.C. § 355, 21 U.S.C. § 360e, 360(k). The Special Reserve Fund may be used to acquire medical countermeasures that are reasonably expected to qualify for FDA approval, clearance, or licensure within a certain number of years. The Project BioShield Act initially stipulated expected FDA approval, clearance, or licensure within 8 years, and PAHPRA subsequently extended this period to 10 years. 42 U.S.C. § 247d-6b(c)(1)(B)(i)(III)(bb). The Secretary of Health and Human Services may also authorize, under specified conditions, the temporary emergency use of products that have not yet received FDA approval, clearance, or licensure. 21 U.S.C. § 360bbb-3.

<sup>9</sup>42 U.S.C. § 247d-6b(g). PAHPRA provides that amounts appropriated pursuant to this section are authorized to remain available until September 30, 2019. PAHPRA stipulated that HHS may use up to 50 percent of the Special Reserve Fund for medical countermeasure advanced research and development.

<sup>10</sup> Pub. L. No. 113-76, 128 Stat. 5, 382 (2014).

<sup>11</sup>See, for example, Pub. L. No. 111-32, 123 Stat. 1859, 1884-86 (2009).

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countermeasures. As part of these activities, HHS develops priorities for which medical countermeasures are needed.

- Within ASPR, BARDA—established by the Pandemic and All-Hazards Preparedness Act of 2006<sup>12</sup>—coordinates and supports advanced research and development,<sup>13</sup> manufacturing, and initial procurement of medical countermeasures for CBRN threats, pandemic influenza, and emerging infectious diseases into the Strategic National Stockpile—the national repository for medications, medical supplies, and equipment for use in a public health emergency. As part of these responsibilities, BARDA oversees HHS’s efforts to develop flexible manufacturing capabilities for medical countermeasures.

HHS’s PHEMCE, which was established in 2006, is composed of officials from ASPR, BARDA, the Centers for Disease Control and Prevention (CDC), FDA, and the National Institutes of Health (NIH), in addition to officials from other federal departments, including the Departments of Agriculture, Defense, Homeland Security, and Veterans Affairs. In 2007, HHS published the PHEMCE Implementation Plan, which identified HHS’s priorities for CBRN countermeasure procurement using the 2004 Special Reserve Fund appropriation. In December 2012, HHS published an updated PHEMCE Implementation Plan,<sup>14</sup> which describes the capabilities HHS wants to establish to support countermeasure development and procurement, including activities to support flexible manufacturing.<sup>15</sup> The 2012 PHEMCE Implementation Plan also identifies

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<sup>12</sup>42 U.S.C. § 247d-7e(c). The act also gave BARDA the authority to make advance and milestone-based payments to vendors prior to product delivery to the Strategic National Stockpile. 42 U.S.C. § 247d-7e(c)(5)(C), (D).

<sup>13</sup>In the advanced research and development stage, potential medical countermeasures are further evaluated to demonstrate safety and effectiveness for preventing, diagnosing, or treating disease. Successful products are then available for development and procurement. In addition, BARDA determines whether scale-up manufacturing, which is the process of increasing the batch size of the countermeasure for production, and licensing of countermeasures can be achieved in a timely and reliable manner.

<sup>14</sup>Department of Health and Human Services, *Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Implementation Plan* (Washington, D.C.: December 2012).

<sup>15</sup>We previously reported on HHS’s capabilities, medical countermeasure activities, and priorities laid out in the 2012 PHEMCE Implementation Plan. See GAO, *National Preparedness: HHS Is Monitoring the Progress of Its Medical Countermeasure Efforts but Has Not Provided Previously Recommended Budget Estimates*, [GAO-14-90](#) (Washington, D.C.: Dec. 27, 2013).

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HHS's priorities for developing and procuring medical countermeasures, such as anthrax vaccine, smallpox antivirals, chemical agent antidotes, and diagnostic devices for radiological and nuclear agents. (See app. I for HHS's advanced development priorities for CBRN countermeasures.)

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## Flexible Manufacturing

Flexible manufacturing generally refers to the equipment and technologies that allow a facility to rapidly develop or manufacture a number of products simultaneously or in quick succession. These technologies include the use of disposable equipment, such as growing cell cultures in disposable plastic bag systems rather than in stainless steel tanks that require more time to clean and sterilize prior to the next use and the use of modular sterile rooms to allow for the manufacture of multiple products simultaneously within a given facility. Other technologies include alternatives to more traditional methods of making influenza vaccine, such as using cell-based or recombinant technologies to make vaccine, rather than the traditional egg-based technology,<sup>16</sup> or using adjuvants to enhance the immune response to vaccines.<sup>17</sup> In addition to alternative vaccine development technologies, platform technologies provide flexible systems that have the potential to produce medical countermeasures for multiple threats. The use of flexible manufacturing technologies also has the potential to help provide surge capacity production in a public health emergency.

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<sup>16</sup>Making influenza vaccine using egg-based technology—typically used to produce both seasonal and pandemic influenza vaccines for the U.S. market—involves growing virus cultures in fertilized chicken eggs. Cell-based technology uses cells other than eggs, such as those originally derived from the kidney cells of monkeys or canines, infected with influenza virus for the production of the vaccine. Recombinant technology uses specific protein(s) or genes from the influenza virus instead of the entire virus as the antigen for the vaccine. This technology can use cells from mammals as the medium for producing the influenza vaccine as well as cells from other sources, such as from bacteria, yeast, insects, or plants. For more information on cell-based and recombinant technologies, see GAO, *Influenza Vaccine: Federal Investments in Alternative Technologies and Challenges to Development and Licensure*, [GAO-11-435](#) (Washington, D.C.: June 27, 2011).

<sup>17</sup>Adjuvants are substances added to vaccines to reduce the amount of antigen—protein that grows on the surface of the bacterium or virus that triggers immune response in the host—needed to stimulate the immune response. By reducing the amount of active ingredients needed to stimulate immune response, adjuvants may reduce the cost per vaccine and the number of doses of the vaccine needed to confer immunity, making more vaccine available for the public during an emergency.

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## Addressing Barriers to Developing Countermeasures and Rapid Response to Pandemic Influenza

We previously reported on the barriers industry faces in developing and manufacturing CBRN and pandemic influenza medical countermeasures, which create challenges for HHS. In April 2011, we found that the barriers HHS identified in the PHEMCE review continued to exist.<sup>18</sup> Specifically, we found that the lack of a commercial market continued to hinder large pharmaceutical companies from developing medical countermeasures. As a result, less-experienced biotechnology companies became the primary developers of such products, but these companies needed more scientific and regulatory assistance for testing the safety and efficacy of their countermeasures in development.<sup>19</sup> In its 2010 PHEMCE review, HHS stated that new approaches to vaccine manufacturing, such as the use of flexible manufacturing technologies, offered promising ways to meet the demands of pandemic vaccine production while simultaneously meeting needs related to other public health emergency threats.<sup>20</sup> In our June 2011 review, HHS officials told us that the CIADMs are intended to support countermeasure developers by providing needed resources for and expertise about manufacturing and to reduce the technical risks of researching and developing medical countermeasures.<sup>21</sup> In addition, HHS officials indicated that such assistance by the CIADMs could reduce the research and development costs of smaller, less-experienced companies.

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<sup>18</sup>See GAO, *Public Health Preparedness: Developing and Acquiring Medical Countermeasures Against Chemical, Biological, Radiological, and Nuclear Agents*, [GAO-11-567T](#) (Washington, D.C.: Apr. 13, 2011).

<sup>19</sup>[GAO-11-567T](#).

<sup>20</sup>Department of Health and Human Services, *The Public Health Emergency Countermeasures Enterprise Review: Transforming the Enterprise to Meet Long-Range National Needs*.

<sup>21</sup>[GAO-11-435](#).

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## HHS Awarded \$440 Million in Fiscal Years 2012 and 2013 in Contracts for Activities to Support Flexible Manufacturing for Medical Countermeasures

In fiscal years 2012 and 2013, HHS's BARDA awarded nearly \$440 million to establish its CIADMs and a network of facilities to provide packaging support to ready the product for distribution, known as the Fill Finish Manufacturing Network. The CIADM contractors are required to develop three activities to support flexible manufacturing: pandemic influenza surge capacity, core services for CBRN medical countermeasure developers, and workforce training programs. According to BARDA officials, the Fill Finish Manufacturing Network will supplement the CIADMs' pandemic influenza surge capacity and CBRN core services activities.

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## HHS Awarded \$440 Million in Contracts to Establish Three CIADMs and the Fill Finish Manufacturing Network

HHS's BARDA awarded approximately \$400 million in fiscal year 2012 to three contractors to establish the CIADMs.<sup>22</sup> Under the terms of the CIADM contracts, the three contractors must retrofit existing facilities or build new ones to incorporate flexible, innovative manufacturing equipment and technologies that can be used to develop and manufacture more than one medical countermeasure either simultaneously or in quick succession. BARDA characterizes the CIADMs as public-private partnerships because the contractors are required to provide their own funds to supplement those awarded by HHS under a cost-sharing arrangement. For example, the total investment in pandemic influenza vaccine surge capacity could include up to \$194 million in contractor funding to supplement the \$400 million government award amount, for a total of about \$594 million in public and contractor funding.

The three CIADM contracts each cover an initial phase, or base period, ranging from 4.5 to 8 years, and subsequent phases, known as annual option periods,<sup>23</sup> which would allow BARDA to extend the CIADM contracts annually for up to 25 years total. During the base period, the

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<sup>22</sup>In fiscal year 2009, BARDA awarded approximately \$487 million for the construction of an influenza vaccine manufacturing facility that has since been incorporated into one of the CIADMs. BARDA did not award funds to support flexible manufacturing for medical countermeasures in fiscal years 2010 or 2011.

<sup>23</sup>An option is a unilateral right in a contract by which, for a specified time, the government may elect to purchase additional supplies or services called for by the contract, or may elect to extend the term of the contract.

CIADMs are required to design, construct, and commission their facilities. These facilities are intended to establish a warm base for pandemic influenza surge capacity. A warm base refers to facilities that, once constructed and commissioned, would be operationally ready to quickly manufacture vaccine during an influenza pandemic. These facilities are also intended to establish the capacity to provide core services for the development of CBRN countermeasures. (See table 1 for information on the CIADM base period amounts, including the government award and contractor cost-share.)

**Table 1: Centers for Innovation in Advanced Development and Manufacturing (CIADM) Contract Base Periods, Option Periods, and Government Awards and Cost-Sharing Amounts for Base Periods**

CIADM	Contract base period	Annual option periods	Government award amount for base period	Contractor cost-share amount for base period	Total government award and contractor cost-share amount for base period
Emergent Manufacturing Operations of Baltimore LLC, Baltimore, MD	06/15/2012 through 06/14/2020	06/15/2013 through 06/14/2037	\$163,221,997 <sup>a</sup>	\$58,630,958	<b>\$221,852,955</b>
Novartis Vaccines and Diagnostics, Inc., of Cambridge, MA	06/15/2012 through 12/31/2016	01/01/2014 through 06/14/2037	\$59,840,746 <sup>b</sup>	\$26,300,862	<b>\$86,141,608</b>
Texas A&M University System (TAMUS) of College Station, TX	06/15/2012 through 12/31/2017	01/01/2015 through 06/14/2037	\$176,664,509	\$108,935,443	<b>\$285,599,952</b>
		<b>Total</b>	<b>\$399,727,252</b>	<b>\$193,867,263</b>	<b>\$593,594,515</b>

Source: GAO analysis of Biomedical Advanced Research and Development Authority (BARDA) contracts.

<sup>a</sup>The total government award to Emergent of \$163,221,997 includes up to \$30 million in incremental payments, funded entirely by the federal government, to offset costs incurred to secure the intellectual property necessary to manufacture a pandemic influenza vaccine candidate.

<sup>b</sup>In fiscal year 2009, BARDA awarded approximately \$487 million to Novartis for the construction of an influenza vaccine manufacturing facility in Holly Springs, North Carolina, which has been incorporated into the Novartis CIADM. The contract called for BARDA and Novartis to share the cost of the facility, with BARDA providing about 40 percent and the company paying about 60 percent.

Contractors may be awarded additional amounts beyond the base period award through the issuance of task orders.<sup>24</sup> Under the CIADM contracts, HHS may issue task orders to purchase (1) core services for CBRN

<sup>24</sup>A task order contract is a contract for services that does not procure or specify a firm quantity of services (other than a minimum or maximum quantity) and that provides for the issuance of orders for the performance of tasks during the period of the contract. Federal Acquisition Regulation § 16.501-1.

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medical countermeasure developers, (2) medical countermeasure vaccine production (including vaccine for pandemic influenza), and (3) workforce training activities. The contracts outline the procedures that HHS is to follow to give contractors a fair opportunity to be considered for the award of task orders.<sup>25</sup> BARDA anticipates issuing task orders in the three service areas, including core services for CBRN countermeasures, during the annual option periods. As shown in Table 1, option periods may overlap the base period for the contracts.

In fiscal year 2013, BARDA also awarded approximately \$40 million to four companies to establish a network of facilities to provide packaging support to ready the product for distribution, known as Fill Finish Manufacturing Network.<sup>26</sup> This network is to provide aseptic product formulation, domestic fill finish manufacturing, as well as packaging and distribution services. The primary purpose of the network is to provide fill and finish manufacturing of products to supplement existing national pandemic influenza vaccine manufacturing surge capacity.<sup>27</sup> The establishment of the new network implements a recommendation from HHS's 2010 PHEMCE review to create a network of existing, pre-qualified facilities that could assist manufacturers with filling and finishing of vaccines in public health emergencies. The Fill Finish Manufacturing Network may provide assistance in the fill finish manufacturing of other aseptic drugs and medicines during drug shortages. The contracts BARDA used to establish the Fill Finish Manufacturing Network are similar to the contracts it used to establish the CIADMs, in that the initial

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<sup>25</sup>The contracts incorporate fair opportunity ordering procedures under Federal Acquisition Regulation § 16.505. The contracts state that for orders over \$5 million, the requirement to provide all awardees a fair opportunity to be considered for each order shall include, at a minimum – (A) a notice of the task or delivery order that includes a clear statement of the agency's requirement; (B) a reasonable response period; (C) disclosure of the significant factors and sub-factors, including cost or price, that the agency expects to consider in evaluating proposals, and their relative importance; (D) where award is made on a best value basis, a written statement documenting the basis for award and the relative importance of quality and price or cost factors; and (E) an opportunity for post-award debriefing.

<sup>26</sup>The filling and finishing of medical countermeasures refers to the process by which individual drugs are packaged for use, such as in vials and syringes, and includes labeling, patient instructions, outside packaging, transport, and promotional materials.

<sup>27</sup>BARDA awarded about \$40 million to four companies: Cook Pharmica of Bloomington, Indiana; DSM Pharmaceuticals, Inc. of Greenville, North Carolina; JHP Pharmaceuticals of Parsippany, New Jersey; and Nanotherapeutics of Alachua, Florida, partnered with Baxter Pharmaceutical Solutions.

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contract amount is intended to fund the necessary up front activities (e.g., formulation and technology transfer) to establish warm base facilities that can be used to provide fill and finish services during both pandemic and nonpandemic periods. After the contractors have completed these start-up activities to establish the fill and finish network, BARDA plans to award additional funding through the issuance of task orders. These task orders may include funding for materials, spare parts, equipment, staffing, and fees necessary to complete the task order.

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### The CIADMs and the Fill Finish Manufacturing Network Are Intended to Provide Three Activities to Support Flexible Manufacturing

BARDA's CIADMs are intended to provide three activities—surge capacity for manufacturing pandemic influenza vaccine, core services for the development of CBRN medical countermeasures, and workforce training—to support HHS's flexible manufacturing activities. According to HHS, the primary goal of the CIADMs is to provide core service assistance to CBRN medical countermeasure developers, their ability to provide some core services depends on the retrofitting of existing, or building of new, facilities that are also needed to provide surge capacity. The Fill Finish Manufacturing Network is to supplement the CIADMs' pandemic influenza surge capacity and CBRN core services activities.

#### Surge Capacity

The three CIADMs are required under their contracts with BARDA to establish surge capacity to quickly manufacture influenza vaccine in a pandemic and secure a pandemic influenza vaccine candidate currently under development. The CIADMs plan to establish surge capacity as follows:

- *Emergent*: Under the CIADM award, Emergent is to design, construct, and commission a biologics development and manufacturing suite in Baltimore, Maryland, intended to support core services for CBRN medical countermeasures on a routine basis and support manufacturing of medical countermeasure vaccines for an influenza pandemic or other public health threats.<sup>28</sup> In addition, Emergent is to design, renovate, and commission a pilot plant at its existing facility in Gaithersburg, Maryland, that is also intended to support core services for CBRN medical countermeasure developers.
- *Novartis Vaccines and Diagnostics (Novartis)*. Under the CIADM award, Novartis is to design, renovate, and commission a pilot plant to

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<sup>28</sup>This facility will function as an addition to an existing Emergent manufacturing facility.



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produce and fill clinical investigational lots of CBRN medical countermeasures in its existing plant in Holly Springs, North Carolina. Also, Novartis is to design, construct, and commission a technical services building in Holly Springs, North Carolina, to house administrative staff and provide maintenance services for the pilot plant.

- *Texas A&M University System (TAMUS)*. Under the CIADM award, TAMUS is to design, construct or renovate, and commission a number of facilities on the Texas A&M campus in College Station, Texas. These facilities are to include a biologics development and manufacturing facility that is intended to provide core services for CBRN medical countermeasures, with the added capability of developing and manufacturing live virus vaccine candidates; a current Good Manufacturing Practices vaccine bulk manufacturing facility dedicated to large-scale surge manufacturing of pandemic influenza vaccines;<sup>29</sup> a laboratory and office building to support process development and technology transfer of CBRN medical countermeasures into the CIADM; and a facility to support the fill and finish requirements for medical countermeasures.<sup>30</sup> The establishment of the TAMUS fill and finish facility is being funded under the CIADM contract and is not a part of BARDA's Fill Finish Manufacturing Network, for which HHS issued separate contracts.

Each of the CIADMs has taken a different approach to acquiring pandemic influenza vaccine candidates:

- Emergent has partnered with VaxInnate, which is developing a pandemic influenza vaccine using recombinant protein technology.<sup>31</sup>

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<sup>29</sup>See 21 C.F.R. parts 210-211. These regulations contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the legal requirements as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

<sup>30</sup>The TAMUS fill and finish facility is expected to have the added capability of processing live virus vaccine candidates and can use lyophilization, or freeze-drying, technology.

<sup>31</sup>Recombinant technology uses specific protein(s) or genes from the influenza virus instead of the entire virus as the antigen for the vaccine. This technology can use cells from mammals as the medium for producing the influenza vaccine as well as cells from other sources, such as from bacteria, yeast, insects, or plants. For more information on cell-based and recombinant technologies, see [GAO-11-435](#).

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- Novartis has developed a pandemic influenza vaccine candidate using cell-based vaccine production, which involves growing flu viruses in mammalian cell cultures instead of the conventional method of making influenza vaccine in chicken eggs.<sup>32</sup>
  - TAMUS has partnered with GlaxoSmithKline to obtain a pandemic influenza vaccine candidate. GlaxoSmithKline plans to grow the vaccine using a proprietary line of cells. A vaccine using the same adjuvant received FDA approval in November 2013 for pandemic response purposes. According to BARDA officials, FDA licensed the vaccine, using this adjuvant, to be manufactured in Canada using egg-based technology. However, the TAMUS CIADM is using GlaxoSmithKline's cell-based influenza vaccine technology to meet HHS surge manufacturing requirements.

The CIADMs are scheduled to have completed construction, acquired an influenza pandemic vaccine candidate, and validated their vaccine surge capacity with FDA by the end of their contract base period (2020, 2016, and 2017, respectively for Emergent, Novartis, and TAMUS). Each of the three CIADMs are to be able and, in the event of an influenza pandemic, be required to produce 50 million doses of vaccine within four months of receipt of the influenza virus strain, with the first doses for the public available to HHS within 12 weeks. BARDA officials told us that they anticipate that at least one CIADM would be able to manufacture pandemic influenza vaccine upon request starting in 2017, and that all of the centers would be capable of manufacturing pandemic influenza vaccine by the end of 2020.<sup>33</sup> BARDA anticipates placing task orders for pandemic influenza vaccine, if needed, during the annual contract option periods available to extend the contracts at the end of the respective base periods.

Once the CIADMs' influenza vaccine surge capacity is operational, the centers are expected to maintain readiness for surge manufacturing, even

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<sup>32</sup>According to BARDA officials, Novartis is using cell-based vaccine manufacturing technology to produce their seasonal influenza vaccine Flucelvax®. Flucelvax was supported by BARDA in its development and was licensed by FDA in November 2012.

<sup>33</sup>According to the BARDA officials, Novartis' manufacturing facility in North Carolina has been able to produce a commercial scale pandemic influenza vaccine using cell-based influenza vaccine technology since 2011. In 2013, Novartis produced commercial scale lots of H7N9 vaccine as a U.S. preparedness measure for HHS in response to the H7N9 outbreaks in 2013 and 2014.

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in nonpandemic periods. According to BARDA officials, in these nonpandemic periods, the CIADMs may use their surge capacity for other activities, including commercial manufacturing, provided they make their influenza vaccine surge capacity available upon request from HHS during an influenza pandemic to produce the required 50 million doses in the specified time period.<sup>34</sup> While surge capacity at the CIADMs is intended for pandemic influenza vaccine production, BARDA officials told us this capacity could be used to manufacture other medical countermeasures, such as an anthrax vaccine, in a public health emergency. BARDA officials told us that based on FDA requirements to maintain the license for the pandemic influenza vaccine, the CIADMs may need to produce one annual lot of the vaccine. BARDA will provide payment for activities required to maintain pandemic readiness.

According to BARDA officials, the four companies that were awarded contracts to establish the Fill Finish Manufacturing Network will provide additional fill and finish surge capacity in an influenza pandemic to supplement the CIADMs and allow for the fill and finish of 117 million additional doses of pandemic influenza vaccine in 12 weeks. The companies in the Fill Finish Manufacturing Network are encouraged to collaborate with the three CIADMs as well as partner with domestic influenza vaccine manufacturers in order to transfer the fill and finish technology into the Fill Finish Manufacturing Network contractors' facilities, which will become alternate locations on the vaccine manufacturers' licenses for fill finish activities. The network is also expected to provide its services to HHS for production of clinical investigational lots of medical countermeasures that are in development. BARDA anticipates that the Fill Finish Manufacturing Network will be available to receive task orders for core services by the end of fiscal year 2014.

## Core Services

For the core services activity, the CIADMs are to provide services for the development and production of CBRN medical countermeasures, such as assisting CBRN medical countermeasure developers in manufacturing small amounts of products that can be used in clinical trials. In the CIADM

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<sup>34</sup>If, in response to a task order request, a CIADM fails to submit a proposal in accordance with the technologies and capabilities highlighted in its statement of work or fails to provide a reasonable cost proposal based on the cost or pricing data submitted, HHS may terminate the contract. In that case, HHS may seek damages, which may include but are not limited to construction costs and facility readiness reimbursement costs.

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request for proposals, BARDA outlined a list of core services it expects the CIADMs to provide. (See app. II for a list and description of these core services.) These core services may be provided by the CIADMs directly or by subcontractors. Once the CIADMs are operational, BARDA will issue task orders to the CIADMs for core services using the fair opportunity process outlined in the contracts. For example, BARDA may issue a task order for a CIADM to provide regulatory or technical assistance for a specific CBRN medical countermeasure to a developer with a current BARDA contract. Under the terms of the contracts, the CIADMs are required to make their core services available to HHS for 50 percent of the time, or 6 months per annual contract option period. If HHS does not issue a task order to use a CIADM for core services, or issues a task order for core services for less than 6 months of an annual option period, HHS will provide the CIADM with a facility readiness reimbursement for up to 6 months of that facility's capacity for that option period.

BARDA officials told us that some of the CIADMs may begin providing some core services during 2014, and that each of the CIADMs should be capable of providing each of the core services by the end of 2015.<sup>35</sup> Once the new or retrofitted CIADM facilities are operational, a CIADM may begin providing core services, such as producing sufficient amounts of a specific countermeasure at a small scale to be tested in clinical trials for safety and efficacy. BARDA officials told us that the Fill Finish Manufacturing Network is also intended to provide these fill and finish services to CBRN medical countermeasure developers to supplement the core services provided by the CIADMs. This would be in cases such as when one or more of the CIADMs is at capacity or for countermeasures that may not be eligible for CIADM core services. According to BARDA officials the CIADMs and the Fill Finish Manufacturing Network are part of BARDA's overall core service assistance programs, which, since 2011, also include an animal studies network and, since 2014, a new clinical studies network to assist developers of CBRN medical countermeasures.

## Workforce Training

For the workforce training activity, the CIADMs are to develop programs to enhance and maintain U.S. capabilities and expertise to develop and produce CBRN medical countermeasures. These workforce training

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<sup>35</sup>According to BARDA officials, the Novartis and TAMUS CIADMs will be able to provide all of the core services by the end of 2014 and the Emergent CIADM by the end of 2015.

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programs are intended to develop a highly-skilled biotechnology and pharmaceutical workforce proficient in bioprocess engineering, production and quality systems, and regulatory affairs. Through these workforce training programs, the CIADMs are to offer training through means such as certificate programs, workshops, industry short courses, and internships. The CIADMs may provide training in subjects such as an introduction to biotechnology, good manufacturing practices procedures and documentation, facility operations and safety, regulatory compliance, and bioprocess control. BARDA officials told us that during the contract base period, the CIADMs are required to develop their workforce training programs, and that the agency may begin to request workforce training activities through task orders in fiscal year 2014.

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## HHS's Flexible Manufacturing Activities Are Designed to Support the Development and Production of CBRN Medical Countermeasures, but It Is Too Early to Determine Their Effectiveness

HHS established the CIADMs to provide needed core services to support the development and production through flexible manufacturing of certain CBRN medical countermeasures that were identified as priorities by PHEMCE. The agency followed the recommendation in the PHEMCE review to establish CIADMs capable of providing such core services. However, it is too early to tell how effective this approach will be because HHS has not begun to issue task orders to CIADMs for core services.

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## Core Services Are Designed to Support the Development of Certain CBRN Medical Countermeasures

Of the three flexible manufacturing activities undertaken at the CIADMs, BARDA officials told us that the provision of core services is the primary activity intended to support the development of certain CBRN medical countermeasures. The core services are specifically designed to provide CBRN developers with needed experience, facilities, and technology to help develop and produce certain medical countermeasures that HHS and PHEMCE identified as priorities. According to BARDA, the three CIADM contractors are entities that have experience in developing, manufacturing, and licensing pharmaceutical products in the United States. BARDA officials told us that the core services to be provided by the CIADMs are the types of services that HHS, PHEMCE, and industry

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representatives identified as necessary. The 2010 PHEMCE review indicated that services such as regulatory support, animal testing, and, if appropriate, clinical trials were needed to help less-experienced countermeasure developers to get through the challenging advanced development phase. Further, the 2012 PHEMCE implementation plan identified, as a programmatic priority, that CIADMs provide experienced biopharmaceutical development staff at the CIADMs to aid in the development of medical countermeasures.

Each of the three CIADMs are to provide 24 core services, directly or by subcontract, to assist countermeasure developers in moving their products through advanced development and production. In addition, BARDA officials indicated that each center can provide specific and slightly different expertise in developing products using alternate technologies, such as recombinant proteins or insect cells. For example,

- Emergent has experience developing products for infectious disease and biodefense. It has developed BioThrax, the only FDA-licensed anthrax vaccine, and has had several medical countermeasure development contracts with U.S. government agencies.
- Novartis has experience in developing a novel influenza cell culture as well as in other areas, and has an additional contract with BARDA to produce pandemic influenza vaccine.
- TAMUS is a large university system with access to a network of experienced partners including GlaxoSmithKline and a highly-rated veterinary school. TAMUS officials told us that their flexible manufacturing capabilities include modular “clean” rooms that can be tailored to each biopharmaceutical product’s specifications.

According to BARDA officials, the CIADMs are designed to provide developers with access to a variety of core services all in the same facility and the project management experience needed to manage the CBRN medical countermeasure development process. BARDA officials indicated that they envision a countermeasure developer working with a single CIADM on a product’s development.

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Core services provided by the CAIDMs would have the potential to support only the development of medical countermeasures that are biologics-based,<sup>36</sup> such as vaccines and recombinant proteins, but not small molecule countermeasures, such as antibiotics or antivirals. Examples of biologics-based countermeasures for CBRN threats include anthrax vaccine, recombinant protein chemical antidotes, and products to diagnose or treat the effects of exposure to radiological or nuclear agents. BARDA officials told us that the CIADMs are intended to assist in developing biologics-based countermeasures because a 2008 study commissioned by HHS and DOD examining vaccine manufacturing facility alternatives found that there is a sufficient domestic supply of contract manufacturing organizations that could be called upon in a public health emergency to produce small molecule countermeasures.

The CIADMs' services are intended to support countermeasure developers who have existing contracts with BARDA and countermeasure developers who have contracts with other PHEMCE partners, such as DOD and NIH.<sup>37</sup> BARDA officials identified 23 of its current biologics-based CBRN countermeasure contracts that are eligible, in whole or in part, to receive core services from the CIADMs. BARDA officials indicated that the CBRN medical countermeasures to be developed under these contracts are consistent with the countermeasures identified as HHS priorities in the 2012 PHEMCE implementation plan. For example, the PHEMCE implementation plan identified the development of an anthrax vaccine as a priority, and 4 of the 23 eligible CBRN medical countermeasure projects focus on developing anthrax vaccine.

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<sup>36</sup>Biologics-based pharmaceuticals are those that are derived from living sources such as cells and whose active ingredients typically consist of proteins. Biologics include vaccines, blood and blood-derived products, as well as recombinant proteins and monoclonal antibodies. Recombinant proteins are formed by combining segments of DNA from two different sources, such as two different organisms, in cultured cells. Monoclonal antibody technology uses immune system cells to make antibodies (proteins) to help the body destroy viruses or bacteria.

<sup>37</sup>DOD is also developing an advanced development and manufacturing center for medical countermeasure developers. BARDA officials told us that once the DOD facility is built and operational, the HHS and DOD centers' services will be available under a unified umbrella to provide medical countermeasure development and manufacturing assistance.

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## As Core Services Have Not Yet Been Provided, It Is Too Early to Tell How Helpful They Will Be to Countermeasure Developers

BARDA has not issued any task orders for core services to date, as the CIADMs are still completing activities associated with the contract base periods. Therefore, it is too early to tell the extent to which countermeasure developers may use CIADM services and how helpful the core services may be to support medical countermeasure development. Under the CIADM contracts, amounts awarded during the contract base period are to fund the construction of physical infrastructure, either the building of new facilities or the retrofitting of existing ones, and other preparations necessary to provide core services to countermeasure developers. As such, the base period of the contract provides a framework to help support countermeasure development, but no direct provision of core services. After the CIADM contractor establishes this framework, BARDA is to award task orders to CIADMs to provide core services to countermeasure developers. Because the CIADMs have not yet completed base period activities, BARDA has not yet issued task orders to provide core services. BARDA officials told us that two CIADMs may be able to provide core services as soon as 2014, a year earlier than planned. According to BARDA officials, once each of the CIADMs have completed construction or retrofitting, so that there is sufficient space to conduct core service activities, BARDA will evaluate and confirm the technical capabilities and capacity of each CIADM to provide core services prior to issuing task orders for these services.

Once the CIADMs are operational, BARDA and other agencies that participate in PHEMCE are to select eligible countermeasure development projects for those developers who want to access the CIADMs and issue task orders for core services. In order to select eligible contracts and issue task orders, HHS and PHEMCE have created a CIADM steering committee consisting of senior level officials from BARDA, CDC, FDA, NIH, and DOD. HHS has completed documents that provide governance for this process: a signed charter for the steering committee, preliminary criteria for selecting eligible contracts, and a signed governance document describing how the process will operate. Under the process, the steering committee issues a data call, and in response, medical countermeasure project managers from BARDA, NIH, and DOD are to submit proposals for current medical countermeasure contracts that would benefit from core services provided by the CIADMs



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to the CIADM steering committee.<sup>38</sup> The steering committee is to then review the proposals and select the countermeasure projects and developers to which it will offer access to the CIADMs' core services. Next, HHS plans to issue task order requests for each selected project, and the CIADMs will be required to submit proposals in response to the task order requests. Finally, according to BARDA officials, BARDA plans to issue a task order to the CIADM contractor whose proposal best satisfies the selection factors for award under the task order. BARDA officials told us that the CIADM steering committee met in January 2014 and plans to meet at least semiannually.

While it is too early to tell how effective HHS's approach to providing core services to CBRN medical countermeasure developers through the CIADMs will be, some industry stakeholders we interviewed expressed concerns about demand, availability of funding, and communication with BARDA. For example, some stakeholders questioned whether there would be a sufficient number of countermeasure developers who need advanced development support and who might choose to receive those services from the CIADMs. BARDA officials told us that they have conducted surveys of developers with current BARDA contracts about their interest in receiving core services from the CIADMs. As a result, according to officials, BARDA anticipates having a greater demand for core services than the CIADMs will be able to supply. Additionally, industry stakeholders we spoke to expressed concern that insufficient funding for task orders may affect the success of the CIADMs. BARDA officials told us that funding for task orders will either come from BARDA's budget for specific medical countermeasures, or from other agencies, such as NIH, through interagency agreements, but that the availability of funds for specific development projects would play a role in deciding which projects would receive core services. BARDA officials told us that they expect to have sufficient funding for task orders in fiscal years 2014 and 2015.

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<sup>38</sup>The steering committee issued its first data call in December 2013 and met to consider projects in January 2014. According to BARDA officials, only BARDA submitted projects for consideration, and the committee selected three of them to receive CIADM core services. The steering committee plans to issue data calls and meet on a semiannual basis to consider and select projects.

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Some industry stakeholders that we talked to also indicated that BARDA has not yet provided detailed information to industry partners about how countermeasure developers will request and use core services from the CIADMs. BARDA officials told us that BARDA featured the CIADMs and explained CIADM operations at its November 2013 Industry Days.<sup>39</sup> At this time, the eligible countermeasure developers are only those who have current development contracts with BARDA, NIH, and DOD.

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## Agency Comments and Our Evaluation

We provided a draft of this report to HHS, and its comments are reprinted in appendix III. In its comments, HHS acknowledged that it is too early to determine whether the Centers are meeting their prescribed goals because their intended core service activities have not yet begun. However, HHS noted that the CIADMs are nearly a year ahead of schedule in completing construction and ramping up activities in anticipation of providing services once HHS begins issuing task orders in 2014. HHS also noted that the CIADMs are a new model for public-private partnerships, and represent one component of BARDA's comprehensive, integrated approach to supporting advanced research and development, innovation, acquisition, and manufacturing of countermeasures for public health emergency threats. In addition to its overall comments, HHS provided technical comments, which we incorporated as appropriate.

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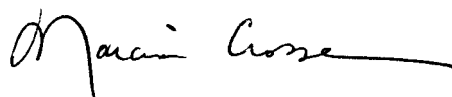
We are sending copies of this report to the Secretary of Health and Human Services. In addition, the report is available at no charge on the GAO website at <http://www.gao.gov>.

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<sup>39</sup>In November 2013 BARDA held a conference titled "BARDA Industry Day" to provide information to industry representatives about opportunities to develop medical countermeasures.

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If you or your staffs have any questions about this report, please contact me at (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix IV.



Marcia Crosse  
Director, Health Care

# Appendix I: The Department of Health and Human Services' Priorities for Chemical, Biological, Radiological, and Nuclear Medical

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## Medical Countermeasure Advanced Development Priorities<sup>a</sup>

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Anthrax antitoxin

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Anthrax vaccine

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Botulism antitoxin

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Broad spectrum antimicrobials<sup>b</sup>

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Chemical decontamination products

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Cyanide antidote

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Diagnostics for biological agents

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Nerve agent antidote

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Nuclear agents, gastrointestinal, skin, and lung therapeutics

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Nuclear agents, hematopoietic therapeutics

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Nuclear agents, thermal burn therapeutics

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Radiological agents, decorporation and blocking agents

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Radiological and nuclear bioassay/biodosimetry<sup>c</sup> (diagnostics)

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Respiratory protective devices<sup>d</sup>

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Smallpox antivirals

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Smallpox vaccine

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Ventilators

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Viral hemorrhagic fever antivirals

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Volatile nerve agent diagnostics

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Source: Department of Health and Human Services.

<sup>a</sup>HHS's medical countermeasure advanced development priorities include new products currently in development and enhancements to current products in the Strategic National Stockpile, the national repository for medications, medical supplies, and equipment for use in a public health emergency.

<sup>b</sup>Broad spectrum antimicrobials include those for anthrax, plague, tularemia, typhus, and secondary infections from pandemic influenza and exposure to radiological and nuclear agents.

<sup>c</sup>Biodosimetry devices and bioassays are tools that determine the level of radiation in the body and the type of radiological isotope to which an individual has been exposed.

<sup>d</sup>Respiratory protective devices include items such as N95 respirators, which are designed to prevent the wearer from breathing in at least 95 percent of airborne particles, and surgical masks.

# Appendix II: Centers for Innovation in Advanced Development and Manufacturing Core Services

	<b>Core Service</b>	<b>Description</b>	<b>Example</b>
1	Program/project management support	Planning, organizing, motivating, and controlling resources to achieve specific goals	Project manager tracks, reports, and ensures that the project deliverables for a new influenza drug product are completed on time and on budget
2	Regulatory affairs support	Provide guidance in establishment of regulatory filing strategy and license submissions to FDA	Submission of a biological license application for a new version of influenza vaccine to the FDA for approval
3	Quality systems and quality control support	Systems are in place and meet current Good Manufacturing Practices to ensure that products are manufactured to meet the identity, strength, quality, and purity they purport	Quality control testing and batch record reviews of consistency lots
4	Nonclinical studies	Early development studies to determine the manufacture, safety, toxicity, and efficacy of the drug product to determine proof of concept	Animal testing of new influenza strains to ensure protection and safety
5	Clinical studies	Human clinical trials proceeding from Phase 1 safety and dose studies through Phase 3 efficacy and safety studies with a potential new vaccine drug product <sup>a</sup>	Phase 3 clinical trial of 3000+ patients to determine the efficacy of a new drug quadrivalent influenza vaccine
6	Upstream process development and optimization	The entire process from early cultivation, banking, expansion, and collection of intermediate product	Growing influenza virus in cells
7	Downstream process development and optimization	The process when upstream product is purified to meet certain purity, quality, and yield requirements	Purification and recovery of an influenza virus
8	Master and working cell bank accession and validation	Preparation of a homogeneous population of cells and stored for future production use	Provide containers of cells for upstream growth
9	Master and working virus seed banking and validation	Preparation of a homogeneous population of virus and stored for future production use	Provide virus to infect cells during upstream growth
10	Pilot bulk manufacturing of clinical investigational lots	Manufacturing development step to provide product, usually at a small scale, that can be used for clinical trials	Provide early stage purified influenza virus for clinical studies
11	Media and buffer formulation, optimization, and validation	Developing the appropriate requirements for growing cells upstream (media) and preparing ingredients for downstream purification (buffers)	Provide the media for growing cells and buffers to purify the influenza virus from the cells
12	Master product stability study programming and validation	Product stability is obtained when purified material remains within specification during storage	Stable influenza vaccine remains within specification during storage
13	Formulation chemistry development	Preparing a purified batch of material by combining chemical components in a specified manner	A batch of influenza virus in a chemical mixture that stabilizes the virus
14	Analytical assay development and optimization	An analytical assay is a method to qualitatively or quantitatively measure the specific parameters of a product	An analytical assay for measuring how much influenza virus is in downstream process

**Appendix II: Centers for Innovation in  
Advanced Development and Manufacturing  
Core Services**

<b>Core Service</b>	<b>Description</b>	<b>Example</b>
15 Raw materials selection and validation	The process of selecting and testing different components used in the manufacture of the product	Selection of chemicals such as sugars and proteins to grow influenza virus
16 Process validation	Ensure a process that consistently produces a result or product that meets certain predetermined specifications	Demonstrating that an upstream process for growing influenza virus can be consistently repeated
17 Validation services to support facilities/utilities/equipment	Functions to ensure that facilities and equipment are operating within defined requirements	Perform a qualification of a bioreactor to ensure the equipment meets specifications
18 Fill/finish manufacturing development support	Develop the process parameter range needed to fill and package a drug product to ensure it meets its final specifications	Perform an engineering run to evaluate the filling equipment's ability to produce product meeting specification
19 Final container product labeling and packaging support	Placing the final label on the container and placing the container in its final package	Apply the vial label to the multi-dose vial of seasonal influenza vaccine and then place 10 vials in a carton with an insert
20 Analytical assay validation for product lot release and clinical testing	Confirm that the test methods for the final product are accurate and repeatable	Confirm a test method which identifies the potency of each influenza strain in a seasonal influenza vaccine
21 Product stability optimization	Develop and evaluate modifications to product and/or processing steps to improve the product shelf life	Evaluate the impact of adding additional triton to an influenza formulation to determine if it makes the product last longer
22 Lyophilization development and validation	Develop the process to freeze dry products to improve shelf life and confirm the process consistently meets final specifications	Develop and confirm the process to freeze dry a yellow-fever vaccine for final container storage
23 Commercial scale bulk manufacturing	Production of product (vaccines, biologics, etc) generally in larger scale batches	Formulate seasonal influenza vaccine for sale to customers
24 Fill and finish manufacturing	Filling and packaging of the formulated product into the final package	Fill multi-dose vials of seasonal influenza vaccine, label, carton, and palletize for storage and shipment

Source: Biomedical Advanced Research and Development Authority.

<sup>a</sup>Clinical trials are research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans. Manufacturers conduct clinical trials in human volunteers in five phases (0 through 4) to determine whether candidate countermeasures are effective and safe.

# Appendix III: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation  
Washington, DC 20201

**MAR 7 2014**

Marcia Crosse  
Director, Health Care  
U.S. Government Accountability Office  
441 G Street NW  
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) draft report entitled, "NATIONAL PREPAREDNESS: HHS Has Funded Flexible Manufacturing Activities for Medical Countermeasures, but It Is Too Soon to Assess Their Effect" (GAO-14-329).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

A handwritten signature in black ink that reads "Jim R. Esquea".

Jim R. Esquea  
Assistant Secretary for Legislation

Attachment

The Department of Health and Human Services' (HHS) General Comments to the Government Accountability Office's (GAO) Draft Report Entitled, "National Preparedness: HHS Has Funded Flexible Manufacturing Activities for Medical Countermeasures, but It Is too Soon to Assess Their Effect ((GAO-14-329)

HHS appreciates the opportunity to review and comments on this draft report. We value the GAO's input and, as always, appreciate any effort that will result in better and more cost effective delivery of government products and services to the taxpayer.

HHS values this preliminary examination of the Centers for Innovation and Advanced Development in Manufacturing (CIADMs) and acknowledges GAO's assessment that it is too early to determine whether the Centers are meeting their prescribed goals because their intended core service activities have not yet begun. As the report notes, HHS has successfully established three CIADMs in response to a specific need to augment support for our domestic medical countermeasure (MCM) development and manufacturing capacity. As of the writing of this report, the CIADMs are in the process of completing construction and ramping up activities in anticipation of providing services once HHS begins issuing task orders in 2014. We are pleased to note that CIADM operations are actually nearly a year ahead of schedule. We are taking advantage of this head start and moving forward with the next step in the process, selecting projects and initiating task orders to get MCMs into the Centers as soon as possible.

HHS established the CIADMs to protect Americans' health during an emergency and expand the nation's domestic ability to respond to bioterrorism threats, pandemic influenza, and other epidemics. The CIADMs are a part of our larger strategy to meet the needs identified in the Secretary's 2010 *Public Health Emergency Medical Countermeasures Enterprise Review*. This review found that the nation needed a nimble, flexible capability to rapidly produce medical countermeasures (MCMs) in the face of any threat, known or unknown. The Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response established and administers the CIADMs to fill this gap.

The CIADMs offer a new model for public-private partnerships, bringing together small biotech companies, academic institutions, and large experienced pharmaceutical companies to develop and deliver MCMs quickly and cost effectively to the American public. Together, we are developing and utilizing innovative technologies to accelerate production, improve quality, and expand our domestic manufacturing capacity in order to increase the nation's preparedness for acts of bioterrorism and the perennial threat of pandemic influenza.

The CIADMs are one component of BARDA's comprehensive, integrated approach to supporting advanced research and development, innovation, acquisition, and manufacturing of countermeasures for public health emergency threats. The CIADMs work closely with other programs and networks as part of our comprehensive strategic approach to MCMs. In 2013, HHS established the Fill Finish Manufacturing Network (FFMN), which partners with the CIADMs and vaccine manufacturers in the final steps of the vaccine manufacturing process. The FFMN will provide vital surge capacity during a pandemic and may be utilized to address other public health threats, including CBRN agents and infectious diseases. Together, the FFMN and the CIADMs build on our public-private partnership model to provide a coordinated national



The Department of Health and Human Services' (HHS) General Comments to the Government Accountability Office's (GAO) Draft Report Entitled, "National Preparedness: HHS Has Funded Flexible Manufacturing Activities for Medical Countermeasures, but It Is too Soon to Assess Their Effect ((GAO-14-329)

MCM manufacturing infrastructure. While we recognize that the FFMN was not the focus of GAO's inquiry, the strategic partnership with the CIADMs is critical to our overall success.

Our approach assists our partners with some of the most pressing problems that hamper successful product development by providing resources, technical assistance, and training. In this context, the CIADMs focus on three primary core service areas: development and manufacturing assistance to developers of chemical, biological, radiological, and nuclear (CBRN) MCMs; manufacture of pandemic influenza vaccines during an emergency; and provision of on-site workforce training for vaccine and biological product development and manufacturing. Each of these areas is of critical value to our partners, the economy, and the American public.

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# Appendix IV: GAO Contact and Staff Acknowledgments

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## GAO Contact

Marcia Crosse, (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov)

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## Staff Acknowledgments

In addition to the contact named above, Sheila K. Avruch, Assistant Director; Matt Byer; Britt Carlson; Shana R. Deitch; Cathy Hamann; and Tracey King made significant contributions to this report.

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# Related GAO Products

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*National Preparedness: HHS is Monitoring the Progress of Its Medical Countermeasure Efforts but Has Not Provided Previously Recommended Spending Estimates.* [GAO-14-90](#). Washington, D.C.: December 27, 2013.

*National Preparedness: Efforts to Address the Medical Needs of Children in a Chemical, Biological, Radiological, or Nuclear Incident.* [GAO-13-438](#). Washington, D.C.: April 30, 2013.

*National Preparedness: Countermeasures for Thermal Burns.* [GAO-12-304R](#). Washington, D.C.: February 22, 2012.

*National Preparedness: Improvements Needed for Acquiring Medical Countermeasures to Threats from Terrorism and Other Sources.* [GAO-12-121](#). Washington, D.C.: October 26, 2011.

*Influenza Pandemic: Lessons from the H1N1 Pandemic Should Be Incorporated into Future Planning.* [GAO-11-632](#). Washington, D.C.: June 27, 2011.

*Influenza Vaccine: Federal Investments in Alternative Technologies and Challenges to Development and Licensure.* [GAO-11-435](#). Washington, D.C.: June 27, 2011.

*National Preparedness: DHS and HHS Can Further Strengthen Coordination for Chemical, Biological, Radiological, and Nuclear Risk Assessments.* [GAO-11-606](#). Washington, D.C.: June 21, 2011.

*Public Health Preparedness: Developing and Acquiring Medical Countermeasures Against Chemical, Biological, Radiological, and Nuclear Agents.* [GAO-11-567T](#). Washington, D.C.: April 13, 2011.

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