U.S. Department of Health and Human Services

2014 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan

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EXECUTIVE SUMMARY

The *2014 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan (SIP)* describes the priorities that HHS, in collaboration with its interagency partners, will implement over the next five years. This plan updates the *2012 PHEMCE SIP* and is now required annually by section 2811(d) of the Public Health Service (PHS) Act as amended by the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) (Public Law 113-5). The *2014 PHEMCE SIP* provides the blueprint for the PHEMCE to use in enhancing national health security through the procurement and use of life-saving medical countermeasures (MCMs).

What is the PHEMCE?

The *Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)* is an interagency coordinating body led by the HHS Assistant Secretary for Preparedness and Response (ASPR), comprising the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and interagency partners at the Departments of Veterans Affairs (VA), Defense (DoD), Homeland Security (DHS), and Agriculture (USDA). It coordinates the development, acquisition, stockpiling, and use of medical products that are needed to effectively respond to a variety of potential high-consequence public health emergencies, whether naturally occurring or intentional.

The PHEMCE has established tracking processes to monitor and evaluate the execution of PHEMCE priorities included in the annual SIP. The *2014 PHEMCE SIP* highlights major accomplishments since the *2012 PHEMCE SIP*. In this time the PHEMCE has made great progress, as detailed in Appendix 7. The PHEMCE has assessed threats to national health security, improved the MCM requirements and acquisition framework that is used to identify MCM needs posed by those threats, conducted early and advanced research and development, advanced regulatory approval mechanisms (including approval of 2 products under the FDA "Animal Rule"), manufactured and procured critical MCMs, addressed the MCM needs of at-risk populations through advanced research and development and procurements, developed and enhanced federal communication plans and MCM utilization guidance, and established policies for the international sharing of MCMs.

The PHEMCE reviewed the goals and objectives in the *2012 PHEMCE SIP*, in the context of intervening events, and determined that they largely continue to be relevant and appropriate in 2014. The *2014 PHEMCE SIP* identifies priority activities over the next five years across the various PHEMCE mission areas, including: requirement-setting; basic research; discovery and early development; advanced development; regulatory science management; procurement and stockpiling; response planning; distribution and dispensing; and monitoring, evaluation, and assessment. Priorities are set along the near- (Fiscal Year [FY] 15-16), mid- (FY17-18), and long-term (FY19 and beyond) timeframes where appropriate. All activities described herein are contingent on available appropriations. These priorities support the PHEMCE's strategic goals and objectives, and are summarized in Table 1. The *2014 PHEMCE SIP* provides both a broad-based description of these priority activities, as well as a more detailed description of individual threat-based and capabilities-based approaches.

The *2014 PHEMCE SIP* also includes additional information required by PAHPRA amendments to the PHS Act, such as : an evaluation of progress of all activities with respect to qualified countermeasures, security countermeasures, and pandemic and epidemic products; progress in addressing the needs of at-risk populations; a description of HHS and DoD coordination; a summary of advanced research and development and procurement awards; information regarding the use of funds and authorities originally added to the PHS Act by the Project BioShield Act; and a summary of PHEMCE interactions with non-federal stakeholders.

The Assistant Secretary for Preparedness and Response (ASPR) will maintain internal tracking processes to monitor and evaluate the execution of priorities identified in the *2014 PHEMCE SIP* and report progress regularly to senior leadership and, to the extent feasible in light of national security and proprietary concerns, to external stakeholders. The PHEMCE SIP will be reviewed and updated annually, as mandated by the PHS Act.

Table 1. PHEMCE Priorities by Goals and Objectives

GOAL / OBJECTIVE	PHEMCE PRIORITIES
GOAL 1. Identify, create, develop, manufacture, and procure critical medical countermeasures	---
Objective 1.1 Develop a strategic framework to prioritize PHEMCE resources and investments. (Lead: ASPR; Partners: PHEMCE agencies)	• Implement, evolve, and evaluate prioritization processes
Objective 1.2 Utilize consistent approaches for medical consequence and public health response assessments and medical countermeasure requirement setting that include consideration of effective production, storage, deployment, and administration strategies. (Lead: ASPR; Partners: PHEMCE agencies)	• Enhance the development of clear and rigorous civilian MCM requirements, including capabilities-based requirements
Objective 1.3 Ensure a robust and sustainable product pipeline for medical countermeasures that emphasizes multi-functional capabilities (e.g., platform technologies, host-based innovations, broad-spectrum medical countermeasures) rather than stand-alone outcomes and includes consideration of viable commercial markets and/or routine public health applicability. (Leads: BARDA, NIH; Partners: DoD, CDC, USDA)	• Invest in basic research, discovery, early and advanced development, and acquisition of current and novel MCMs according to the prioritization framework
Objective 1.4 Promote effective domestic and international partnerships with developers and manufacturers and support core services. (Leads: ASPR, NIH, DoD; Partners: CDC, FDA, HHS Office of Global Affairs (OGA))	• Maintain a wide array of product development and support service contracts to provide infrastructure capabilities for MCM development • Enter into strategic bilateral and multilateral engagements with international partners to identify joint opportunities for product development

GOAL / OBJECTIVE	PHEMCE PRIORITIES
GOAL 2. Establish and communicate clear regulatory pathways to facilitate medical countermeasure development and use.	---
Objective 2.1 Identify scientific and regulatory issues that challenge medical countermeasure development or use during public health emergencies and coordinate activities among PHEMCE partners to address those challenges. (Lead: FDA; Partners: PHEMCE agencies)	• Enhance product review and approval processes for the highest-priority MCMs • Advance regulatory science to support MCM development and regulatory assessment • Assess the legal, regulatory, and policy environments regarding MCM development, distribution, administration, and use and propose new approaches where necessary
Objective 2.2 Assist medical countermeasure developers in working interactively with FDA during product development and regulatory review (Lead: FDA; Partners: NIH, ASPR, BARDA, DoD)	• Clarify regulatory pathways and reduce regulatory barriers for MCM developers • Provide product development core services to MCM developers and manufacturers
GOAL 3. Develop logistics and operational plans for optimized use of medical countermeasures at all levels of response.	---
Objective 3.1 Promote innovative approaches to inventory management to enable a sustainable preparedness infrastructure (Lead: CDC; Partners: ASPR, DHS)	• Optimize the Strategic National Stockpile (SNS) formulary to seek long-term sustainability and enhanced flexibility • Cost-effectively manage SNS assets
Objective 3.2 Develop and communicate medical countermeasure utilization policy, guidance, and response strategies, including FDA regulatory frameworks, that are responsive to end-user needs and that are integrated with regional, state, local, tribal, territorial, and private sector response plans, and when possible international partners, and that ensure timely, safe, and effective MCM distribution and utilization. (Leads: ASPR, CDC; Partners: PHEMCE agencies)	• Strengthen the feedback loop between the end-users and developers of MCMs • Develop MCM policies, clinical use guidelines, and federal response strategies to inform end-user planning • Ensure preparedness in key federal policy and response capabilities • Support regional, state, local, tribal, and territorial response efforts • Identify and address barriers to building a sustainable MCM global infrastructure

GOAL / OBJECTIVE	PHEMCE PRIORITIES
Objective 3.3 Develop and provide medical countermeasure communications, training, and education information to inform all stakeholders. (Leads: CDC, ASPR; Partners: FDA, USDA, DoD)	• Test the effectiveness of MCM-related public health communication materials • Develop and implement a plan to disseminate best practices for establishing and maintaining regional coordination for public health emergencies
Objective 3.4 Develop and implement strategies to assess, evaluate, and monitor medical countermeasure safety, performance, and patient compliance during and after a public health emergency response. (Leads: FDA, CDC, ASPR; Partners: DoD)	• Support drug manufacturers in fulfilling post-marketing commitments, during an event, of recently approved MCMs • Implement plans for real-time monitoring of the safety and clinical benefit of MCMs during public health emergencies
GOAL 4. Address medical countermeasure gaps for all sectors of the American civilian population.	---
Objective 4.1 Develop medical consequence and public health response assessments and requirements setting for at-risk individuals. (Lead: ASPR; Partners: PHEMCE agencies)	• Consider at-risk population needs in every stage of the MCM requirement-setting process • Support research to close important knowledge gaps regarding susceptibility differences and/or altered disease severity in at-risk populations • Incorporate subject matter expertise to inform the development of MCM requirements and response strategies to ensure availability of safe and effective MCMs for at-risk populations
Objective 4.2 Support medical countermeasure advanced development and procurement for at-risk individuals. (Leads: BARDA, NIH, FDA; Partner: CDC, DoD)	• Include consideration of at-risk population needs in SNS formulary analyses • Support expanding MCM label indications to at-risk populations during the development of priority MCMs, including development of new dosage forms as needed • Leverage existing at-risk population databases for drugs approved for other indications to demonstrate efficacy for biodefense applications in these populations without the need for additional studies

GOAL / OBJECTIVE	PHEMCE PRIORITIES
Objective 4.3 Develop and implement strategies, policies, and guidance to support the appropriate use of medical countermeasures in all civilian populations during an emergency. (Leads: ASPR, CDC; Partner: FDA)	• Address regulatory challenges associated with use of products intended for at-risk populations • Ensure that public health and medical information is delivered in a manner that takes into account the range of communication and other functional needs of the intended recipients, including at-risk individuals • Identify and comprehensively integrate departmental activities related to the needs of children • Anticipate and proactively address the needs of at-risk populations during a disaster

INTRODUCTION

The United States (US) continues to face a range of serious threats to its national health security from the deliberate use or accidental release of chemical, biological, radiological, and nuclear (CBRN) agents, as well as from naturally occurring and emerging infectious diseases (EID), including pandemic influenza (see Box 1 below). A failure to anticipate these threats – or the lack of a capacity to effectively respond to them – could result in substantial illness and death among the American people. The US must have the nimble, flexible capability to produce and effectively use medical countermeasures (MCMs)[1] in the face of any attack or threat, whether known or unknown, novel or reemerging, natural or intentional. In addition, these capabilities must be communicated to the American public both before and during an emergency.

Box 1: High-Priority Threats

The Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) will continue to address MCM needs to protect against high priority threats that have been determined by the Secretary of Homeland Security to pose a material threat sufficient to affect national security and/or that PHEMCE leadership have determined to have the potential to seriously threaten national health security. The high-priority threats are (in alphabetical order):

- *Bacillus anthracis* (anthrax)
- *Clostridium botulinum* toxin (botulism)
- Cyanide
- Emerging infectious diseases
- Gram negative organisms
    - *Burkholderia mallei* (glanders) and *Burkholderia pseudomallei* (melioidosis)
    - *Francisella tularensis* (tularemia)
    - *Rickettsia prowazekii* (typhus)
    - *Yersinia pestis* (plague)
- Multi-drug resistant *Bacillus anthracis* (MDR anthrax)
- Nerve agents
- Nuclear agents
- Pandemic influenza
- Radiological agents
- Variola virus (smallpox)
- Viral Hemorrhagic Fevers
    - Marburg
    - Ebola

[1] Medical countermeasures include both pharmaceutical interventions (e.g., vaccines, antimicrobials, antidotes, and antitoxins) and non-pharmaceutical interventions (e.g., ventilators, diagnostics, personal protective equipment, and patient decontamination) that may be used to prevent, mitigate, or treat the adverse health effects of an intentional, accidental, or naturally occurring public health emergency. They include qualified countermeasures as defined in section 319F–1(a)(2) of the Public Health Service Act (42 U.S.C. § 247d–6a(a)(2)); qualified pandemic or epidemic products as defined in section 319F–3(i)(7) of the Public Health Service Act (42 U.S.C. § 247d–6d(i)(7))), and security countermeasures as defined in section 319F-2(c)(1)(B) of the Public Health Service Act (42 U.S.C. § 247d–6b(c)(1)(B)).

A number of National Strategies and Presidential Directives establish the Department of Health and Human Services (HHS) as the lead federal department responsible for the protection of the health of the civilian population against both intentional and accidental or naturally occurring threats.[2] The Secretary of Health and Human Services leads all federal public health and medical response to public health and medical emergencies covered by the National Response Framework.[3] Additionally, the HHS Strategic Plan Fiscal Year (FY) 2014-2018 calls for reducing the occurrence of infectious diseases, protecting Americans' health and safety during emergencies, and fostering resilience in response to emergencies; these goals are also reflected in strategic initiatives set by the Secretary.[4] The National Strategy for Combating Antibiotic Resistant Bacteria, released in September 2014, prioritized addressing the on-going public health crisis of antibiotic-resistant pathogens.[5] Effectively fulfilling this responsibility and accomplishing these goals requires coordination of MCM-related activities across multiple federal departments. To provide this coordination, HHS established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) [6] in July 2006 to coordinate federal efforts to enhance civilian preparedness[7] from a MCM perspective. The PHEMCE is charged with addressing the development, production, and availability of MCMs to limit potential adverse health impacts on the large and diverse US civilian population. The PHEMCE is working to meet the public health emergency needs of the entire civilian population, including groups that require special medical considerations, such as children, pregnant women, and older adults, as well as first responders, health care personnel, and other critical infrastructure personnel, by taking a "whole of community" approach in planning, response, and recovery efforts.

The PHEMCE is led by the Assistant Secretary for Preparedness and Response (ASPR).[8] Core HHS members are the Director of the Centers for Disease Control and Prevention (CDC), the Director of the National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH), and the Commissioner of the Food and Drug Administration (FDA). Key PHEMCE interagency partners include senior leadership from the Department of Veterans Affairs (VA), the Department of Defense (DoD), the Department of Homeland Security (DHS), and the Department of Agriculture (USDA). These partners work together under the PHEMCE

[2] These include but are not limited to the National Strategy for Public Health and Medical Preparedness (Homeland Security Presidential Directive-21, October 2007); the National Response Framework (January 2008); the National Health Security Strategy (December 2009; anticipated for revision in 2014); and the National Preparedness Goal (Presidential Policy Directive – 8, March 2011).
[3] See section 2801 of the Public Health Service Act (42 U.S.C. 300hh)
[4] Available at http://www.hhs.gov/strategic-plan/priorities.html
[5] Available at www.whitehouse.gov/sites/.../carb_national_strategy.pdf
[6] Available at http://www.gpo.gov/fdsys/pkg/FR-2006-07-06/pdf/06-6004.pdf
[7] This mandate includes consideration of the particular needs of first responder populations who are placed at particular risk in the course of their duties and critical infrastructure workers. The role of HHS in working with interagency partners to ensure these populations have access to the support they need, including MCMs, is primarily described elsewhere. While particularly relevant activities may be called out in this document, the broader efforts are not detailed here but can be found at http://www.phe.gov/Preparedness/planning/cip/Pages/default.aspx , and http://www.phe.gov/preparedness/planning/postal/Pages/default.aspx.
[8] The Office of the ASPR includes component offices with key PHEMCE roles such as the Immediate Office, Biomedical Advanced Research and Development Authority (BARDA), Office of Policy and Planning (OPP), Office of Acquisition Management, Contracts, and Grants (AMCG), and the Office of Emergency Management (OEM).

governance structure described in Appendix 2. Additionally, the PHEMCE works with HHS and US Government (USG) partners, when appropriate, to consider international aspects of its mission. The PHEMCE also works closely with non-federal partners including state, local, tribal, and territorial (SLTT) governments, health systems, academia, private industry, non-governmental organizations (NGOs) and ultimately the American people.

A periodic assessment of strategy and capabilities in light of changing scientific and fiscal circumstances is appropriate to ensure the optimal allocation of resources to address high-priority threats. Difficult choices must be made to manage risk in ways that favor success in meeting a public health emergency. As required by section 2811(d) of the Public Health Service (PHS) Act[9], as added by section 102 of the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) (Public Law 113-5), a *PHEMCE Strategy and Implementation Plan* (SIP) will be released annually. While they are examined annually for revision or update as needed, it is anticipated that PHEMCE goals and objectives are likely to remain constant over a more extended period. The goals and objectives in the *2012 PHEMCE Strategy* will be intensively re-examined in the *2018 PHEMCE SIP*. The associated implementation activities in pursuit of these goals and objectives, however, will be updated more frequently as progress is made and new opportunities arise.

Fulfilling the PHEMCE mission will also require balanced investments in consideration of the long-term sustainability of the Enterprise. Toward this end, consistent with section 2811 of the PHS Act,[10] the HHS Secretary has implemented a five-year budget planning process across the HHS components of the PHEMCE in order to achieve closer coordination and prioritization of investments in public health emergency preparedness that will be tied to the framework provided by the annual *PHEMCE SIP*. Given currently existing resources from the federal to the SLTT levels and the existing public health infrastructure challenges, the PHEMCE will continue to assess risks and establish and communicate clear priorities, seek multi-use solutions wherever possible, and work to develop innovative MCM development, manufacturing, stockpiling, and fielding alternatives.

The *2014 PHEMCE SIP* has five main sections: (1) a high-level description of the programs and initiatives that will be pursued by HHS, in coordination with its interagency partners, to accomplish each PHEMCE goal and objective; (2) an overview of PHEMCE interagency partner roles and collaborations; (3) a summary of the use of authorities under the PHS and Food Drug and Cosmetic (FD&C) Acts originally provided as part of the Project BioShield Act of 2004; (4) a detailed description of the priority activities organized by threats; and (5) a description of specific activities addressing multiple needs and/or threats – also known as capability-based approaches. Detailed information addressing other particular PAHPRA requirements for the SIP, as well as progress made against *2012 PHEMCE SIP* objectives, are found in the various appendices to the main document. Plans to pursue and accomplish the activities and initiatives detailed are dependent on federal funding levels over the next five years.

[9] 42 U.S.C. 300hh-10(d)
[10] 42 U.S.C. 300hh-10(b)(7)

Box 2: Responding to the 2014-15 Ebola Outbreak

The current Ebola outbreak in West Africa shows that communicable diseases do not recognize national borders and that foreign outbreaks can directly affects Americans' safety and security. Therefore, infectious disease outbreaks are a top national security priority requiring global response and responsibility. Ebola specifically was recognized as a potential threat to national health security through the issuance of a Material Threat Determination by DHS in 2006. During the current outbreak, each partner agency across the PHEMCE has contributed to the national and international response efforts. As will be further detailed below, ASPR's Biomedical Advanced Research and Development Authority (BARDA)[11], the NIH and DoD are rapidly moving medical countermeasures to advanced development and manufacturing scale-up. NIH, BARDA, CDC, FDA and DoD are pursuing novel clinical trial approaches and overarching strategies to efficiently obtain data on product safety and efficacy for antivirals, biologics and vaccines to combat the Ebola virus. Many of the PHEMCE partners are coordinating on development of point-of-care diagnostics to speed identification of those infected with Ebola. CDC mobilized an unprecedented emergency response to ensure that: 1) cases of Ebola in the U.S. are quickly detected and managed so as to minimize domestic transmission; 2) control the ongoing epidemic of Ebola in West Africa, and 3) importantly, to strengthen global health security capacity in vulnerable countries to prevent, detect, and rapidly respond to outbreaks before they become epidemics by standing up emergency operations centers; providing equipment and training needed to test patients and report data in real-time; providing safe and secure laboratory capacity; and developing a trained workforce to track and end outbreaks before they become epidemics. CDC also developed and distributed training materials, held on-site training sessions and conducted other outreach to U.S. and international health care systems to enhance patient and laboratory management, infection control and risk communication. Protecting Americans from the threat posed by Ebola is a top priority for the PHEMCE core agencies and the best way to do that is to extinguish the epidemic at the source. U.S. government partners are working to ensure layers of protection are in place for the U.S. population, starting in the affected countries and reaching all the way down to America's local hospitals and clinicians.

ACCOMPLISHMENTS SINCE 2012

The past two years of PHEMCE accomplishments have greatly enhanced the Nation's public health emergency preparedness for a wide range of threats and scenarios, and have informed the future directions of the PHEMCE. This section highlights some key accomplishments since

[11] Throughout this document, activities that are led by the BARDA component of ASPR are so identified, while activities that involve BARDA in coordination with other ASPR components, or are predominantly led by these other components, are designated with an "ASPR" lead.

the publication of the *2012 PHEMCE SIP*; a more detailed description of progress can be found in Appendix 7.

Threat and Risk Assessments and MCM Requirements

HHS and DHS clearly articulated roles, responsibilities, policies, and procedures in conducting and using threat and risk assessments for MCM planning. The *Material Threat Assessment 2.0 Strategic Implementation Plan,* signed in late 2012, describes an improved process for developing and updating the Material Threat Assessments (MTAs) that inform the Material Threat Determinations (MTDs) required for use of the Project BioShield Special Reserve Fund (SRF). Anthrax is the first agent being reassessed using the MTA 2.0 process. Anthrax consensus scenario types have been developed to ensure consistency and the use of the best available scientific information to inform medical consequence and public health response assessments. The *Terrorism Risk Assessment* (TRA) *Stakeholder Engagement Strategy* was created to coordinate the activities of key stakeholders and subject matter experts in the development of updated risk assessments.

Since the release of the *2012 PHEMCE IP*, following concurrence by the Enterprise Senior Council, the PHEMCE leadership body, the ASPR had approved 14 civilian MCM requirements documents (as of February 27, 2014). These requirements focused efforts to increase civilian preparedness and prevent or mitigate the adverse health impacts of CBRN agents and pandemic influenza by informing MCM research, advanced development, stockpiling, and utilization efforts across the PHEMCE.

Research and Development

NIH and DoD support PHEMCE goals and objectives through comprehensive and rigorous basic research programs focused on high priority threats, while also maintaining a strong translational science program to advance candidate MCMs through preclinical studies and into Phase 1 clinical testing in humans. In addition, NIH supports the testing of medical products that have already achieved FDA-approval[12] for other indications in order to obtain indications for high-priority threat agents. While NIH scientific accomplishments are too numerous to report, there are a number of significant product development efforts that are noteworthy, including:

- Submitting datasets to FDA in support of approval of off-patent antibiotics for pneumonic plague as well as to support the pursuit of an indication for Neupogen® (Amgen) to treat acute radiation syndrome (ARS). These datasets will support manufacturers' future requests for labeling changes as well as inform guidance for clinicians and other first responders;
- Completing a Phase 2 trial for a next-generation anthrax vaccine that is anticipated to require fewer doses than the currently approved vaccine;

[12] For purposes of this document, the term "approval" refers to FDA approval, licensure, or clearance under sections 505, 510(k), or 515 of the FD&C Act or section 351 of the PHS Act.

- Developing, in collaboration with CDC, an animal model to support assessment of a shortened antimicrobial post-exposure prophylaxis (PEP) duration following anthrax exposure. If this research is successful, it may allow for a significant reduction in antimicrobial stockpiles to address anthrax with no decrease in preparedness. Shorter antimicrobial treatment courses could also increase compliance and reduce known drug-related adverse events;
- Initiating evaluation of candidate influenza H7N9 vaccines, in collaboration with PHEMCE partners;
- Establishing a program, in collaboration with DoD, to address occupational exposures to Biosafety Level (BSL)-4 pathogens by enabling the rapid submission of an Emergency Investigational New Drug (emergency IND or eIND) application to FDA;
- Supporting the development of multiple Ebola MCMs including the therapeutic candidates ZMapp, BCX-4430, and favipiravir and two vaccine candidates, the first expressed in a chimpanzee adenovirus vector (ChAd3), and the second in a recombinant vesicular stomatitis virus (rVSV)vector (EBOV); and
- Advancing both a novel class of antibiotics and a broad-spectrum antiviral agent to Phase 1 clinical testing.

Advanced Research and Development and Procurement

Calendar year 2013 brought to an end the first chapter of the Project BioShield program, which was initiated in 2004 with the passage of the Project BioShield Act and the advanced appropriation of the $5.6 billion SRF. These funds supported BARDA's late-stage development and procurement of critical MCMs to protect the American people during and after intentional or natural disasters involving CBRN agents. During this time period, the Project BioShield program evolved to a program with clear successes recognized by HHS leadership, ASPR, and our industry and academic partners. The initial SRF funding expired at the end of FY2013 and BARDA, in alignment with PHEMCE priorities, invested all of the funds prior to their expiration by building a robust portfolio of 85+ CBRN product candidates under advanced development and procuring 12 new MCMs for inclusion in the Strategic National Stockpile (SNS) formulary. These products address threats that include anthrax, smallpox, botulism, radiological and nuclear events, and chemical nerve agents.

- Two of these products, an anthrax antitoxin to treat individuals with anthrax disease, and a heptavalent botulinum antitoxin to treat individuals with botulism intoxication, have been approved under the FDA "Animal Rule".[13] These are the first novel products to achieve this milestone. In addition, both products are approved for pediatric populations, and can be used in obstetric populations if the benefits outweigh

[13] Under certain 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 efficacy studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans. Demonstration of the product's safety in humans is still necessary (21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products).

the risks, addressing a mandate under PAHPRA to develop products for at-risk individuals.

- In calendar year 2014, two biological license applications (BLAs) were submitted to the FDA for review. Anthrax immunoglobulin (AIG), a polyclonal anthrax antitoxin derived from human plasma and developed by Cangene/Emergent was submitted in July 2014. In October, Emergent submitted their supplemental BLA for their anthrax vaccine candidate, Anthrax Vaccine Absorbed (AVA or BioThrax) for a post-exposure prophylaxis (PEP) indication.
- Over 20 million doses of modified vaccinia Ankara (MVA) smallpox vaccine have been delivered to the SNS starting in 2010. This vaccine has the potential for use during an emergency under Emergency Use Authorization (EUA)[14] in individuals of all ages with HIV or who have atopic dermatitis, including those who are pregnant or nursing.
- Products with a commercial market outside of the CBRN arena are also candidates for alternative approaches to stockpiling, such as vendor managed inventory (VMI). Two examples include the recent procurement of the cytokines Neupogen® (Amgen) and Leukine® (Sanofi-Aventis). Both products are commercially available to treat neutropenia associated with myelosuppressive therapy used in the treatment of cancer and for other indications. NIH and BARDA have also funded research to support use of these products to address the hematopoietic sub-syndrome of ARS resulting from exposure to ionizing radiation. Under VMI, BARDA has procured product that will be immediately accessible to the USG when needed, and will rotate through the commercial market when not needed. This rotation prevents the expiry associated with stockpiling product in a USG warehouse and dramatically decreases the overall life cycle management costs to the PHEMCE.

PAHPRA added section 319L to the PHS Act, providing BARDA the authority to invest in advanced research and development (ARD).[15] This authority is meant to bridge the "valley of death" between early MCM development and late stage MCM development. BARDA first received ARD funding in FY07 and to date has invested approximately $2.2 billion supporting ARD programs. These investments have stimulated the pharmaceutical and biotechnology industries and academic institutions to develop essential MCMs to meet national health security needs. BARDA's portfolio of CBRN candidate products has grown from 8 in 2008, addressing only ARS, to 85+ aggregate candidate products addressing anthrax; plague; tularemia; melioidosis and glanders; the broader public health concern of antimicrobial resistance; smallpox; the need for biodosimetry and biodiagnostic devices; hematopoietic, skin, lung, and gastrointestinal injuries and thermal and radiation burns from exposure to ionizing radiation; and chemical agents. This robust portfolio of candidate products is designed to yield those that will transition to potential procurement in the coming years as BARDA continues to address preparedness gaps identified by the PHEMCE. The DoD is also partnering with BARDA to leverage BARDA's ARD efforts to address military-specific requirements for radiological and

[14] 21 U.S.C. 360bbb-3
[15] 42 U.S.C. 247d-7e

nuclear threat MCMs. This includes biodosimetry and biodiagnostic devices, and treatments for the various effects resulting from the exposure to ionizing radiation.

BARDA and DoD have shown that the USG can successfully partner with pharmaceutical industry partners in ARD MCM efforts and BARDA now has attracted the interest of large pharmaceutical companies. For example, BARDA formed a partnership with GlaxoSmithKline under its Other Transactional Authority (OTA)[16] to develop a portfolio of candidate products to address both biothreat pathogens and antimicrobial resistance. Additional large pharmaceutical companies are now approaching BARDA to discuss possible partnerships. DoD has also partnered with GlaxoSmithKline to develop a product to overcome antibiotic resistance in bacterial biothreat species.

DoD and NIAID have successfully tested MCMs against Marburg virus, and Ebola virus in non-human primate (NHP) models, movingthem closer to Phase 1 clinical trials. DoD has also advanced a broad spectrum antiviral (favipiravir) into a Phase 3 clinical trial for an influenza indication; this trial is expected to complete enrollment by the end of the 2014/2015 Northern Hemisphere flu season. Favipiravir will also undergo clinical trials for Ebola in West Africa in 2015 (see below).

BARDA received $58M under the FY2015 Continuing Resolution to transition Ebola vaccine and therapeutic candidates from early development into advanced development and manufacturing in response to the Ebola epidemic. At the time of writing, BARDA has invested all of the funds supporting development of multiple therapeutic and vaccine candidates. BARDA's support is critical to ensuring the availability of both therapeutic and vaccine candidates for evaluation in the clinical trials slated to begin in West Africa in 2015, as well as the potential mass vaccination campaigns.

BARDA, in collaboration with NIH and DoD, has accelerated the advanced development and increased the manufacturing for ZMapp, a therapeutic against Ebola that has been shown to rescue animals that are severely ill with Ebola disease and which has been administered to Ebola patients on a limited basis. BARDA is also currently in discussions with manufacturers of additional Ebola therapeutics to potentially provide support for advanced development and manufacturing activities based on the previously mentioned supplemental funds.

BARDA is currently supporting development of three Ebola vaccine candidates, specifically vaccines from Profectus, BioProtection Services/Newlink (now partnered with Merck), and GlaxoSmithKline (GSK). The vaccines from Newlink and GSK have been evaluated in multiple Phase 1 clinical studies. BARDA is working closely with NIH and DoD colleagues on these efforts, as both programs received prior funding from those agencies. Finally, BARDA is in discussions with another large pharmaceutical company that is supporting development of an

[16] 42 U.S.C. 247d-7e(c)(5)

additional Ebola vaccine candidate and anticipates providing support for this candidate under the supplemental funding. BARDA also provided the resources of its Clinical Study Network to CDC for conducting a Phase 2 clinical trial in Sierra Leone in early 2015 to evaluate the safety and efficacy of Ebola vaccine candidates.

There have also been significant achievements in pandemic influenza preparedness supported by BARDA since 2012:

- Flucelvax®, developed and manufactured by Novartis Vaccines and Diagnostics, Inc., became the first cell-based seasonal influenza vaccine licensed in the US (November 2012);
- FluBlØk®, developed and manufactured by Protein Sciences Corporation, became the first FDA-approved recombinant-based seasonal influenza vaccine (January 2013);
- GlaxoSmithKline's Q-Pan® vaccine became the first FDA-approved adjuvanted pandemic influenza vaccine (November 2013);
- A BLA for a second cell-based influenza vaccine was submitted for FDA review (December 2013);
- Rapivab™ (peramivir) was the first single-dose influenza antiviral drug administered intravenously for hospitalized settings approved by the FDA (December 2014);
- Simplexa, a point-of-care diagnostic device developed by 3M and Focus for detection of influenza and respiratory syncytial virus, was cleared by the FDA (June 2012);
- Aura, a next generation portable ventilator developed by Covidien, was cleared by the FDA for adults (December 2012);
- In 2013 BARDA, with CDC, NIH, and FDA, developed, manufactured, tested, and stockpiled new vaccines with adjuvants in record time as a response to the fatal avian influenza H7N9 outbreaks in China. One of BARDA's Centers for Innovation in Advanced Development and Manufacturing at Novartis' Holly Springs facility played a key role in this response.
- In 2013 BARDA established the Fill-Finish Manufacturing Network in order to address a critical bottleneck in pandemic vaccine production and availability. This network includes four US companies that will supplement influenza vaccine manufacturers' filling capacity during a public health emergency, increasing the domestic capacity by up to 20%. It is currently filling final containers of Ebola vaccine and therapeutic candidates for clinical trials.
- In 2014 BARDA established a Clinical Studies Network to assist MCM developers with clinical trial activities and supplement existing clinical networks during public health emergencies. It is currently assisting CDC with clinical trials in Sierra Leone to evaluate Ebola vaccine candidates.

Additional PHEMCE accomplishments in ARD and procurement include:

- The DoD Next Generation Diagnostic System Increment 1 (NGDS Inc 1) system was selected for advanced development after DoD evaluation of several diagnostic

systems. NGDS Inc 1 will enable diagnosis of multiple biological agents in a more affordable and sustainable manner;

- Expansion of the approval for use of the influenza antiviral oseltamivir to treat children as young as 2 weeks of age;
- Preparation of MCMs for potential use under EUA against a diverse array of threats including smallpox, anthrax, and pandemic influenza;[17]
- FDA issuance of EUAs for diagnostic tests for the avian influenza A (H7N9) virus and Middle East Respiratory Syndrome coronavirus (MERS-CoV) to facilitate preparedness for these emerging biological threats;[18]
- DoD developed a PCR-based diagnostic assay for the detection of Ebola and submitted a pre-EUA data package to the FDA in 2011 to enable rapid issuance of an EUA for this assay in an emergency situation. In 2014, FDA issued EUAs allowing these and other diagnostics to be used to detect Ebola infection in U.S. citizens, following a Secretarial declaration that circumstances exist to justify such EUAs based on an existing 2006 MTD for Ebola virus made by DHS. A similar Ebola surveillance assay also developed by DoD has been used since April to support Ebola diagnosis and contact tracing in West Africa;
- DoD development of its Advanced Anticonvulsant System (AAS) autoinjector delivery system for the treatment of convulsions resulting from nerve agent exposure. An NDA was submitted to FDA, and the DoD is prepared to initiate production if the NDA receives FDA approval;
- ASPR and CDC charged their respective federal advisory committees - the National Biodefense Science Board (NBSB; re-named since 2014 as the National Preparedness and Response Science Board or NPRSB) and the CDC's Office of Public Health Preparedness and Response (OPHPR) Board of Scientific Counselors (BSC) - to develop a joint report addressing the future of the SNS considering the responsibility to procure and maintain PHEMCE-approved MCM stockpiling goals. The joint report is available on the ASPR website[19], and CDC has developed a response to these recommendations.
- In 2014, CDC in collaboration with DoD, deployed to the Laboratory Response Network (LRN) an EUA assay for the detection of Ebola virus. The assay is used for travelers and returning citizens entering the U.S. from Ebola outbreak affected countries that are exhibiting symptoms.

[17] To facilitate the issuance of EUAs, FDA has developed a pre-EUA submission process. FDA works with product sponsors or government agencies, such as CDC and DoD, to develop pre-EUA packages that will form the basis of an EUA request and decision when circumstances justify. Pre-EUA packages contain data and information about the safety and efficacy of the product, its intended use under an EUA, and information about the potential emergency situation that might unfold.

[18] Available at: http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm

[19] http://www.phe.gov/Preparedness/legal/boards/nprsb/recommendations/Documents/nbsb-bsc-sns-2020-final.pdf

Effective Utilization of MCMs

The PHEMCE has made great progress in supporting the effective utilization of critical MCMs during public health emergencies. Specific recent accomplishments in this area include:

- CDC and ASPR hosted meetings and workshops to develop updated clinical guidance for anthrax MCMs for use in children, pregnant women, and the general population, and under mass casualty conditions; MCMs to be used in a mass casualty botulism incident; and MCMs for the hematopoietic subsyndrome of ARS. CDC also led the development of an anthrax vaccine prioritization strategy and a smallpox vaccine response strategy.
- CDC, together with the American Academy of Pediatrics, developed and provided clinicians with dosing and use guidance for stockpiled MCMs for anthrax for pediatric populations, with the caveat that this guidance could only be used in an emergency (e.g.,if such MCMs are authorized for use under an EUA). The final report was published in *Pediatrics* in April 2014[20].
- CDC, working with FDA and other PHEMCE partners, including the Pediatric and Obstetric Integrated Program Team (PedsOB IPT), developed video instructions on the home preparation of crushing doxycycline tablets and mixing them with food for children and adults who cannot swallow pills, in anticipation of a potential shortage of liquid formulations of doxycycline during public health emergencies. The video instructions incorporate feedback received from various internal and external groups, including the PedsOB IPT; it also has captioning for persons who are hearing impaired.

International Sharing of MCMs

In 2013, the *HHS Policy Framework for Responding to International Requests for Public Health Emergency Medical Countermeasures* was established as the official policy by which the USG, through an interagency process, will receive, consider, decide, communicate, and respond to international requests for the sharing of public health emergency MCMs. This framework established the International Sharing of Medical Countermeasures Policy Group, which will continue to develop recommendations for HHS and USG leadership in response to international requests for USG MCMs, as well as address ongoing barriers to the international deployment of MCMs. Discussions with international partners on the deployment of MCMs can be used to explore strategic bilateral and multilateral engagements and identify joint opportunities for product development.

[20] Available at http://pediatrics.aappublications.org/content/133/5/e1411.full

PHEMCE COORDINATION WITH NON-FEDERAL STAKEHOLDERS

The PHEMCE coordinates and collaborates with non-federal stakeholders through a variety of venues. This section highlights some recent activities with SLTT, regional, international, industrial, and professional society stakeholders. These interactions are critical in shaping federal MCM planning and in identifying new ways to address national MCM needs.

ASPR and its partner agencies have led broad engagements with SLTT stakeholders through the National Association of County and City Health Officials (NACCHO) to provide an overview of the PHEMCE and current federal plans for ensuring MCM preparedness. These engagements highlight the areas where federal plans may intersect with and impact state and local health department planning and encourage increased connectivity at all levels of government.

ASPR also prioritizes the engagement of MCM developers and end-users to inform the civilian MCM requirement process and desired product characteristic development, federal MCM distribution and dispensing strategies, MCM response integration, and preparedness policy development. Such engagements also ensure alignment of federal MCM policy and planning activities with the needs and priorities of the ultimate end-users of these MCMs. For example, in 2013, ASPR conducted clinical utilization guidance workshops to develop recommendations for health care professionals to consult when utilizing MCMs provided by the SNS for botulism and hematopoietic-ARS. These workshops gathered together subject matter experts from clinical and technical backgrounds to provide individual recommendations to the federal government that were considered in the development of the clinical guidance documents. These guidance documents are expected to be released in 2015.
BARDA specifically engages with industry stakeholders and other organizations in several ways.

- BARDA hosts an annual Industry Day. This event provides a key opportunity to communicate new MCM initiatives, long-range strategic priorities, the availability of core services to developers, and information on HHS/ASPR contracting roles and processes. Stakeholders also have the opportunity to arrange individual meetings to discuss their specific development and manufacturing technologies with federal officials. These events are well-attended; for example the successful 2014 BARDA Industry Day included over 600 participants from diverse backgrounds including industry, other federal agencies, local and state government, and academia.
- BARDA collaborates with organizations such as the Biotechnology Industry Organization (BIO), the Alliance for Biosecurity (Alliance), and the Center for a New American Security (CNAS) to inform stakeholders of BARDA and PHEMCE-wide priorities.
- BARDA held a pre-proposal conference for the reissuing of the Broad Agency Announcements (BAAs) for CBRN, Influenza, and Strategic Science and Technology,

respectively, on September 4, 2013. More than 250 attendees had the opportunity to meet with BARDA personnel in one-on-one meetings.

- BARDA has worked with ASPR's Regional Emergency Coordinators (RECs) from across the country to engage the end-users of MCMs in identifying product characteristics that would be essential for effective administration during an incident. In addition, BARDA works with professional societies, such as the American Burn Association (ABA) and Infectious Diseases Society of America (IDSA), to gain valuable feedback on how end-users would respond to a CBRN incident.

Another key opportunity for stakeholders to engage with BARDA is the TechWatch program. TechWatch meetings organized by BARDA are attended by senior subject matter experts, project managers, and contracting staff. In these interactions, federal staff can evaluate promising products and technologies, suggest techniques and strategies for meeting technical and regulatory challenges, and provide insight on how a particular product or technology may best address federal priorities. These meetings are intended to provide the USG with the latest information about emerging technologies and tools that may guide its strategic and programmatic planning for effective public health emergency response. In turn, the meetings give organizations the opportunity to receive input from scientific and contracting staff on possible next steps in the development of their MCM products and how they may work with the USG as part of this process. On average, BARDA hosts over 100 TechWatch meetings annually with industry and academic partners. The TechWatch program has been very valuable during the Ebola response, providing BARDA with the latest information on products that are under development and may be of interest to BARDA and our PHEMCE partners. For the current Ebola epidemic, BARDA's Tech Watch has hosted more than 125+ meetings with potential and existing partners for development of Ebola vaccine, therapeutic, diagnostics, and medical device and equipment candidates.

ASPR seeks to improve health care preparedness and response at the state and local levels by providing leadership, funding, evaluation, and technical assistance through the Hospital Preparedness Program (HPP) to 62 awardees, including all states, four directly-funded cities, and eight territories. For example, "Building Responder Safety and Health" is one of eight capabilities that awardees work toward using HPP funding and guidance. As part of this capability, awardees must assist health care organizations with pharmaceutical protection for health care workers. States, in coordination with health care organizations, health care coalitions, emergency management, public health, and other stakeholders, develop, refine, and sustain plans to provide MCMs to treat or provide prophylaxis to the affected health care worker population in accordance with public health guidelines and/or recommendations. This planning is supported by guidance from ASPR and CDC (e.g., the recent joint FY14 ASPR HPP - CDC Public Health Emergency Preparedness (PHEP) continuation grant guidance (CDC-RFA-TP12-120102CONT14)[21] provides opportunities and guidelines for HPP sub-awardee healthcare coalitions/hospitals to exercise the responder safety and health capability during joint

[21] Available at https://www.ndhealth.gov/EPR/PHP/NOA%20PHEP%20BP3.pdf

exercises). This guidance also includes health care coordination with federal MCM programs such as the SNS and other relevant programs.

As called for by the Global Health Security Agenda launched in February 2014, ASPR engages with international stakeholders to "improve global access to medical and non-medical countermeasures during health emergencies"[22]. To identify and overcome barriers to providing mutual MCM assistance and move toward building a sustainable MCM global infrastructure, ASPR engages with stakeholders on bilateral, regional, and multilateral bases, through the Global Health Security Agenda and other partnerships, such as the Beyond the Border Initiative, the North American Plan for Animal and Pandemic Influenza, and the Global Health Security Initiative (GHSI).

CDC administers the PHEP cooperative agreement program and provides funding, technical assistance, and resources that support SLTT public health departments in demonstrating measurable and sustainable progress toward achieving public health preparedness capabilities that promote prepared and resilient communities. This progress includes the development and maintenance of capabilities and capacities to ensure successful distribution and dispensing of MCMs during a response. To strengthen MCM distribution and dispensing at the local level, designated PHEP funding is provided to 72 Cities Readiness Initiative (CRI) jurisdictions to support MCM preparedness in the nation's largest cities and metropolitan statistical areas (MSAs) where more than 50% of the US population resides. Through CRI, state and large metropolitan public health departments have developed plans to respond to a large-scale biological agent attack by dispensing antimicrobials to their entire populations within 48 hours.

CDC also engages state and local stakeholders through collaborative planning, training, exercises, and reviews, and shares resources and programmatic and scientific expertise. These stakeholders, as well as public health practitioners, clinicians, and clinicians' associations, are engaged during the development of public health policies, clinical guidance, and recommendations for existing and new MCMs. CDC's Healthcare Preparedness Activity also actively collaborates with other federal agencies, state governments, medical societies, and other public and private organizations to promote integrated health care preparedness planning. Finally, CDC's Community Resilience Activity engages community and private sector partners across the nation to expand the dispensing network through partner-staffed point-of-dispensing (POD) sites to ensure medication is dispensed quickly and to strengthen the resilience of the community during an emergency.

FDA works with state and local public health authorities and responders and public health non-governmental organizations (NGOs) to support MCM preparedness and response capabilities at the state and community levels, including responding to numerous EUA-related inquiries and participating in multiple national-level workshops, meetings, and webinars.

[22] http://www.globalhealth.gov/global-health-topics/global-health-security/ghsagenda.html

DEVELOPMENT OF THE *2014 PHEMCE STRATEGY AND IMPLEMENTATION PLAN*

As in 2012, ASPR led the development of the *2014 PHEMCE SIP* through an interagency steering committee comprised of representatives from across the PHEMCE agencies. The steering committee reviewed the PHEMCE-wide strategic goals and objectives contained in the *2012 PHEMCE Strategy* and determined that they remained largely relevant and appropriate for 2014, and continued to be aligned with agency-level strategies and priorities (see Appendix 4). The sole exception was Objective 3.2[23], which was broadened to include explicit coordination with regional organizations, in addition to ongoing collaborations with SLTT and private sector partners.

Based on the progress made in pursuit of these goals and objectives since 2012 (as summarized above and in Appendix 7), and in alignment with the prioritization framework developed in the *2012 PHEMCE Implementation Plan*, the steering committee identified those priority activities needed to achieve the PHEMCE goals and objectives. These included both activities still ongoing from the *2012 Implementation Plan* as well as new initiatives. Plans to pursue and accomplish the activities and initiatives detailed here are based on currently anticipated funding levels for PHEMCE organizations over the next five years. Following review and input from across the PHEMCE, the *2014 PHEMCE SIP* was approved by HHS and publicly released.

Consideration of Perspectives from the National Biodefense Science Board (NBSB)

The *2014 PHEMCE SIP* was also informed by previous recommendations provided to the HHS Secretary on PHEMCE-related issues by the NBSB, now known as the National Preparedness and Response Science Board (NPRSB). Past NBSB engagements of particular relevance included those conducted on the *2012 PHEMCE SIP*[24]; the long-term sustainability of the SNS[25]; and the PHEMCE development of MCM preparedness goals[26].

[23] The 2012 version of Objective 3.2 read "Develop and communicate medical countermeasure utilization policy, guidance and response strategies, including FDA regulatory frameworks, that are responsive to end-user needs and that are integrated with state, local, tribal, territorial (SLTT) and private sector response plans, and when possible international partners, and that ensure timely, safe, and effective medical countermeasure distribution and utilization." In 2014 this has been broadened to include the need to integrate with regional organizations as well.
[24] NBSB Evaluation of the 2012 HHS Public Health Emergency Medical Countermeasures Enterprise [PHEMCE] Strategy and Implementation Plan [SIP], 2012.
[25] National Biodefense Science Board and the Office of Public Health Preparedness and Response Board of Scientific Counselors, Anticipated Responsibilities of the Strategic National Stockpile (SNS) in the Year 2020: An Examination with Recommendations, 2013.
[26] http://www.phe.gov/Preparedness/legal/boards/nprsb/meetings/Pages/publicmeeting-140110.aspx

SECTION 1:
ACTIVITIES TO ACHIEVE STRATEGIC GOALS AND OBJECTIVES

The *2012 PHEMCE Strategy* presented four major goals, aligned to capture: (1) the overall prioritization of PHEMCE resources and MCM development and procurement activities; (2) regulatory enhancements to facilitate MCM development and use; (3) logistical and operational plans for optimal MCM use in a public health emergency; and (4) consideration of at-risk individuals' MCM needs.

This section describes the broad programs and initiatives that HHS, in collaboration with its interagency partners, will implement over the next five years to advance these strategic goals and underlying objectives. Where appropriate, lead and partner agencies are identified, and activities are projected for near-term (FY15-16), mid-term (FY17-18) and long-term (FY19 and beyond) timeframes. More detailed information on these priorities is provided in Sections 4 and 5 of this SIP, organized by specific threat area and cross-cutting technologies or approaches, respectively.

GOAL 1. Identify, create, develop, manufacture, and procure critical medical countermeasures.

Objective 1.1 Develop a strategic framework to prioritize PHEMCE resources and investments. **(Lead: ASPR; Partners: PHEMCE agencies)**

PHEMCE Prioritization Framework: Principles and Criteria

Effective use of MCMs in a public health response in part depends on strategic decisions in research and development, manufacturing, and acquisition of MCMs. Additionally, given the range of potential threats and the resources available to address them, prioritization of HHS and PHEMCE-wide resources across the MCM development, acquisition, and utilization continuum is necessary. In 2012, the PHEMCE developed a coordinated, strategic framework through which to focus investments across the PHEMCE and will continue to apply this framework to inform resource allocations for research, development, manufacturing, and procurement.

The PHEMCE Prioritization Framework is based on two core principles: (1) the medical and public health imperatives to limit the potential adverse health impacts posed by a variety of threats; and (2) the fiduciary responsibility to be prudent with the resources entrusted to the programs by Congress and the nation while maximizing preparedness. It then uses three primary and three moderating criteria for identifying priority investments. These are listed to the right, and described in more detail in the *2012 PHEMCE Implementation Plan*[27].

Box 3:
Primary Criteria

1. Threat Priority
2. Multi-Functionality
3. Operational Capacity

Moderating Criteria

1. At Risk-Population Needs
2. Time to Product Availability
3. Life Cycle Cost

PHEMCE Prioritization Processes

The following activities will be conducted to implement the prioritization framework over the next five years:

- *(1.1.1)* ***Portfolio Reviews (ongoing):*** ASPR leads the periodic (at least every 18 months) review of specific MCM portfolios across the PHEMCE to monitor progress in MCM preparedness, identify remaining gaps and challenges, and develop potential solutions. These Portfolio Reviews will continue to provide venues to foster coordination among PHEMCE partner agencies in the identification of those areas requiring additional attention and resource prioritization.
- *(1.1.2)* ***Multi-Year Budgeting (ongoing):*** Development of the multi-year budgeting initiative, called for in the *2010 PHEMCE Review*[28]*,* and subsequently required by law under the PHS Act, as amended by PAHPRA[29], was initiated in 2011 and has continued to evolve since then, with the first PHEMCE multiyear budget report (covering FY14 to FY18) anticipated for submission to Congress in early 2015. This budget process will be used in the future to more tightly link investments across NIH, ASPR, CDC, and FDA. It will help to project future budget needs within and among agencies as MCM products mature and move across agency boundaries in the development and procurement processes.
- *(1.1.3)* ***Portfolio Management (near and mid-term):*** ASPR and DoD will implement PHEMCE-wide portfolio tracking tools by the beginning of FY15 to further enable coordinated planning and management of CBRN MCM development. *(1.1.4)* The PHEMCE will consider expansion of the portfolio tracking tools to include pandemic influenza or other EID portfolios, as needed, by FY18. These tools will provide a common set of business practices and harmonized performance metrics that will facilitate benchmarking and data-driven management practices to achieve shorter timelines and greater cost-efficiencies in MCM development portfolios. *(1.1.5)* Furthermore, these tools will be incorporated into BARDA's annual strategic portfolio-

[27] http://www.phe.gov/Preparedness/mcm/phemce/Pages/strategy.aspx
[28] https://www.phe.gov/Preparedness/mcm/phemce/Pages/review-2010.aspx
http://www.phe.gov/Preparedness/mcm/phemce/Pages/review-2010.aspx
[29] 42 U.S.C. 300hh-10(b)(7)

wide management assessment review that will help align resources to programs that demonstrate acceptable returns on investment.

The depth, complexity, and breadth of information necessary for the PHEMCE to implement the prioritization framework also require the use of decision analysis tools. Policy-relevant considerations include, but are not limited to: the best scientific evidence; assessment of scientific promise; MCM needs projections; an assessment of national and regional capability to effectively utilize MCMs in a public health emergency; cross-threat prioritization; resource availability ; evidence-based clinical utilization protocols; and the readiness of end-users to respond to multiple scenarios involving potential threats. In response, the PHEMCE and agency partners have developed several decision analysis tools to inform senior leaders at all levels.

(1.1.6) In the near-term, ASPR will lead the development of metrics for the PHEMCE preparedness goal framework and *(1.1.7)* interagency Integrated Program Teams (IPTs) will implement the framework and associated metrics to assess current and target levels of MCM preparedness against five preparedness determinants: (1) operational capacity; (2) research and development; (3) manufacturing capacity; (4) procurement and stockpiling; and (5) response planning and guidance. This analysis will be used by PHEMCE leadership to inform resource prioritization to best achieve target levels of preparedness *(1.1.8)* In the mid-term, ASPR will also lead PHEMCE-wide deliberation on additional decision analysis tools that may enhance the process by which PHEMCE leadership prioritizes resource allocations and seek to develop them as appropriate. This approach will allow for a consistent process to develop best practices that most effectively meet the needs of PHEMCE decision-makers in evaluating investment strategies.

Objective 1.2 Utilize consistent approaches for medical consequence and public health response assessments and MCM requirement setting that include consideration of effective production, storage, deployment, and administration strategies. **(Lead: ASPR; Partners: PHEMCE agencies)**

Simply stated, the PHEMCE MCM requirement process must address the questions of “Who needs what, when, and how?” The requirement process serves to improve the outcomes of public health emergencies by focusing federal investments toward an aligned research, advanced development, acquisition, deployment, and use agenda by HHS agencies. Moreover, the requirement process informs private industry and academia about civilian MCM needs and facilitates effective coordination of programs with PHEMCE interagency partners.

Working with public health, technical, and scientific experts across the PHEMCE, ASPR leads the civilian MCM requirement process and vets requirement documents through the PHEMCE governance structure prior to finalization by the ASPR. For intentional CBRN threats, the requirement framework uses the DHS MTAs, which estimate the number of individuals who might be exposed to each threat in a range of scenarios up to and including high-consequence scenarios. These assessments are then used as the basis for public health response and medical consequence modeling that define the populations that could benefit from intervention

with pharmaceutical or non-pharmaceutical MCMs (the need-based quantity). The core capabilities required of the medical and public health systems to effectively utilize various types of MCMs are then analyzed, thereby allowing the PHEMCE to project the quantity of various MCMs that could be effectively used under the planning scenarios (the operational quantity).

The need-based and operational quantities, along with the development of product specifications, outreach to the ultimate end-users of MCMs (e.g., first responders, physicians, nurses, other allied health professionals, local and hospital laboratory directors, state and local emergency planners, and others), and other policy considerations are assessed to establish stockpiling goals. This process ensures that MCM stockpiling goals are based on sound scientific, medical, and epidemiological principles and result in a national stockpile of MCMs that can be utilized most effectively during a public health emergency.

The need-based quantities, operational quantities, and stockpiling goals thus provide critical information to support PHEMCE leadership's allocation of resources. Prior to making investment decisions and pursuing specific acquisition targets, however, the PHEMCE considers MCM needs across the entire threat portfolio, along with scientific opportunity, existing resources, and other factors, using the PHEMCE prioritization framework described previously.

Specific activities to be taken in support of developing civilian stockpiling goals include:

- *CBRN threat and risk assessments:* *(1.2.1)* In the near-term, DHS and HHS will update the initial anthrax MTA using the *MTA 2.0 Strategic Implementation Plan*. *(1.2.2)* In the mid-term, DHS and HHS will review the need to update MTAs for all CBRN agents and develop any required MTAs under the *MTA 2.0 Strategic Implementation Plan* protocols. *(1.2.3)* In addition, HHS and DHS modeling groups are coordinating modeling efforts to ensure that their models and parameters are consistent. These activities will bring the MTAs and the TRAs into alignment in support of MCM planning. *(1.2.4)* In the near-term, DHS is also updating the TRA development process in accordance with the *TRA Stakeholder Engagement Strategy* (e.g., including a thorough vetting of biothreat agent parameters – including bacterial, viral, and toxin threats – with PHEMCE subject matter experts). *(1.2.5)* DHS will also work with HHS and other PHEMCE partners to produce a TRA program implementation plan. *(1.2.6)* In the mid- and long-terms, DHS will continue to conduct TRAs and update them as necessary. *(1.2.7)* In the near- and mid-terms, DHS will continue to work with PHEMCE partners to develop tailored assessments that use risk-informed methodologies to answer key questions (e.g., assess the need for completing a full MTA of a CBRN agent to support consideration of an MTD).
- *Emerging infectious disease risk assessments:* As noted in the *2012 PHEMCE Implementation Plan*, there are also naturally occurring and accidental threats to national health security that are outside the realm of the DHS threat and risk assessments. EIDs, including influenza, require other methods for risk assessment. *(1.2.8)* HHS will continue to refine the Influenza Risk Assessment Tool (IRAT), the current tool for assessing pandemic risk for emerging strains of influenza. *(1.2.9)* For other EIDs, CDC

and DHS will lead development in the near-term of a risk assessment methodology and process that will inform PHEMCE leadership decisions on which EID threats require PHEMCE response at the research and development, requirement, advanced research and development, large-scale production, stockpiling, and/or utilization planning levels.

- *CONOPs considerations*: Consideration of the current and anticipated Concepts of Operations (CONOPs) and public health response capabilities at the federal and SLTT levels is critical to ensuring that stockpiled MCMs can be safely and effectively used in a public health emergency. The PHEMCE requirement framework is based on present and future programmed federal and SLTT capabilities to rapidly ship, distribute, and dispense MCMs. For example, CDC and BARDA have developed several modeling tools that facilitate planning at the federal and SLTT levels, providing officials with ways to evaluate plans without resource-intensive drills or exercises. CDC and BARDA have also developed epidemiologic modeling tools that can be used in response to a public health emergency, such as a pandemic influenza outbreak, to inform MCM utilization policy, clinical guidance, and response strategies.[30] *(1.2.10)* In the near-term, CDC and BARDA will continue to enhance such modeling capabilities and collaborations.

(1.2.11) In the near- and mid-terms, ASPR, working with subject matter experts from across the PHEMCE, will develop or update specific MCM requirement documents including those listed in Table 2.

[30] Examples include FluAid and FluSurge. FluAid provides a range of estimates of impact in terms of deaths, hospitalizations, and outpatient visits due to pandemic influenza, while FluSurge predicts the surge in demand for hospital-based services during an influenza pandemic, yielding estimates of the number of hospitalizations (including ICU admissions) and deaths caused by a pandemic in comparison to existing hospital capacity.

Table 2. Civilian MCM Requirement Priorities

Near-Term (FY15-16)
Anthrax Scenario-Based Analysis (SBA)[31]
Anthrax Diagnostic SBA
Addendum to Acetylcholinesterase Reactivator PSR[32]
Neuroprotectants Research Requirements[33]
Patient Decontamination Research Requirements
Improvised Nuclear Device SBA
Blood Products for Improvised Nuclear Device PSR
Thermal Burn for Improvised Nuclear Device PSR
Radiological Dispersal Device SBA
Antimicrobials for Improvised Nuclear Device PSR
Smallpox SBA
Respiratory Protective Devices Integrated Capabilities Document (ICD) Annex[34]
Filovirus Diagnostics PSR
Mid-Term (FY17-18)
GABA Antagonists SBA
Chemical Diagnostics PSR
Hematopoietic-ARS for Improvised Nuclear Device PSR
Radiocesium for Radiological Dispersal Device PSR
Bioassay Diagnostics for Radiological Dispersal Device PSR
Oral Delivery ICD Chapter
Intravenous Delivery ICD Chapter

(1.2.12) In addition, as priorities dictate and resources allow, the PHEMCE will apply the requirement process to address any new threats determined by DHS to pose a material threat to national security or those EIDs identified by PHEMCE leadership.

Priority PHEMCE stockpiling goals, based on the PHEMCE requirement process and prioritization framework, are publicly communicated to stakeholders, including industry, at the time of ARD or acquisition solicitations. In the long term, all MCM requirements-related

[31] Scenario-Based Analysis assesses the scenarios, details the critical types of MCMs, and identifies the need-based quantity (i.e., the number of people who would benefit from being pretreated, diagnosed, or treated with a particular MCM class to optimally reduce morbidity and mortality)
[32] Product-Specific Requirements establish the desired product profiles of MCMs called for in the SBAs and identify the stockpiling goal (i.e., the number of MCMs that the PHEMCE recommends stockpiling based on consideration of policy considerations relevant to the threat, the need-based quantity, and the operational quantity)
[33] Research Requirements prioritize research goals to assist in the future advanced development or acquisition of products or services
[34] Integrated Capabilities Document describes the core cross-threat capabilities required of the medical and public health system, prioritizes solutions to improve operational capacity, and projects the operational quantity (i.e., the number of MCMs that the medical and public health system can currently distribute, deliver, and effectively utilize during the planning scenarios)

documents will be revisited periodically to allow incorporation of new threat and risk assessments, MCM technologies, and response capabilities.

(1.2.13) Analytical tools will be developed to demonstrate the effect of fulfilling any particular stockpiling target on overall threat preparedness, in support of strategic decision-making within the PHEMCE prioritization framework. In addition to the threat, risk, medical consequence, and public health response assessments that estimate risk mitigation from MCMs, several analytical decision support tools are currently under development or in a pilot phase to address specific metrics identified in the prioritization framework:

- *(1.1.6)* The preparedness determinants that will be developed by ASPR in the near-term will provide high-level metrics for ARD, stockpiling, response planning and guidance, manufacturing capacity, and operational capacity;
- A five-year budgeting tool was developed as part of the SNS Annual Review that allows the PHEMCE decision-makers to see the financial impacts of changes to the SNS formulary;
- *(3.1.2)* The DHS-CDC SNS Risk Formulary study will be completed in the near-term to inform the risk-based optimization of SNS assets;
- *(1.2.14)* BARDA will develop metrics and a decision-support tool to assess the total life-cycle costs of all MCMs in the product development pipeline;
- *(1.2.15)* BARDA will develop end-user planning tools under the *MTA 2.0 Strategic Implementation Plan* to assist SLTT stakeholders by providing planning scenarios and rapid consequence assessments for MCM utilization; and
- *(1.2.16)* BARDA will develop additional decision support tools on an ad-hoc basis to support examination of MCM sustainability through the five-year budgeting process.

Objective 1.3 Ensure a robust and sustainable product pipeline for MCMs that emphasizes multi-functional capabilities (e.g., platform technologies, host-based innovations, broad-spectrum MCMs) rather than stand-alone outcomes and includes consideration of viable commercial markets and/or routine public health applicability. **(Leads: BARDA, NIH; Partners: DoD, CDC, USDA)**

A robust product pipeline is one in which the number of MCM candidates in the research and development process is sufficient to assure a high probability of successfully developing a candidate with sufficient safety and efficacy information to support FDA approval for the desired indication(s). The PHEMCE will seek to maintain robust product pipelines where they exist and to build them in areas where critical gaps still remain. The PHEMCE will take a portfolio management approach, including through the use of portfolio tracking tools and multi-year budget planning across HHS agencies, to ensure that research and development activities are well-coordinated across PHEMCE partners. Additionally, the President's Combatting Antimicrobial-Resistant Bacteria (CARB) initiative (2014) will have a high priority in PHEMCE planning and implementation over the next five (5) years to address the on-going public health crisis. It is anticipated that the portfolio of MCM investments may shift over time to address unmet needs. For example, the PHEMCE considers some MCM portfolios, such as those for

anthrax, botulism, and smallpox, to be mature and will seek to focus any future research investments in these areas on improvements to the current capabilities rather than development of new capabilities.

Wherever possible, the PHEMCE will pursue MCMs that can address multiple high-priority threats and/or have routine medical applications and thus commercial viability. The PHEMCE is mindful that a "one bug, one drug" or fixed defense[35] approach for MCM development is still required for some of the highest-priority threats, such as anthrax and smallpox. However, a broad-spectrum approach, when scientifically well-supported, may offer more effective and efficient capabilities to address both known and unknown threats. Multi-use products, such as broad-spectrum therapeutics and multiplex diagnostic platforms, support response in a public health emergency and could also provide routine medical and public health benefits that enhance the sustainability of the MCM mission and improve daily national health security. Continued investment in current and new technologies will be based on satisfying the prioritization criteria and requirements process defined above.

The civilian MCM product pipeline predominantly consists of research and development efforts supported through the combined efforts of NIH and BARDA, in coordination with DoD and CDC, that have direct relevance to civilian national health security. The PHEMCE considers at-risk individuals' needs throughout its efforts to ensure a robust and sustainable product pipeline; activities specifically directed at addressing at-risk individuals' needs will be described in detail under Goal 4 of this section.

NIH focuses on the basic and translational research, and the expansion of research infrastructure and research resources, that are the fundamental building blocks for developing civilian MCMs. *(1.3.1)* NIH will also evaluate previously approved, off-patent MCMs in an effort to expand approved indications to other threat agents or infectious diseases as well as to increase the repertoire of MCMs with pediatric indications. *(1.3.2)* In addition, NIH will continue to develop and test new products and approaches to treatment and infection control (e.g., multi-component vaccines, broad-spectrum antimicrobials, and point-of-care (POC) and broad-spectrum diagnostics).

(1.3.3) Through FY18, NIH will emphasize the early-stage research programs listed in Table 3 (more details on particular programs are provided in Sections 3 and 4). Early-stage products that demonstrate promise for advanced development will be brought to the attention of BARDA through regular communications and opportunities for technology transfer. *(1.3.4)* For example, over the next five years, multiple candidates for next-generation anthrax vaccines or botulinum antitoxins, broad-spectrum antibacterials and antivirals, and influenza antivirals may be available for advanced development consideration.

[35] Relman DA. Bioterrorism – Preparing to Fight the Next War, *NEJM*, 2006, 354 (2): 113-115. In the context of defense against biological threats, a fixed defense is a MCM intended for use against a specific organism and not useful in scenarios that employ a different organism.

Table 3. NIH Near- and Mid-Term Research Priorities

Threats	Research Priorities
Biological (intentional or naturally emerging diseases, including Ebola and pandemic influenza)[36]	*(1.3.3a)* Therapeutics, including broad-spectrum antimicrobials, immunomodulators, and host-based therapeutics for bacterial and viral threats *(1.3.3b)* Vaccines with emphasis on post-exposure prophylactic potential and those that provide protection of health care workers and the local population in outbreak scenarios and enhancements to allow for more effective and efficient utilization during public health emergencies *(1.3.3c)* Development of vaccine-related technologies such as adjuvants, temperature stabilization, and alternative delivery devices to enhance the performance, life cycle costs, and utilization/operational capacity for existing biodefense vaccines, with applicability to other infectious diseases or public health situations *(1.3.3d)* Diagnostic platforms and biomarkers *(1.3.3e)* Development and utilization of animal models to support FDA licensure or approval under the "Animal Rule", as well as to inform utilization policy and optimal treatment regimens (e.g., antimicrobial course-duration shortening when combined with vaccination)
Radiological/nuclear (intentional or accidental)	*(1.3.3f)* Mechanisms of radiation injury at the systemic, organ, cellular, and molecular levels, with particular focus on skin and the hematopoietic, gastrointestinal, immune, pulmonary, renal, and nervous systems *(1.3.3g)* Approaches to minimize short- and long-term adverse health effects of radiation exposure, including cytokines, growth factors, anti-apoptotics, anti-inflammatory candidates, and antioxidants *(1.3.3h)* Identification and evaluation of biomarkers of radiation injury for use in biodosimetry and bioassay systems for rapid triage, radiation dose estimation, prediction of organ-specific effects and/or delayed health risk; these will be developed into high-throughput modalities for use in a mass-casualty incident *(1.3.3i)* Identification and development of decorporation and blocking agents that prevent the uptake and/or increase the elimination of radionuclides of concern. Investigation of candidate MCMs that increase the mucociliary clearance of particulates in the lung
Chemical (intentional or accidental)	*(1.3.3j)* Elucidation of mechanisms of chemical injury at the systemic, organ, cell, and molecular levels, with particular focus on chemicals affecting the nervous system, respiratory tract, skin, eyes, and mucous membranes, and cellular respiration *(1.3.3k)* Identification and characterization of approaches to minimize short- and long-term adverse health effects of chemical exposure *(1.3.3l)* MCMs against traditional chemical warfare agents[37], highly toxic industrial chemicals[38], highly toxic agricultural chemicals[39], and poisons

[36] This includes all Category A, B, and C agents, including influenza.

[37] These include the nerve agents (i.e.G, sarin, VX, soman), and sulfur mustard.

[38] Such as cyanide, chlorine, and phosgene

[39] Such as parathion, chlorpyrifos, disulfoton, and the rodenticides sodium fluoroacetate, strychnine, and tetramethylenedisulfotetramine (TETS)

(1.3.5) In FY15, NIH plans to make awards under a BAA entitled *Targeting Therapeutics Development to Relieve Bottlenecks in Translational Research*. This initiative will support lead identification, optimization, and preclinical testing to enhance the pool of candidate small-molecule therapeutics available for future clinical development. *(1.3.6)* In CY15 NIH plans to release a BAA entitled "Development of Therapeutic Medical Countermeasures for Biodefense and Emerging Infectious Diseases" with awards to be made in FY16. The disease focus for these two BAA efforts will be biodefense and emerging infectious diseases with particular interest in broad-spectrum antimicrobials addressing antimicrobial resistance, as well as broad-spectrum antivirals and small molecule antitoxins.

(1.3.7) NIH will also continue to manage the Concept Acceleration Program (CAP) to create and coordinate teams of scientific, medical, and product development experts to guide investigators working on multi-use products for biodefense, drug resistance, and emerging disease applications. The CAP was initiated as a result of the *2010 PHEMCE Review* to accelerate the development of promising, high-priority MCMs. For example, a CAP-supported and augmented grant working toward development of a novel antibiotic was sufficiently productive to successfully compete for an NIH contract to develop the candidate MCM through Phase 1 human testing.

NIH's long-term focus (FY19 and beyond) will increase the emphasis on platform technologies that either allow for the development of broad-spectrum MCMs or permit more rapid development of agent-specific MCMs. Additionally, NIH will focus on MCMs with commercial applicability for routine (non-emergency) public health diseases of both domestic and international significance.

DoD, NIH and BARDA use Technology Readiness Levels (TRLs),[40] which track product development stages, to coordinate development projects, provide seamless programmatic transition, and promote continuity of funding throughout MCM development. NIH will typically carry development efforts through TRL 6 (including clinical Phase 1 studies), while BARDA picks up development of priority MCMs in TRLs 6-7 (following Phase 1). NIH will also invest in development efforts at early TRLs to address at-risk individuals' needs and enhance the characteristics of current MCMs to optimize their effectiveness. BARDA will continue to support preclinical development (i.e., TRL 5) of certain MCMs to address radiological, nuclear, and chemical threats due to the lack of robust alternative funding sources. *(1.3.8)* In this context, BARDA is currently re-evaluating the medical consequences of the threat posed by radiological dispersal devices (RDDs) and developing recommendations for further research, development, and procurement of MCMs to address these threats.

(1.3.9) DoD will continue to support PHEMCE objectives through its investments in MCMs for DoD-prioritized threat agents, including Ebola. Additional investments will continue in activities

[40] For more information, see https://www.medicalcountermeasures.gov/federal-initiatives/guidance/about-the-trls.aspx

to enable MCM development, including in aerosolized and parenteral models of Ebola and Marburg infection in *Rhesus macaques* and *cynomolgus macaques.*

The BARDA CBRN MCM portfolio strategy has evolved over the past ten years to a multi-faceted approach that seeks to:

- Provide support to CBRN MCM developers with BARDA core assistance programs;
- Expand BARDA's broad spectrum antimicrobial and diagnostics programs in alignment with the CARB initiative;
- Test and evaluate products under development for CBRN indications, those approved for non-CBRN indications that could be repurposed to meet PHEMCE stockpiling goals, and multi-purpose product candidates that could meet both PHEMCE stockpiling goals and unmet everyday healthcare needs;
- Develop next-generation MCMs that present improvements over existing ones with regard to effectiveness, ease of administration, cost, and logistics;
- Support ARD of host-directed therapeutics;[41]
- Continue establishment of public-private partnerships with industry and academia;
- Continue federal interagency alliances that enable cost-sharing in the development of key CBRN MCMs; and
- Develop innovative technologies to address challenges encountered in CBRN MCM development.

This emphasis on cross-cutting and platform technologies will enhance the value of USG investments by stimulating a more sustainable commercial base for these products and positioning the PHEMCE to respond more effectively to the unknown threats of the future.

The BARDA influenza portfolio strategy is also focused on developing products with potential for increased effectiveness, greater multi-functionality, and improved operational utility. In addition to maintaining pre-pandemic influenza vaccine stockpiles and domestic influenza vaccine manufacturing infrastructure, BARDA's chief emphasis for pandemic influenza will be directed towards advanced development of more effective influenza vaccines with potential universal vaccination capability and influenza immunotherapeutics for life-threatening influenza cases. BARDA will continue to support development of non-neuraminidase inhibitor therapeutics, including host targets, immunomodulators, and drugs used in combination, with a focus on products suitable for all populations, including young children and the severely ill. This approach is also demonstrated in investments in next-generation ventilators that are reusable and easy to use by health care workers and the public – including children – during infectious disease outbreaks. BARDA will also invest in development of reusable, more intuitively fitting and easier to use respiratory protective devices (RPDs). These and other advanced development efforts are described in more detail in Section 3.

[41] These are therapies that reduce morbidity or mortality by targeting key host-cell molecules involved in immune-modulation, inflammation, and regulation of innate immunity.

(1.3.10) The projected advanced development and acquisition priorities through FY18, as determined by the PHEMCE prioritization framework, are shown in Table 4. More details on particular programs and timelines are provided in Sections 4 and 5. BARDA is able to both support the advanced development of products through annual appropriations, and acquire products for the SNS using funds appropriated to the SRF, as authorized under section 319F-2 of the PHS Act, as amended by PAHPA and PAHPRA.[42] Products can be acquired for the SNS by BARDA if and when the product has sufficient safety and efficacy information to permit use under an EUA or may reasonably be concluded to qualify for FDA approval within ten years of the decision to procure. MCMs currently FDA-approved for the desired indication are available for direct purchase by the CDC for the SNS.

Table 4. Advanced Development (AD) and Procurement Priorities

Medical Countermeasure Category	*(1.3.10a)* AD Priorities Through FY18[43]	Current HHS Holdings[44]	*(1.3.10b)* Procurements Programmed Through FY14[45]	*(1.3.10c)* Additional Procurements Projected Through FY18[46]
Anthrax Antitoxin	X	X	SRF[47]	SRF[48]
Anthrax Vaccine	X	X	DSNS[49]	DSNS, SRF
Botulism Antitoxin	X	X	--	--
Broad Spectrum Antimicrobials	X	X[50]	DSNS	DSNS, SRF
Cyanide Antidote	X	--	--	--
Diagnostics – Bioassay	X	--	--	SRF
Diagnostics – Biodosimetry	X	--	--	SRF
Diagnostics – Biological Agents	X	--	--	SRF
Diagnostics – Pandemic Influenza	X	--	--	--
Diagnostics – Volatile Nerve Agents	X	--	--	--
Nerve Agent Antidote	X	X	DSNS	DSNS, SRF
Nuclear Agents – ARS – Gastrointestinal, Skin, and/or Lung Therapeutics	X	--	--	SRF
Nuclear Agents – ARS – Hematopoietic Therapeutics	X	X	SRF	--

[42] 42 U.S.C. 247d-6b – additional detail provided in Section 3

[43] These priorities include new products coming through the research and development pipelines, as well as enhancements to current products in the SNS.

[44] Includes inventory held in both the SNS and alternative stockpiles

[45] Contingent upon existing resources

[46] Assuming appropriations are available to maintain currently stockpiled and programmed levels

[47] Solicitations are ongoing to maintain existing preparedness levels and manufacturing capacity established under previous contracts.

[48] Purchase of MCMs using the SRF between FY15 and FY18 are planned pending annual appropriations.

[49] DSNS refers to the Division of Strategic National Stockpile, the CDC division responsible for managing the SNS, whose mission is to deliver critical medical assets to the site of a national emergency.

[50] This includes antimicrobials for the following threat agents: anthrax, plague, tularemia, typhus, and secondary infections resulting from radiological and nuclear agents or pandemic influenza.

Medical Countermeasure Category	*(1.3.10a)* AD Priorities Through FY18[43]	Current HHS Holdings[44]	*(1.3.10b)* Procurements Programmed Through FY14[45]	*(1.3.10c)* Additional Procurements Projected Through FY18[46]
Nuclear Agents – Antiemetics	--	X	DSNS	DSNS
Nuclear Agents – Thermal Burn Therapeutics	X	X	--	DSNS, SRF
Pandemic Influenza Antivirals	X	X	DSNS	DSNS
Pandemic and Pre-Pandemic Influenza Vaccines	X	X	BARDA	BARDA
Patient (Chemical) Decontamination	X	--	--	--
Personal Protective Equipment (PPE)	-	X	-	-
Radiological Agents – Decorporation/ Blocking Agents	X	X	DSNS	SRF, DSNS
Respiratory Protective Devices	X	X	--	DSNS
Smallpox Antivirals	X	X	--	SRF
Smallpox Vaccine	X	X	DSNS, SRF	DSNS, SRF
Ventilators	X	X	--	DSNS
Viral Hemorrhagic Fever (Marburg and Ebola) Antivirals and Therapeutics	X	--	--	SRF
Viral Hemorrhagic Fever (Marburg and Ebola) Vaccine	X	--	--	SRF

Objective 1.4 Promote effective domestic and international partnerships with developers and manufacturers and support core services. **(Leads: ASPR, NIH; Partners: DoD, CDC, FDA, HHS OGA)**

Developers and manufacturers of MCMs for the public health emergency threats described in this SIP face technical, regulatory, manufacturing, testing, commercialization, and other business challenges that can exceed the resources of private entities. Financial and technical partnerships among government, developers, and manufacturers can help foster business sustainability and diversify business risk for private companies and non-profit organizations. USG scientists from within HHS and its interagency partners will continue to work with developers, beginning at the early stages of development, to anticipate and resolve problems that could create bottlenecks in the process.

The USG is focused on maintaining adequate domestic manufacturing capacity for key MCMs. *(1.4.1)* BARDA will continue to support public-private partnerships with manufacturers to build and/or retrofit MCM production facilities within the US to increase domestic vaccine and biological therapeutics manufacturing capacity.

To secure a willing and capable partnership with the commercial sector for these unique products, the USG helps to ensure that these innovators and manufacturers have access to core manufacturing and downstream services to promote the availability of critical MCMs needed to meet civilian goals. NIH, BARDA and DoD maintain a wide array of product

development and support services that provide infrastructure capabilities for MCM development.[51] The NIH core services[52] cover the spectrum of capabilities that are required for early stages of product development and include animal model development support, research facilities, manufacturing support, and advice on working with other federal agencies, such as BARDA, DoD, and FDA. *(1.4.2)* In particular, NIH, in conjunction with BARDA, CDC, and DoD partners, works closely with the FDA to develop animal models and consider submissions to the FDA's Animal Model Qualification Program. Efficacy evaluations of CBRN MCMs will be performed in adequate animal models in compliance with data quality and integrity procedures (e.g., Good Laboratory Practices (GLP)). Additionally, the DoD supports a facility that enables testing and evaluation of MCM against agents requiring BSL-4 containment. *(1.4.3)* Efforts are ongoing to standardize the reagents, protocols, and assays used within the facility to provide a GLP testing service for the government and industry partners.

BARDA is now positioned to provide a range of core services to assist MCM developers in various aspects of product testing, development, validation, and production. BARDA has established:

- The Nonclinical Studies Network (in 2010) to provide core services (e.g., product testing, animal model qualification for use under the "Animal Rule", assay development, and reagent qualification) to product developers to ensure that scientific and regulatory requirements for approval and utilization of MCMs can be met; more than 30 MCM testing projects in animal models have been initiated since its inception;
- The Centers for Innovation in Advanced Development and Manufacturing (CIADMs) (in 2012) (additional information provided in Section 5); additional MCM development technologies and capabilities may be added in coming years;
- A domestic Fill-Finish Manufacturing Network (in 2013) to supplement manufacturing of pandemic influenza vaccines and other sterile injectable products needed in an emergency or during shortages; and
- A Clinical Studies Network (in 2014) to allow BARDA to conduct clinical trials with investigational or approved MCMs. This network consists of several Clinical Research Organizations (CROs) that are capable of conducting Phase 1-4 clinical trials, and of expediting clinical trials in the event of a public health emergency.

Notably, all four of BRADA's core service capabilities have been engaged to support medical countermeasures development during the response to the Ebola epidemic ongoing at the time of this writing.

(1.4.4) PHEMCE partners will also enter into strategic bilateral and multilateral engagements with international partners to identify joint opportunities for product development, including

[51] The PHEMCE will also work with other federal partners with resources in this area, including the Advanced Manufacturing Partnership National Program Office recently established by the National Institute of Standards and Technology (NIST). More information is available at http://www.manufacturing.gov/welcome.html.

[52] For more information, see http://www.niaid.nih.gov/labsandresources/resources/Pages/default.aspx.

efforts to support the establishment of sustainable international pandemic influenza vaccine production capacity. *(1.4.5)* To that end, BARDA will maintain its financial and technical support of the World Health Organization (WHO) Global Action Plan, working in concert with the Developing Countries Vaccine Manufacturers Network and other partners to expand sustainable influenza vaccine manufacturing capacity in developing countries.

HHS is also a member of the Chemical, Biological, and Radiological (CBR) Memorandum of Understanding (MOU), of which DoD is the primary USG signatory. The CBR MOU is an agreement among the defense and public health agencies of Australia, Canada, the United Kingdom, and the US. The aim of the MOU is to achieve greater cooperation in research, development, production and procurement in the field of CBRN Defense. Specifically, the Quadrilateral Medical Countermeasures Consortium (Quad-MCMC) under the MOU supports the effective fielding of MCM systems and components against CBRN threat agents to support military and civilian health protection. *(1.4.6)* ASPR will integrate the defense and health establishments of the four member nations of the CBR MOU into the Portfolio Tracking and Coordination Initiative (PTCI), including a harmonization of metrics across all groups, to enable portfolio data interoperability and to provide appropriate access to data and information. *(1.4.7)* In addition, ASPR will conduct an integrated portfolio data call from the defense and health establishments of the four member nations of the CBR MOU for inclusion into the PTCI.

GOAL 2. Establish and communicate clear regulatory pathways to facilitate medical countermeasure development and use.

Reducing regulatory uncertainties is critical for fostering both MCM development and availability. Regulatory oversight of medical product development for high-consequence but low-frequency events includes both the stewardship that the USG exercises to assure products are safe and effective, as well as the regulatory oversight of MCM utilization. The PHEMCE will continue support for regulatory science to develop new tools, standards, and approaches to accelerate the development, approval, and effective utilization of a wide range of MCMs for both emergency response and daily health needs, while maintaining the high standards for safety and efficacy that the American people expect.

Objective 2.1 Identify scientific and regulatory issues that challenge MCM development or use during public health emergencies and coordinate activities among PHEMCE partners to address those challenges. **(Lead: FDA; Partners: PHEMCE agencies)**

The regulatory assessment of MCMs by FDA for approval is data-driven.[53] However, there are often gaps in scientific knowledge that may impede or prevent a thorough assessment. These

[53] In situations where potentially useful MCMs are available but not yet FDA-approved for the particular use contemplated, FDA has a variety of regulatory mechanisms that can allow for the use of these products, including as part of a clinical trial or as part of an expanded access program or under an emergency use authorization. For additional information on expanded access to investigational drugs, see

gaps in knowledge arise from multiple sources, including intrinsic uncertainties about the effects of threat agents in potential public health emergencies, as well as from insufficient product development tools, such as animal models, for generating the necessary data to support regulatory decision-making. Discrepancies in available scientific information and tools result in regulatory uncertainties that many developers perceive as contributing to a higher-than-typical risk environment for engaging in MCM development.

(2.1.1) The FDA, through its Medical Countermeasures Initiative (MCMi),[54] engages with PHEMCE partners in identifying and resolving the regulatory and scientific challenges that impede MCM development and use, based on near-, mid-, and long-term PHEMCE priorities and requirements. The MCMi addresses key challenges in three areas: (1) enhancing FDA's product review and approval processes for the highest-priority MCMs and related technologies; (2) advancing regulatory science to create the tools necessary to support MCM development and regulatory review; and (3) modernizing the legal, regulatory, and policy framework to facilitate MCM development and availability.[55]

(2.1.2) To enhance the MCM review and approval processes, FDA has established multidisciplinary Public Health and Security Action Teams (Action Teams) to identify and help resolve regulatory and scientific challenges for high-priority MCMs and related technologies.[56] Since 2011, FDA has established five Action Teams. The work of the Surveillance Action Team, co-led by CDC, will now be handed over to a new Integrated Program Team, as discussed under Objective 3.4. The other Action Teams include:

- *(2.1.2a) Multiplex* In Vitro *Diagnostic Action Team:* This Action Team is working to facilitate the development of multiplex *in vitro* diagnostic tests. In 2011, FDA established a working relationship with the DoD's Defense Threat Reduction Agency (DTRA) and the National Center for Biotechnology Information (NCBI) to establish a publicly available, well-curated reference database that will be critical to developers seeking to validate their candidate multiplex *in vitro* diagnostic tests. Through this collaboration, draft quality standards for microbial sequence information have been identified and a publicly available reference database has been established.[57] Regulatory-grade sequences are now being deposited in this database. FDA is continuing to refine the quality standards

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http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccesstoInvestigationalDrugs/default.htm. For additional information on emergency use authorization, see http://www.fda.gov/emergencypreparedness/counterterrorism/ucm182568.htm .

[54] FDA launched the MCMi in August 2010 in response to the *2010 PHEMCE Review* and to build on the substantive MCM work ongoing at FDA. The MCMi mission is to promote the development of MCMs by enhancing FDA's regulatory processes and fostering the establishment of clear regulatory pathways for MCMs, and to facilitate timely access to available MCMs by establishing effective regulatory policies and mechanisms. For more information, see http://www.fda.gov/EmergencyPreparedness/MedicalCountermeasures/default.htm.

[55] FDA accomplishments under the MCMi are detailed in the MCMi annual status reports available at http://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/aboutmcmi/ucm270744.htm

[56] More information on FDA's Action Teams can be found at http://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/protectingnationalhealthandsecurity/ucm263066.htm

[57] FDA MicroDB: Microbial Confirmatory Reference Database can be found at http://www.ncbi.nlm.nih.gov/bioproject/231221

for microbial sequence information as well as to support the sequencing of high-priority pathogens for inclusion in the reference database to facilitate the development and regulatory review of multiplex microbial sequencing-based diagnostic devices for regulatory and clinical use.

- *(2.1.2b)* ***ARS/Biodosimetry Action Team:*** This Action Team is working to facilitate the development and regulatory review of MCMs for ARS indications. *(2.1.2b1)* This Action Team will continue to clarify the regulatory pathway for candidate ARS products in the BARDA pipeline. *(2.1.2b2)* In addition, this Action Team will work to facilitate the development and regulatory review of biodosimetry devices and will continue to provide regulatory support on establishing the performance of radiation biodosimetry devices.
- *(2.1.2c)* ***Warfighter-Trauma Action Team***: This Action Team is working to facilitate the development and evaluation of MCMs and related technologies to support the warfighter and trauma victims. This Action Team is collaborating with DoD to identify programs, products, and technologies of high-priority for the DoD and is providing assistance on selected regulatory and policy issues. Focus areas include traumatic brain injury, hemorrhage, nerve agents, and research that involves minimal risk to human subjects.
- *(2.1.2d)* ***Pediatrics and Maternal Action Team:*** This Action Team is working to ensure that the MCM needs of at-risk individuals, specifically pediatric and maternal populations, can be met during public health emergencies. For example, this Action Team is assessing MCMs in the SNS to identify outstanding issues that may prevent or impede their availability and usability for the pediatric population during emergencies. The Action Team will work with the PHEMCE's PedsOB IPT to develop action steps to address the issues identified in the analysis to help ensure that there is sufficient access to and information about MCMs necessary to treat and/ or prevent illness in the pediatric population during public health emergencies.

FDA will sustain these Action Teams as necessary through FY18 and will establish new Action Teams as needed based on evolving PHEMCE priorities.

(2.1.3) FDA will also continue to build the science base necessary to support MCM development and regulatory assessment through its MCMi Regulatory Science Program.[58] The goal of this program is to develop the tools, standards, and approaches to assess MCM safety, efficacy, quality, and performance and to help translate cutting-edge science and technology into innovative, safe, and effective MCMs, including for at-risk populations. The MCMi Regulatory Science Program includes both an internal FDA component and an external, collaborative component that focuses on partnerships with USG agencies, academia, NGOs, and industry[59].

[58] More information on FDA's MCM Regulatory Science Program is available at http://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/mcmregulatoryscience/ucm263071.htm

[59] Extramural MCM regulatory science is primarily funded through a BAA, which accepted responses until May 22, 2014, available at https://www.fbo.gov/?s=opportunity&mode=form&id=862c0ec16447bad7c7196f5d451ec601&tab=core&_cview=0

To ensure that the MCMi Regulatory Science Program is appropriately targeted and coordinated with USG MCM priorities, FDA established a Steering Committee for Advancing MCMi Regulatory Science—which includes representatives from the NIH, CDC, BARDA, and DoD—that evaluates MCMi Regulatory Science Program research proposals for scientific and technical merit and feasibility as well as for alignment with PHEMCE priorities. Priority research areas being supported under the MCMi Regulatory Science Program include: developing animal models and tools to evaluate safety and efficacy; identifying and qualifying biomarkers for safety and efficacy; using protein engineering to stabilize vaccine proteins; developing methods to assess MCM product quality and related product release assays; validating next-generation *in vitro* diagnostics platforms; assessing the performance of emergency medical equipment and enhancing emergency preparedness and response capabilities, including risk communication; and tracking and evaluating the safety and clinical benefit of MCMs used during public health emergencies. FDA has established a broad and robust intra- and extramural research portfolio under the MCMi Regulatory Science Program to meet its goals in these priority research areas.

(2.1.4) Other PHEMCE partners also fund regulatory science projects and work closely to identify and fill priority data gaps related to stockpiled MCMs and other needs, fostering rapid response and maximizing preparedness. *(2.1.5)* PHEMCE partners will work with the FDA's Drug Development Tool (DDT) Qualification Program[60] to develop tools – such as animal models for use under the 'Animal Rule' and biomarkers – facilitating MCM development and identifying and filling priority data gaps. The DDT Qualification Program enables the product-neutral evaluation of animal models for use under the 'Animal Rule' and provides the potential for product-neutral determination of whether a particular model is appropriate for the demonstration of efficacy to support approval for use under the 'Animal Rule'.

(2.1.6) FDA has also established a policy team that works closely with the Action Teams to ensure that FDA laws, regulations, and policies adequately support MCM development, distribution, administration, and use. When changes are needed to better protect public health, FDA works with appropriate partners to develop and propose new approaches.[61] PAHPRA included a number of important provisions amending the FD&C Act to clarify FDA's EUA authority and to allow for certain preparedness activities and rapid deployment of certain FDA-approved MCMs, without having to issue an EUA. *(2.1.7)* FDA will, in the near-term, update its 2007 *Guidance on the Emergency Use Authorization of Medical Products*, which details FDA's recommendations and procedures for issuance of EUAs, to be consistent with the amendments to its EUA authorities made by PAHPRA.[62]

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[60] A qualified DDT can be included in an IND or a New Drug Application (NDA)/Biologics License Application (BLA) submission without the need for FDA to reconsider and reconfirm the suitability of the DDT as long as there are (1) no serious study flaws; (2) no attempts to apply the DDT outside the qualified context of use; and (3) no new and conflicting scientific facts not known at the time the qualification was determined. For more information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

[61] http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm263073.htm

[62] http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm359581.html

PAHPRA also amended the FD&C Act to codify many of the activities already ongoing at FDA under the MCMi to foster the development of MCMs, including provisions related to the provision of technical assistance on animal model development activities, maintaining action teams, and training for FDA reviewers. It also included provisions for a formal Regulatory Management Plan (RMP) process for regulatory engagements for certain eligible, prioritized MCMs. *(2.1.8)* FDA continues to work to establish a formal process for obtaining RMPs, as required under the FD&C Act. *(2.1.9)* In addition, FDA will continue to provide policy assistance for relevant partners as necessary on issues including first responders' ready access to and use of MCMs; MCM development challenges that are unique to the warfighter; expiration dating as it pertains uniquely to stockpiled MCMs; data collection during a public health emergency; guidance development; and MCM import and export during emergency responses.

Objective 2.2 Assist MCM developers in working interactively with FDA during product development and regulatory review. **(Lead: FDA; Partners: NIH, ASPR, BARDA, DoD)**

Most of the developers engaged in MCM development are small biotechnology companies that bring a nimble and innovative approach to the development of new products. However, these companies are often challenged by their limited experience in taking a product through advanced development to FDA approval. For example, these companies often lack experience with animal testing, assay development, product manufacturing, clinical trials, and navigating the regulatory process. For companies without existing infrastructure in these areas, accessing specialized services is difficult and expensive.

The PHEMCE is committed to assisting MCM developers in navigating the USG MCM regulatory assessment and review processes. *(2.2.1)* FDA will assist in the clarification of regulatory pathways and reduction of regulatory challenges using the following methods:

- Meetings with product sponsors or applicants seeking technical assistance related to the development, regulatory assessment of MCMs, and manufacturing;
- Enhanced inspection, including pre-approval and compliance activities, to support early identification of problems that might impede MCM development;
- Issuance of guidance documents and rules and regulations based on the laws that FDA enforces to help foster MCM development and availability;
- Stakeholder engagements, including meetings, conferences, and workshops, to educate the public on both FDA regulatory processes and its current thinking on regulatory issues, and to garner input from interested parties on regulatory issues; and
- Public Advisory Committee meetings to obtain independent expert advice on scientific, technical, and policy matters on specific topics.

(2.2.2) BARDA regulatory and quality affairs subject matter experts will assist private-sector partners in the development of regulatory strategies, including the design and execution of pivotal animal studies and clinical studies, preparation of regulatory documentation, and strategic communication on regulatory issues.

GOAL 3. Develop logistics and operational plans for optimized use of medical countermeasures at all levels of response.

The Nation must be prepared to use MCMs appropriately in an emergency. This requires robust relationships among federal planners and the regional and SLTT stakeholders who would ultimately be at the operational edge of a public health emergency response. Activities required to support this goal include development of optimal approaches for MCM inventory management and of plans, policies, procedures, and guidance to ensure timely, safe, and effective MCM distribution and utilization. Preparedness will also require ensuring that fiscal and administrative authorities and practices that govern the funding, procurement, contracting, hiring, and legal capabilities necessary to mitigate, respond to, and recover from public health threats and emergencies can be accelerated, modified, streamlined, and accountably managed at all levels of government. Achieving these objectives will require communications, training, and education with response stakeholders and ultimately with the American people. In addition, strategies must be developed to evaluate and monitor the use, safety, and performance of MCMs during a response to allow adjustment of operations as needed.

Objective 3.1 Promote innovative approaches to inventory management to enable a sustainable preparedness infrastructure. **(Lead: CDC; Partners: ASPR, DHS)**

The PHEMCE will focus on issues of long-term sustainability and enhanced flexibility to ensure cost-effectiveness of federal MCM stockpiles while maintaining readiness. This will be accomplished through optimizing the SNS formulary and ensuring cost-effective formulary management. CDC will also encourage continued collaboration regarding federal, state, local, regional, and private MCM stockpiles and put in place systems that facilitate sharing and promote optimal MCM use during public health emergencies. ASPR and CDC will ensure that the PHEMCE inventory management and sustainable preparedness infrastructure is aligned with the ASPR response logistics and DSNS distribution mechanisms and socialized with regional partners to achieve the best allocation of resources during a response and to provide a consistent national framework for the regional coordination of prevention, mitigation, preparedness, response, and recovery activities.

Optimization of the SNS Formulary

(3.1.1) The PHEMCE SNS Annual Review represents a continuous process for optimizing the contents of the SNS. The Review, required by both statute[63] and Presidential Directive[64], comprehensively examines the SNS formulary each year, including non-pharmaceutical MCMs and ancillary supplies; identifies and prioritizes formulary gaps; and recommends additions or modifications to the contents of the SNS, in alignment with the PHEMCE prioritization framework. For example, based on a recent reassessment of the Federal Medical Stations

[63] 42 U.S.C. 247d-6b(a)
[64] Homeland Security Presidential Directive-21

(FMSs) held in the SNS, CDC will maintain 32 of the large, 250-bed capacity FMSs, create 10 more nimble, 50-bed capacity FMSs, and develop stand-alone bariatric modules for deployment with FMS assets as needed. *(3.1.2)* Over the near-term, the PHEMCE will develop a risk-based analysis of investment needs by using perspectives from the intelligence community and DHS risk assessment processes. This project will inform the optimization of SNS contents by demonstrating how particular formulary options may decrease the risks arising from CBRN threats. *(3.1.3)* The PHEMCE is also actively exploring alternatives to central stockpiling as appropriate, such as "just-in-time" manufacturing and procurement, support for surge manufacturing capabilities, stockpiling of bulk product, and alternative stockpiling options, such as rotated inventory, home or business caching, and/or other vendor- or user-managed inventory approaches.

Cost-Effective Management of SNS Assets

CDC will effectively and efficiently maintain, replace, and manage assets in the SNS across their life cycles to ensure they can be accessed and provided when and where needed, within operational and logistical constraints. To accomplish these functions, the CDC will utilize a robust inventory management system, including state-of-the-art monitoring systems, Quality Control Unit evaluation of storage facilities, and comprehensive annual inventories and inventory tracking mechanisms. MCMs requiring rapid administration for clinically effective use may be held in forward-placed or prepackaged storage for ready access.[65] *(3.1.4)* CDC will also continue to participate in the FDA/DoD Shelf Life Extension Program (SLEP)[66] to extend the useful life of appropriate stockpiled products when it is cost-effective, to improve efficiency, and to maximize existing investments. *(3.1.5)* Finally, CDC will continue to examine ways to reduce the time required to deploy assets at the federal level, and better understand the costs at the federal and SLTT levels.

Objective 3.2 Develop and communicate MCM utilization policy, guidance, and response strategies, including FDA regulatory frameworks, that are responsive to end-user needs and that are integrated with regional, state, local, tribal, territorial, and private sector response plans, and when possible international partners, and that ensure timely, safe, and effective MCM distribution and utilization. **(Leads: ASPR, CDC; Partners: PHEMCE agencies)**

The success of the PHEMCE will be measured by the ability to quickly, safely, and effectively utilize MCMs and to effectively develop, communicate, and provide guidance and education on the role of MCMs in a public health emergency response. To accomplish this, the federal PHEMCE agencies must work closely with non-federal partners at all levels. In this *2014*

[65] Examples include the CHEMPACK program of more than 1,900 forward-placed caches of nerve agent antidotes held in local custody throughout the nation, and the SNS 12-Hour Push Packages, which are poised to support arrival anywhere in the nation within 12 hours of the federal decision to deploy SNS assets.

[66] The DoD/FDA Shelf Life Extension Program (SLEP) is a fee-for-service program used to defer drug replacement costs for large stockpiles of date-sensitive pharmaceuticals held in environmentally controlled locations by extending their shelf life beyond the manufacturer's original expiration date. The program is limited to DoD and selected federal agencies.

PHEMCE SIP, the important role of regional partners, in addition to those at the SLTT and private sector levels, is explicitly highlighted in this objective.

Linking Bench to Community **(Leads: ASPR, NIH)**

End-user needs are key drivers in MCM development. For example, NIH early research into vaccine adjuvants is aimed not only at increasing vaccine efficacy, but also at developing a faster onset of protection with fewer vaccine doses, resulting in decreased stockpiling costs and improved response logistics. Similarly, NIH research into temperature stabilization for critical MCMs may decrease or eliminate the need for cold chain storage, thereby decreasing stockpiling costs and allowing for a more rapid delivery and faster administration in the event of an emergency.

(3.2.1) In the advanced development of priority MCMs, BARDA will work with developers and end-users through external outreach to ensure that MCM development plans take into account the most up-to-date utilization policies, response strategies, evolving regulatory guidance for use, and other relevant factors. Strengthening this feedback loop between the end-users and the developers of MCMs will result in products that can be most effectively used in public health emergencies.

Developing Additional Federal Operational and Response Plans **(Leads: ASPR, CDC; Partners: PHEMCE Agencies)**

(3.2.2) Over the next five years, the PHEMCE, through the leadership of the CDC and ASPR, and as supported by other USG partners and external experts,[67] will leverage the lessons learned at all levels from previous incident responses to develop and share MCM response strategies, clinical utilization guidelines, and MCM CONOPs with end-users as appropriate. *(3.2.3)* ASPR will collaborate with PHEMCE partners to ensure MCM strategies and clinical guidelines are appropriately captured in the federal all-hazards emergency response planning process as well as the ASPR all-hazards and regional emergency response planning processes. *(3.2.4)* ASPR will assess, streamline, and enhance deployment and sustainment protocols and tracking processes.

First responders are critical in supporting and assisting communities as they recover from the impacts of public health and medical incidents. *(3.2.5)* Planning for the protection of first responders is primarily done at the state and local levels, but PHEMCE agencies will continue to provide general recommendations, modeling projections, and other supporting information to guide such planning efforts. For example, recently a federal interagency working group that included subject matter experts from DHS and HHS issued its *Guidance for Protecting Responders' Health during the First Week Following a Wide-Area Aerosol Anthrax Attack*. This non-binding guidance provides recommendations for protecting first responders and addresses pre- and post-event vaccination, use of personal protective equipment (PPE), and personal decontamination processes. In addition, HHS and DHS recently collaborated on a letter to first

[67] Including clinical experts and state and local health officials

responder occupational health providers to promote the implementation of a program to provide MCMs to first responder personnel prior to a biological event. In this correspondence, federal officials outlined the benefits of such a program and suggested how it could be implemented with individual first responders contacting their personal health care providers to obtain prescriptions for recommended antimicrobials. The cost of the MCMs would be borne by the individual first responder, if not by the state or local responder organization.

The CDC Division of State and Local Readiness (DSLR) currently provides SLTT planning guidance and conducts annual reviews with state and local MCM stakeholders. The 2014 document, *Receiving, Distributing, and Dispensing Strategic National Stockpile Assets: A Guide for Preparedness*, provides detailed MCM planning guidance for SLTT preparedness programs. *(3.2.6)* In 2015, CDC DSLR will implement a new method of reviewing state and local MCM operational readiness through the use of the Operational Readiness Review (ORR), which replaces the legacy Technical Assistance Review (TAR) assessment tool. *(3.2.7)* Through ongoing collaborative efforts with PHEMCE partners and external stakeholders, the FDA will work to modernize the legal, regulatory, and policy frameworks to facilitate the development and availability of MCMs; enhance pre-event planning; and foster rapid MCM deployment and use in public health emergencies. *(3.2.8)* The VA's Office of Public Health will lead an effort to study and streamline closed PODs as a means to distribute MCMs during a public health crisis.

Also, over the course of this *Strategy and Implementation Plan*, the PHEMCE will develop the following deliverables to facilitate national public health emergency response for high-priority threats:

- *(3.2.9)* National response strategies for anthrax (FY15), botulism, glanders and melioidosis, and smallpox (FY16)
- *(3.2.10)* Clinical practice guidelines for MCMs to address chemical agents, smallpox, anthrax, and botulism in the near-term and ARS-associated neutropenia[68] in the mid-term
- *(3.2.11)* Assessment of state and local capacity to utilize cytokines for ARS-associated neutropenia following use of an improvised nuclear device (FY15)
- *(3.2.12)* CONOPs for MCMs to address neutropenia (mid-term), glanders and melioidosis (mid-term), and botulism (long-term)
- *(3.2.13)* Planning guidance for patient decontamination in a mass exposure chemical incident (FY15).

Adding to Key Federal Policy and Response Capabilities **(Lead: ASPR)**

ASPR and CDC are leading several initiatives to ensure preparedness in key functional areas critical for an effective national response:

- *(3.2.14) Emergency Policy Coordination:* ASPR has established the Disaster Leadership Group (DLG) as the mechanism to ensure a coordinated, department-wide, strategic

[68] As may occur following, for example, use of an improvised nuclear device

approach to HHS emergency response and recovery efforts among the HHS executive leadership. As the Secretary's principal advisor on all matters related to public health and medical emergency preparedness and response, the ASPR will chair and convene the DLG in a public health emergency to discuss, coordinate, and promote approaches to address the policy, budget, legislative, and external communication strategies and needs associated with the response. The DLG will identify and resolve policy issues and potential barriers, including those related to MCM production, distribution, dispensing/administration, and use, which may directly impact effective response operations during specific emergency events.

- *(3.2.15)* ***Fiscal and Administrative Preparedness:*** Recent public health emergencies, such as 2009 H1N1 pandemic influenza and the 2010 Gulf of Mexico oil spill, highlighted the need for a much more responsive fiscal and administrative framework to most effectively utilize resources during an emergency. *(3.2.15a)* In support of the MCM-related aspects of this larger effort, ASPR will ensure that the fiscal and administrative practices to rapidly produce and effectively distribute MCMs are incorporated into pre-event planning activities. *(3.2.15b)* In the near-term, the PHEMCE, through collaboration with finance, budget, and contract management partners, will identify strategies to accelerate the MCM-related administrative decision-making processes. This will be accomplished by informing the budget estimation process for MCM needs; ensuring seamless communication regarding accessing financial resources; engaging in post-event accountability evaluations related to MCM budget and financial processes; and contributing to the development of mechanisms to better understand and articulate funding utilization.
- *(3.2.16)* ***Science Preparedness:*** ASPR will lead an initiative to coordinate science preparedness and response efforts across the diverse span of interagency emergency preparedness efforts, including those related to MCMs. Research before, during, and after an emergency is critical to our future capacity to better prevent injury, illness, disability, and death, while supporting recovery. This effort can also ensure that the appropriate subject matter experts from government, academic institutions, non-governmental organizations, and the private sector can be used to assist in response to a public health emergency. Over the next five years, ASPR will focus on areas such as clinical protocols and datasets, specimens, workforce, policies, rapid funding mechanisms for research, and surveys.
- *(3.2.17)* ***MCM Resource Allocation***: CDC has already developed, in collaboration with other PHEMCE partners, guidance on the allocation of anthrax vaccines in the event current stockpiles were inadequate to meet the need in a large-scale event. *(3.2.17a)* ASPR, with the support of CDC, will work with partners to identify other current efforts by states, academia, health care experts, biomedical ethicists, medico-legal experts, behavioral health experts, and others to address MCM resource allocation in public health emergencies in which these critical assets may be in short supply. *(3.2.17b)* ASPR will then develop frameworks and processes to inform such MCM resource allocations as needed.

Support for State, Local, Tribal, and Territorial Response Efforts **(Leads: CDC, ASPR; Partners: FDA, DHS)**

Some SLTT public health and health care systems face reduced funding and greater demands in general and for public health preparedness activities. The PHEMCE will seek to support SLTT authorities by ensuring that federal MCM emergency response plans are flexible enough to fit into SLTT and private response partners' activities.

ASPR will continue to develop, refine, and sustain health care coalitions consisting of a collaborative network of hospitals, health care organizations, public health, emergency medical service, and other public and private sector health care partners within a defined region to ensure the delivery of medical care, including MCMs, during emergencies that exceed the limits of conventional medical capabilities within a community. *(3.2.18)* The CDC, in collaboration with ASPR, will continue to provide guidance to SLTT partners on receiving and effectively utilizing (i.e., deploying, distributing, and dispensing) MCMs provided by the SNS. *(3.2.19)* CDC will also work with PHEMCE partners to promote exercises of these capabilities at the community, SLTT, and federal levels. *(3.2.20)* ASPR and DHS will encourage regional emergency planning alliance participation in these exercises, while ASPR and CDC will work to include health care coalitions as well. *(3.2.21)* ASPR, CDC, and DHS will work to continue to conduct regular call-down/notification and assembly drills to test staff and volunteer mobilization.

(3.2.22) ASPR will collaborate broadly with PHEMCE and non-federal partners, to include regional healthcare coalitions and state authorities, to develop resilient systems of care that will be able to optimally respond to and recover from public health emergencies. Such efforts will include direct funding support, as well as initiatives aimed at building MCM delivery and utilization capabilities at the regional level, including the HPP[69]. *(3.2.23)* ASPR and DHS/FEMA will continue to develop regional MCM annexes to complement and supplement the MCM dispensing plans developed by the 10 largest Urban Areas Security Initiative (UASI) areas under the CRI program. These regional MCM annexes will describe the Federal support to be provided to supplement CRI plans for MCM dispensing following an aerosolized anthrax attack. These efforts implement a key provision of the Presidential Executive Order #13527 (Dec 2009), "Establishing a Federal Capability for the Timely Provision of Medical Countermeasures Following a Biological Attack" and are anticipated for completion in FY15. *(3.2.24)* ASPR will also enhance coordination on preparedness among regional HHS partners by developing a consistent national framework for the regional coordination of prevention, mitigation, preparedness, response, and recovery activities, including those required for effective MCM utilization.

International Efforts **(Lead: ASPR; Partners: DoD, FDA, CDC, HHS OGA, USDA)**

While the PHEMCE focus is predominantly on meeting US domestic MCM needs, the need for capacity to distribute and utilize MCMs is also a challenge to the global community. US

[69] See http://www.phe.gov/preparedness/planning/hpp/Pages/default.aspx

utilization policies, clinical guidance, and response strategies should be integrated with those of our international partners where appropriate. Building on the lessons learned during the 2009 H1N1 influenza pandemic and the nuclear power plant incident in Fukushima in 2011, the PHEMCE will identify and address barriers to building a sustainable global infrastructure for MCMs. *(3.2.25)* Relevant HHS agencies and PHEMCE partners will continue to engage international partners to identify joint opportunities for product development. *(3.2.26)* For example, DoD is currently working with the United Kingdom's Ministry of Defence to develop animal models for the testing and evaluation of MCMs against bacterial and filovirus threats. *(3.2.27)* PHEMCE partners will collaborate with WHO and the GHSI partners[70] to overcome barriers and develop protocols to facilitate the international deployment and distribution of MCMs during public health emergencies. *(3.2.28)* Additionally, ASPR will lead US efforts under Objective 9 of the recently launched Global Health Security Agenda to engage with international partners to "improve global access to medical and non-medical countermeasures during health emergencies."[71] *(3.2.29)* Regionally, ASPR will work with Canada and Mexico over the next three years to overcome barriers to providing mutual assistance and to harmonize utilization policies for MCMs during international public health emergencies under the framework of the US-Canada Beyond the Border Initiative,[72] and as called for in the North American Plan for Animal and Pandemic Influenza (NAPAPI).[73]

Objective 3.3 Develop and provide MCM communications, training, and education information to inform all stakeholders. **(Leads: CDC, ASPR; Partners: FDA, USDA)**

The PHEMCE will continue to focus attention on ensuring that accurate evidence and science-based information and training are provided on the use of MCMs during a public health emergency. The PHEMCE will ensure effective communications with both responders and the public through the timely release of credible, understandable, and actionable information both prior to and during public health emergencies. The PHEMCE will work with partners to deliver messages to audiences and make national health security messages available in multiple formats and languages and covering such topics as preparedness, response, and recovery. *(3.3.1)* The CDC, in coordination with FDA and ASPR, will test the effectiveness of MCM-related public health communication materials through qualitative and quantitative research methodologies, such as focus groups and surveys. *(3.3.2)* CDC will also work with partners to ensure that SLTT public health officials and designated hospital authorities have sufficient knowledge of the contents and dispensing policies associated with the materiel from the SNS. *(3.3.3)* CDC will continue to implement and maintain training programs in risk communication to train government leaders and partners in risk communications through its Crisis and Emergency Risk Communication (CERC) program. CERC offers in-person training, online training, and resource materials for risk communication training. CDC's FY15 activities include updating the

[70] See http://www.ghsi.ca/english/index.asp
[71] See http://www.globalhealth.gov/global-health-topics/global-health-security/ghsagenda.html
[72] See http://www.dhs.gov/beyond-border-shared-vision-perimeter-security-and-economic-competitiveness
[73] See http://www.phe.gov/Preparedness/international/Documents/napapi.pdf

CERC manual and materials as needed, coordinating sponsored training for government leaders and partners, and maintaining a trained cadre of people able to give CERC trainings.

(3.3.4) ASPR will provide training for the response and recovery workforce on the use of MCMs against all hazards, including making available just-in-time advanced training for MCMs targeting particular threat agents. *(3.3.5)* In addition, ASPR will develop and implement a plan to disseminate best practices for establishing and maintaining regional coordination for public health emergencies. Specifically, the PHEMCE will promote partnerships among emergency management, health care, behavioral health care, and human services stakeholders by providing technical assistance and education to SLTT and non-governmental partners in a sustainable, scheduled forum.

Objective 3.4 Develop and implement strategies to assess, evaluate, and monitor MCM safety, performance, and patient compliance during and after a public health emergency response. **(Leads: FDA, CDC, ASPR)**

Optimal use of MCMs in an emergency response situation requires rapid feedback on how well these interventions are working to protect individuals and their families. This information may be used to inform real-time refinement of clinical utilization policies during the response. The availability of this information can also allow public health officials and medical professionals to adjust their medical response strategies as needed. *(3.4.1)* CDC and FDA will continue to assist drug manufacturers in creating registries to capture information during events as part of specific post-marketing requirements for recently approved MCMs.

(3.4.2) The PHEMCE has established an interagency IPT charged with the development of systems for, and coordination of, real-time tracking and evaluation of MCM safety and clinical benefit during public health emergencies. *(3.4.3)* ASPR will incorporate information gained in this way into the lessons learned and corrective action process, thus allowing for feedback into Federal Emergency Management Agency (FEMA)-led interagency MCM federal and regional planning. *(3.4.4)* During public health emergency responses, CDC will use media monitoring services, as well as work with response partners, to monitor public reaction to the distribution of MCMs, including rumors and misperceptions. CDC may refine its messages or develop new content based on the findings from these services. *(3.4.5)* DHS's Science and Technology Directorate, in collaboration and coordination with CDC, will develop and enhance the CDC Laboratory Response Network (LRN) capability with Rapid Antimicrobial Susceptibility Assays for high-priority bacterial threat agents. This critical asset will support rapid response and expedite MCM distribution-, dispensation-, and administration-related decisions in a timely manner to save lives.

GOAL 4. Address medical countermeasure gaps for all sectors of the American civilian population.

At-risk individuals[74], who make up a significant proportion of the American civilian population at any given time, may have diverse and unique vulnerabilities and MCM needs. The PHEMCE remains fully committed to working toward the goal of protecting the entire US population, including at-risk individuals, from intentional threats, pandemic influenza, and other EIDs posing a threat to national health security. Significant progress has been made in this area since the release of the *2012 PHEMCE Strategy* and subsequent *Implementation Plan*, as summarized in Appendix 3. While the PHEMCE considers the needs of at-risk individuals throughout all of the activities described in Goals 1-3 above, the following objectives describe the specific activities directed at at-risk individuals' needs that the PHEMCE will pursue, with the ultimate goal of protecting the whole spectrum of the American population in the event of a public health emergency.

Objective 4.1 Develop medical consequence and public health response assessments and requirements for at-risk individuals. **(Lead: ASPR; Partners: PHEMCE agencies)**

(4.1.1) The PHEMCE requirement framework, as detailed in Objective 1.2 above, will assess at-risk individuals' needs at every stage of the process. This includes examining age, sex, gender, racial, and ethnic influences in health and disease to inform MCM formulation and dosage requirements when data is available and appropriate. Additionally, BARDA and CDC have collated the existing, albeit limited, clinical and scientific literature on agent susceptibility and MCM utility in these populations. At-risk populations, such as children, pregnant women, older adults, and those with underlying medical conditions, potentially have differences in susceptibility to CBRN agents and/or altered disease severity following exposure. In many cases, the first-line treatments for CBRN agents have not been tested or are not recommended for use in at-risk populations. *(4.1.2)* Important gaps exist in the scientific knowledge regarding the use of MCMs in these at-risk groups, and BARDA will support research efforts to close these gaps, in alignment with the prioritization criteria detailed previously, and as ethically feasible. This data collection will inform utilization of current MCMs and the desired characteristics of future products. *(4.1.3)* The PedsOB IPT and other PHEMCE partners will assist in the development of scenarios and validate assumptions for specific at-risk populations in public health and medical consequence assessments.

(4.1.4) The PHEMCE established the PedsOB IPT to provide subject matter expertise for assisting with the MCM requirements framework, for developing MCM strategies, and for

[74] At- risk individuals have needs in one or more of the following access or functional areas: communication, maintaining health, independence, services/support/self-determination, and transportation. At-risk individuals may include children, older adults, and pregnant women as well as people who have disabilities, live in institutionalized settings, are from diverse cultures, have limited English proficiency or are non-English speaking, are transportation disadvantaged, have chronic medical disorders, or have pharmacological dependency. http://www.phe.gov/preparedness/planning/abc/pages/default.aspx

promotion of the availability of pediatric[75] and obstetric MCMs in public health emergencies. Notably, dosage forms suitable for pediatric populations may also benefit other at-risk groups. For example, in parallel with its evaluation of the minimum practical age for using crushed tablets instead of more expensive antimicrobial suspensions in pediatric populations, the PedsOB IPT also considered use of these suspension dosage forms for geriatric populations and people who have difficulty swallowing.

Objective 4.2 Support MCM advanced development and procurement for at-risk individuals. **(Leads: BARDA, NIH, FDA; Partner: CDC)**

The needs of at-risk individuals pose challenges to the development and acquisition of MCMs specifically formulated for these groups. The PHEMCE will continue to support evaluation of those MCMs currently held in the SNS for use among at-risk individuals, as well as development of additional dosage forms where needed[76], including maximizing use of MCM dosage forms that are suitable for use in multiple populations.

HHS currently stockpiles MCMs that could potentially be used by at-risk individuals; such usage is restricted in some cases under regulatory mechanisms including Investigational New Drug (IND) protocols or EUAs. Box 3 lists the currently stockpiled MCMs for potential use in pediatric populations, along with the associated threats addressed by those MCMs.

[75] Pediatric populations refer to individuals under the age of 21 years.
[76] The SNS authority specifically requires that the emergency health security of children and other at-risk individuals be taken into account in determining which MCMs and supplies are needed for the SNS (Section 319F-2 of the Public Health Service Act (42 USC 247d-6b)).

Box 4:
Stockpiled Medical Countermeasures
Potentially Available for Use in Pediatric Populations

- Oral Solid and Liquid Antimicrobials – *Anthrax, Plague, Tularemia, Typhus*
- IV Antimicrobials – *Anthrax, Pandemic Influenza^, Plague, Radiological and Nuclear Threats^, Tularemia, Typhus*
- Vaccines – *Anthrax, Pandemic Influenza, Smallpox*
- Antitoxins or Immunoglobulins – *Anthrax, Botulism, Smallpox*±
- Oral and IV Chelators – *Radiological Threats*
- Hematopoietic Agents – *Radiological and Nuclear Threats*
- Thermal Burn Supplies – *Radiological and Nuclear Threats*
- Nerve Agent Antidotes – *Chemical Threats*
- Oral Solid Antivirals – *Pandemic Influenza, Smallpox*±
- Inhaled and Oral Liquid Antivirals – *Pandemic Influenza*
- IV Antivirals – *Pandemic Influenza, Radiological and Nuclear Threats^, Smallpox*±
- Ventilators – *All Hazards*

^for secondary infections

± includes potential treatments (including investigational) for vaccine complications

The PHEMCE will support MCM development and FDA approval to address the needs of at-risk individuals, including expansion of label indications and/or development of new dosage forms as needed. Specifically, the PHEMCE will implement the following initiatives:

- *(4.2.1)* NIH, in collaboration with BARDA and DoD, will explore the development of rodent and porcine juvenile models of ARS. (near-term)
- *(4.2.2)* NIH established the Pediatric Trials Network in 2010 to create an infrastructure to study critical drugs and diagnostic devices in children with the goal of improving their labeling for pediatric use. The Network plans to conduct 16 trials over the next five years that may enhance pediatric labeling. (mid-term)
- *(4.2.3)* BARDA will support studies to develop pediatric and geriatric indications and dosage forms as needed in all MCM late-stage development and procurement projects. BARDA contracts for product development also include considerations of safety in pregnant women and immunocompromised individuals. (ongoing)
- *(4.2.4)* In the area of off-patent, approved drugs being pursued for additional CBRN indications, NIH and FDA have specifically identified products for which pediatric safety databases exist, and will focus efforts to assess existing data necessary to demonstrate efficacy for pediatric populations using those data without the need for additional studies in these populations. (near-term)
- *(4.2.5)* At-risk individuals' needs are explicitly taken into account through the SNS Annual Review. Appropriate products or dosage forms for these groups, and/or suitable

operational alternatives, will be advanced when available and as resources allow. (ongoing)

- *(4.2.6)* BARDA, working with CDC, will support efforts to achieve FDA licensure (in healthy populations) for a smallpox vaccine that is ultimately intended for use in immunocompromised individuals in an emergency. (near-term)

Objective 4.3 Develop and implement strategies, policies, and guidance to support the appropriate use of MCMs in all civilian populations during an emergency. **(Leads: ASPR, CDC; Partner: FDA)**

At-risk individuals must have coordinated and equitable access to MCMs during public health emergencies. To support the use of stockpiled MCMs in at-risk individuals, in the near- and mid-terms, the PHEMCE will pursue policies and programs related to regulatory challenges associated with products intended for at-risk individuals, including filling priority data gaps associated with developing pre-EUA packages to support the use of stockpiled MCMs in these populations.

(4.3.1) The PedsOB IPT will develop dosing and use recommendations for using stockpiled MCMs in pediatric populations (e.g., amoxicillin and other antimicrobial agents and Prussian blue, an oral chelator, in children less than two years of age) that could be used to inform EUA guidance provided to clinicians during an emergency, with the caveat that these instructions should only be used in an emergency.

(4.3.2) In support of new requirements added to the PHS Act under PAHPRA and the *2013 HHS Language Access Plan*[77], ASPR and CDC will work to increase the coordination around messaging for at-risk individuals, which will support meaningful access to programs and services, including emergency communications, to people with limited English proficiency. *(4.3.3)* CDC guidance provided to federal and SLTT partners on MCM distribution and dispensing/administration, as described under Objective 3.2, will likewise include consideration of at-risk individuals' needs. *(4.3.4)* The PHEMCE will use its established relationships with the American Academy of Pediatrics and other clinical organizations serving the needs of at-risk individuals to help inform MCM strategies and policies.

ASPR and the Administration for Children and Families (ACF) established the Children's HHS Interagency Leadership on Disasters (CHILD) Working Group in 2010 to identify and comprehensively integrate departmental activities related to the needs of children across all HHS inter- and intra-governmental disaster planning initiatives and operations. The CHILD Working Group, which includes representatives from ASPR, CDC, FDA, and NIH, developed six recommendations specific to pediatric MCM needs in its 2011 report, several of which have already been implemented.[78,79] The CHILD Working Group has now prioritized three new areas

[77] Available at http://www.hhs.gov/open/execorders/2013-hhs-language-access-plan.pdf
[78] Public summary available at: http://www.phe.gov/Preparedness/planning/abc/Documents/2011-children-disasters.pdf

of focus for future efforts and recommendations: (1) neonates and pregnant women; (2) children at heightened risk; and (3) interdepartmental and non-governmental collaboration. *(4.3.5)* PHEMCE agencies will address new recommendations in these areas as they are promulgated.

ASPR will also focus resources toward anticipating and addressing the needs of at-risk individuals during a disaster as follows:

- *(4.3.6)* During an emergency, ASPR/OEM will assist and supplement state and local MCM distribution and dispensing efforts as needed, including those aimed at pediatric and other at-risk individuals.
- *(4.3.7)* ASPR's Division of Health System Policy (DHSP) will continue to help bridge federal resources to existing private sector distribution centers (e.g., EMS, hospitals, pharmacies) including at public and critical access hospitals serving at-risk individuals.
- *(4.3.8)* ASPR, through its engagement and support of the Federal Education and Training Interagency Group and the National Center for Disaster Medicine and Public Health, will support the development of training curriculum guidance for managing at-risk population needs in times of disasters. (ongoing)
- *(4.3.9)* The PedsOB IPT will continue to work with ASPR on incorporating at-risk individual needs into the new HHS All-Hazards Plan and threat-specific annexes that outline key options and actions to aid the HHS Secretary and the ASPR in making necessary decisions in an emergency. (near-term)

SECTION 2: INTERAGENCY PARTNER ROLES AND COLLABORATIONS IN SUPPORTING STRATEGIC GOALS AND OBJECTIVES

Accomplishing the PHEMCE goals and objectives will require the coordination of MCM-related activities across multiple federal departments. Key PHEMCE interagency partners to HHS in this endeavor include DHS, DoD, VA, and USDA. The critical roles these agencies play, and will continue to exercise, in support of these goals and objectives are detailed below.

Department of Homeland Security

DHS leads the federal response to incidents involving interagency and multi-jurisdictional response. DHS has the responsibility for developing and conducting threat and risk assessment processes that integrate the findings of the intelligence and law enforcement communities with input from the scientific, medical, and public health communities to inform investment priorities

[79] For example, an integrated program team to advise the PHEMCE on pediatric/obstetric MCM priorities has been stood up and is continuing its work. To increase regulatory clarity for pediatric MCMs, in 2012, FDA held a Public Workshop on Ethical and Regulatory Challenges in the Development of Pediatric Medical Countermeasures. In addition, the FDA Pediatric and Maternal Public Health Security Action Team worked with CDC to identify data gaps that could inhibit the effective use of stockpiled MCMs in children, and are now working with HHS partners to address identified data needs. Finally, HHS partners have worked together to make investments in MCMs that include coverage for pediatric populations. Such expanded or recent (2012-2014) approvals include products to treat plague, inhalation anthrax, influenza, and botulism.

for current and anticipated threats. DHS identifies high-risk threats that hold potential for catastrophic consequences to civilian populations and warrant development of targeted countermeasures. *(I.1)* Pursuant to the Project BioShield Act of 2004, DHS will continue to use this capability to make determinations about which CBRN agents pose a material threat sufficient to affect US national security. *(I.2)* DHS will further advance this capability to provide strategic, integrated all-CBRN risk assessments to facilitate prioritization of MCM development across the CBRN threat spectrum. The Secretaries of DHS and HHS must jointly recommend the use of the SRF created under Project BioShield to the Director of the Office of Management and Budget, acting on behalf of the President, prior to its use.

DHS and HHS Coordination

Section 304(a) of the Homeland Security Act requires HHS to work in collaboration with DHS to develop priorities, goals, objectives, and policies for the civilian human health-related MCM research and development activities addressing CBRN and other threats[80]. Executive Order 13527, *Medical Countermeasures Following a Biological Attack*, also requires DHS and HHS, in coordination with the Secretary of Defense, to develop a CONOPs and establish requirements for a federal rapid response to dispense MCMs to an affected population following a large-scale biological attack. In 2012, CDC and FEMA started a collaborative planning effort in the top ten UASI cities to identify operational gaps in SLTT MCM distribution and dispensing plans. *(I.3)* Working closely with regional SLTT partners, both agencies continue to identify federal rapid response assets that could assist with local dispensing operations.

Department of Defense

The Secretary of Defense has primary responsibility for the research, development, acquisition, and deployment of MCMs for the Armed Forces. DoD will continue to direct strategic planning for and oversight of programs to support MCM development and acquisition for Armed Forces personnel. Through their work in the PHEMCE, DoD and HHS will coordinate their efforts to promote synergy, minimize redundancy, and, to the extent feasible, harmonize MCM development efforts. DoD will continue to draw upon its longstanding investment and experience in CBRN MCM research, development, acquisition, and deployment to ensure protection of the Armed Forces, and also to accelerate and improve the overall national effort, consistent with DoD authorities and responsibilities. *(I.4)* DoD will continue to place a special focus on MCM development for CBRN threats that are of concern for the Armed Forces due to the unique facilities, testing capabilities, and trained and experienced personnel available at DoD for this purpose. *(I.5)* HHS and DoD will continue to coordinate on the research, development, and procurement of safe and effective MCMs of mutual interest.

[80] 6 U.S.C. 182, 184

DoD and HHS coordination

Section 2811(d) of the PHS Act requires that the first PHEMCE SIP submitted under this provision include a description of DoD and HHS coordination regarding MCM activities.[81] As stated above, DoD and HHS collaborate and coordinate in this area in many ways.

- *PHEMCE collaboration* – The entire PHEMCE structure, as outlined in Appendix 2, was put in place by HHS to serve as a framework to support coordination and collaborative decision-making, where appropriate, of MCM efforts across federal departments. Under the auspices of the PHEMCE, DoD and HHS collaborate and share information on research, advanced research, development, procurement, stockpiling, and distribution of MCMs. DoD and HHS both have voting membership within the PHEMCE at multiple levels, including at the subject matter expert level (e.g., IPTs, Requirements Working Group, and Project Coordination Teams as described in Appendix 2); program manager level at the Enterprise Executive Committee (EEC); and senior leadership level on the ESC. For example, DoD representation throughout the PHEMCE SNS Annual Review process ensures consideration of DoD-specific concerns and equities during the development of SNS stockpiling recommendations. Additionally, DoD participates in all In-Process Reviews conducted for BARDA programs and in the PHEMCE-wide portfolio reviews led by ASPR. BARDA program managers participate in a number of the DoD Integrated Product Teams, to include specifically those associated with chemical and radiological/nuclear MCMs. More senior level individuals participate in DoD's Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD) Joint Life Cycle Management Reviews, and in various In-Process Reviews (for all DoD MCM programs), as well as on the DoD Overarching Integrated Product Team. The response to the Ebola epidemic in 2014 demonstrates the effectiveness of DoD-HHS relationships. CDC and DoD worked together to develop and implement Ebola diagnostics in West Africa and in U.S. laboratories. DoD successfully transitioned Ebola vaccine and therapeutic candidates from early development to BARDA for advanced development.
- *BARDA Centers for Innovation in Advanced Development and Manufacturing (CIADMs) and DoD MCM Advanced Development and Manufacturing Capabilities (ADMC)* - Each organization has visibility regarding the other's program in establishing their respective Centers and the ADMC. These are high-value, public-private partnerships established with pharmaceutical and academic leaders to assist in advanced development and surge capacity for MCMs addressing both intentional CBRN threats, pandemic influenza (CIADMs only), and outbreaks of naturally occurring emerging and genetically engineered infectious diseases. The HHS Centers and DoD ADMC each have unique capabilities that can potentially be used to accommodate the needs of the other program. Coordination has been established to maximize this potential (more information detailed in Section 3).

[81] 42 U.S.C. 300hh-10 notes

- *Integration of resources between DoD and HHS* – Beyond information sharing, DoD and HHS also coordinate on the research, development, and procurement of safe and effective MCMs of mutual interest. For example, DoD and HHS (CDC) collaborate closely on the acquisition and management of MCMs for anthrax and smallpox. There are Interagency Agreements (IAAs) and a Memorandum of Agreement (MOA) between CDC's SNS and DoD to purchase, store, and distribute anthrax and smallpox vaccines. Additionally, HHS (BARDA) and DoD collaborate on the acquisition and management of pre-pandemic influenza vaccines. Development of the smallpox antiviral drug, ST-246 (Tecoviromat), currently in the SNS, was also supported by both DoD and HHS (BARDA and NIH) and treatment courses of this drug have already been provided to DoD for use under IND. HHS and DoD are jointly supporting development of MCMs against chemical threats and to address gastrointestinal injury associated with ARS. Finally, HHS (BARDA) and DoD have technology transfer agreements and an MOU on contingency medical materiel requirements in place and are currently working on developing an MOU for co-development of antimicrobials to address shared MCM needs.
- *PHEMCE Integrated Portfolio for CBRN MCMs* – This program was established within the PHEMCE in 2008 to provide a framework for collaboration among the MCM-related program components of HHS and DoD. The Portfolio Advisory Committee (PAC), co-chaired by DoD and HHS, comprises program representatives from the various organizations responsible for the CBRN MCM programs within each department. Through the PAC, the EEC, and the ESC, DoD and HHS coordinate their efforts to promote synergy, minimize redundancy, and, to the extent feasible, harmonize requirements for MCM development. A significant example of collaboration is the development of the Portfolio Tracking Tool, which was developed jointly by HHS and DoD to capture contract performance information for all CBRN MCM development efforts across HHS and DoD. Both organizations have currently populated the data set with all contracts related to work at or above TRL 4, and the full, web-based tool is anticipated for rollout in late 2014.
- *International Collaboration* - Finally, as previously noted, DoD and HHS are members of an international allies organization termed the CBR MOU. This body coordinates biomedical product development among the defense and public health organizations of the United States, Canada, Australia, and the United Kingdom. A subgroup, termed the Medical Countermeasures Committee, works on developing products such as point-of-care diagnostics, novel antibiotics, and MCMs against chemical and toxin threats that are of mutual benefit among the signatory nations.

Department of Veterans Affairs

VA serves a critical role in its mission of providing health care to the Veteran population, as well as providing support to DoD and the nation in times of emergencies impacting public health. VA coordinates with DHS and HHS to promote synergy, minimize redundancy, and use common requirements for MCMs to ensure the VA can continue to fulfill its mission. *(I.6)* The VA also provides contracting services for the SNS.

Department of Agriculture

USDA leads USG efforts to protect against any agent that poses a threat to plant or animal[82] health. These efforts protect public health as it relates to the adulteration of food and other products regulated by the Secretary of Agriculture. These efforts also address the environment as it relates to agriculture facilities, farmland, and air and water within the immediate vicinity of an agricultural disease or outbreak. More broadly, USDA leads in the research, development, and licensure of products, practices, technologies, or other agricultural countermeasures (i.e., those not used solely in response to a human medical incident or in a non- agriculture-related public health emergency) necessary to enhance or maintain the agricultural biosecurity of the US. In particular, USDA has research activities specifically focused on veterinary MCMs, and maintains veterinary MCM stockpiles. *(I.7)* Also, USDA coordinates with HHS, through the FDA Commissioner and the CDC Director, on the surveillance of zoonotic diseases. USDA helped establish the One Health Initiative[83] that provides a focal point for the department to comprehensively consider and address zoonotic threats.

SECTION 3: PROJECT BIOSHIELD AUTHORITIES AND REPORTING REQUIREMENTS

The Project BioShield (PBS) Act of 2004 amended the PHS Act and the FD&C Act to provide additional and more flexible authorities and funding to support financially the development and procurement of MCMs against CBRN threat agents. It was also designed to provide the government with the authority to quickly authorize such MCM use during emergencies. These authorities were further delineated, clarified, expanded, and extended by PAHPA and PAHPRA. Section 5 of the PBS Act (42 U.S.C. 247d-6) required the Secretary of HHS to submit to Congress an annual report describing the use of specific provisions within the following authorities:

- **Research and Development of Qualified Medical Countermeasures** – Section 2 of the PBS Act enacted Section 319F-1 of the PHS Act (42 U.S.C. 247d-6a), authorizing the use of a variety of streamlined procedures in awarding grants, contracts, and cooperative agreements relating to the research and development of qualified countermeasures. Reporting is required on the use of limited competition, expedited peer review, and increased simplified acquisition thresholds.
- **Security Countermeasure Procurements and Special Reserve Fund** – Section 3 of the PBS Act enacted section 510 of the Homeland Security Act (6 U.S.C. 321j) to authorize the appropriation of up to $5.593 billion over the period of FY04 through FY13 in a Special Reserve Fund (SRF) for the procurement of security countermeasures that may be placed in the SNS. Furthermore, Section 3 of the PBS Act enacted section 319F-2 of the PHS Act, which authorizes the use and reporting of simplified acquisition procedures, the modified

[82] The Animal Health Protection Act of 2002 defines the term “animal” as any member of the animal kingdom (except a human).
[83] See http://www.onehealthinitiative.com/

use of other than full and open competition, and the payment of premiums in multiple-award contracts.

- **Emergency Use Authorization for Medical Countermeasures** – Section 4 of the PBS Act enacted section 564 of the FD&C Act, as amended by PAHPRA which allows the HHS Secretary to issue an EUA after declaring that circumstances exist to justify the authorization based on one of four declarations or determinations by the Secretary of Defense, Homeland Security, or Health and Human Services. This EUA declaration is a required step in authorizing the emergency use of an FDA approved, licensed, or cleared product for an unapproved indication or an unapproved product for an indication pending approval, licensure, or clearance, or until the emergency ceases. The HHS Secretary has delegated the authority to issue an EUA to the FDA Commissioner. Reporting is required on emergency uses of certain biologicals, drugs and devices, emergency declarations, and conditions of authorization.

In 2013, under PAHPRA, Congress repealed Section 5 of the PBS Act, and instead required reporting on these same PHS Act and FD&C Act authorities as part of the annual *PHEMCE Strategy and Implementation Plan*, enacted by PAHPRA as section 2811(d) of the PHS Act . This information is therefore provided here[84].

Authority Usage

In 2013, HHS used two of the authorities for the procurement of security countermeasures and issuance of EUAs. HHS did not utilize the additional authorities of expedited peer review, simplified acquisition procedures, or premium provision in multiple-award contracts. The standard Federal Acquisition Regulation (FAR) practices were deemed adequate for the majority of the acquisition activity during 2013. New to HHS, the use of other transactional authority (OTA) was employed for one project within the BARDA portfolio.

Security Countermeasure Advanced Research and Development (ARD) and Procurements for Calendar Years 2013 and 2014

Highlights of the CY 2013 and CY 2014 BARDA SRF procurements and ARD CBRN MCM portfolio activities follow.

- *Anthrax antitoxin*: In September 2013, BARDA made multiple awards under PBS to maintain anthrax antitoxin preparedness. To enhance the nation's preparedness to respond to an anthrax attack, BARDA awarded contracts to five companies developing anthrax antitoxins: Elusys (Pine Brook, NJ), Emergent BioSolutions (Gaithersburg, MD), PharmAthene (Annapolis, MD), Cangene (Winnipeg, Canada) and GSK (Research

[84] Additional detail and a summary of the use of PBS authorities between 2004 and 2013 are anticipated for posting at https://www.medicalcountermeasures.gov/

Triangle Park, NC). Each base contract was valued at $100,000 and provided the opportunity for each company to bid on task orders to deliver cell banks (as a risk mitigation strategy), monoclonal anthrax antitoxin, or plasma to manufacture polyclonal anthrax antitoxin. Under separate task orders to deliver cell banks used in manufacturing monoclonal products, awards were made to Emergent BioSolutions ($353,000), PharmAthene ($980,000) and GSK ($299,000). Under a task order to deliver monoclonal anthrax antitoxins, a single award valued at $196.4 million was made to GSK to deliver 60,000 doses of Raxibacumab over four years. This acquisition will maintain the stockpile at the current level, replenishing expiring doses. Under a task order to deliver plasma to be stored in bulk and manufactured at a later date to replenish polyclonal anthrax immune globulin (AIG) as the current product in the SNS expires, a $63.3 million contract was awarded to Cangene to reinitiate the program to collect and store plasma from individuals vaccinated with anthrax vaccine.

  - The goal of these awards was two-fold. First, obtaining the cell banks used to manufacture monoclonal anthrax antitoxins serves as a risk mitigation strategy for the USG. In the event that any of the companies that currently manufacture monoclonal antibodies are no longer able to manufacture those products, the USG would have the cell banks necessary to produce these products if and as circumstances warrant. The cell banks could be used, for example, by the CIADMs to manufacture the products to supplement the SNS stockpiles if needed. The second goal is to maintain the current SNS formulary for anthrax antitoxins at 60,000 doses of monoclonal and 10,000 doses of polyclonal products. These awards will maintain the current levels of these anthrax antitoxin products until 2017 and 2018, respectively.

- *Smallpox Vaccine*: In March 2013, BARDA exercised a $110M option under PBS with Bavarian Nordic to procure 4 million additional doses of their smallpox vaccine, modified vaccinia Ankara (MVA). This program was the first PBS award to utilize advance and milestone payments. With support from BARDA, Bavarian Nordic was able to generate data to support the potential use of the product under an EUA. MVA deliveries to the SNS began in 2010 and the originally contracted amount of 20 million doses was delivered to the SNS by November 2013. Furthermore, in November Bavarian Nordic initiated deliveries of the 4 million doses under the option executed earlier in 2013, maintaining the existing inventory level in the SNS. The additional procurement of the liquid frozen product in FY 2015 will maintain the current level of preparedness for the MVA vaccine and serve as a bridge until BARDA can transition to a new lyophilized (freeze-dried) formulation of the MVA vaccine that over time will offer significant cost savings to the USG. The new lyophilized formulation will have a longer shelf-life than the current product, can be stored at warmer temperatures, and can be deployed without the need for freezing during shipment. MVA might be used under EUA in individuals for whom the current licensed vaccine ACAM2000 is ordinarily contraindicated. This subset of patients includes individuals with human immune deficiency virus (HIV) or those with

atopic dermatitis. MVA may be given to pediatric patients and nursing or pregnant women afflicted with either condition. This MCM is one of several supported by BARDA that addresses a mandate under the PHS Act to develop MCMs for "at risk" populations.

- *Smallpox Antivirals*: ST-246 (Tecovirimat), an antiviral medication for the treatment of smallpox disease, initiated deliveries to the SNS in March 2013. Development of ST-246 has been a true USG partnership, with development activities being funded by NIH/NIAID, the DoD, and BARDA. BARDA's continued support under ARD and PBS has allowed SIGA Technologies to generate the data necessary for the potential use of the product under EUA to treat individuals symptomatic with smallpox disease. Initial deliveries to the SNS were made under a CDC-held contingency use IND and the CDC has submitted the pre-EUA package to the FDA for review. BARDA continues to support late stage development of ST-246 under the PBS program to generate additional data necessary to support FDA approval of the product. BARDA also supports the advanced development of Chimerix's CMX-001 antiviral drug candidate for treatment of smallpox infections.

- *Botulism Antitoxin*: Also in March 2013, the FDA licensed the heptavalent botulism antitoxin (BAT), manufactured by Cangene Corporation, under the "Animal Rule". The product was licensed to treat individuals symptomatic with botulism following documented or suspected exposure to serotypes A-G of botulism neurotoxin in adults and pediatric patients. This product has been used to treat naturally occurring cases of botulism in infant, pediatric patients, adult and elderly patients in the United States and Mexico. BAT is the only licensed product available in the SNS to treat botulism and its licensure represents a significant achievement for BARDA, ASPR and the PHEMCE. With the PBS procurements, BARDA has fulfilled the established national requirement for BAT. BARDA continues to collect additional plasma from the hyperimmune horse herd, which provides the starting material for BAT. As doses currently in the SNS begin to expire, collection and storage of the plasma with subsequent manufacturing beginning in 2016 will ensure preparedness for this critical MCM to 2025. BAT was the second novel PBS product to be approved under the FDA's 'Animal rule'; the first being raxibacumab, a monoclonal anthrax antitoxin, in December 2012.

- *Viral Hemorrhagic Fever* – BARDA began support to Mapp Biopharmaceutical in 2014 with $29 million for advanced development of ZMapp, a tobacco-based Ebola monoclonal antibody therapeutic cocktail, supported previously by DoD and NIH in early development. Additionally BARDA partnered with Genentech and Regeneron to develop and test effective CHO mammalian cell-based Ebola monoclonal antibodies as therapeutic candidates. BARDA began support for advanced development and manufacturing scale up of three Ebola vaccine candidates in 2014 – rVSVN4CT1 (Profectus - $6 M), rVSV EBOV (Newlink/Merck - $30 M), and ChAd3 EBOV

(GlaxoSmithKline - $12 M) to make available clinical study materials and ensure vaccine manufacturing at commercial scale for potential mass vaccination campaigns.

- *Antimicrobials*: In May 2013, BARDA entered into an agreement with GlaxoSmithKline (GSK) for $40 million of ARD funds to support development of a portfolio of novel antimicrobial products. The agreement, executed under BARDA's OTA is the first use of this authority by BARDA. The agreement provides a flexible partnership in which drug candidates can be moved in or out of the portfolio based on their developmental stage and other technical considerations, as assessed during joint semi-annual portfolio reviews. The approach balances the business risk for both the federal government and GSK. Supporting the simultaneous development of multiple drug candidates increases the likelihood that one or more will advance to the level at which the company can apply for FDA approval. BARDA provided $20 million to Rempex in 2014 for advanced development of Carbavance to treat glanders, melioidosis, and antibiotic-resistant gram-negative public health pathogens. This brings BARDA's BSA portfolio to nine drug candidates with six companies. Three of these candidates entering pivotal Phase 3 clinical studies for public health indications in 2014.

- *Cytokines for neutropenia*: Also in September 2013 BARDA made awards to add new cytokine products to the SNS to treat neutropenia, one of the sub-syndromes of acute radiation syndrome (ARS) that may result from exposure to high doses of ionizing radiation following a nuclear detonation. There are currently four products approved by the FDA to treat neutropenia associated with cancer therapy and these products have the potential to be used under an EUA to treat the neutropenia subsyndrome of ARS. Under the solicitation, base contracts, each valued at $500,000, were awarded to Amgen (Thousand Oaks, CA) and Sanofi-Aventis (Bridgewater, NJ). In addition, Sanofi-Aventis was provided $23.3 million for late stage development of their product (Leukine) to support the ARS indication. Awards were made under separate task orders to Amgen for the immediate delivery of 35,203 treatment courses of their product Neupogen ($157 million) and to Sanofi-Aventis for the delivery of 4,340 treatment courses of Leukine ($14 million). Both products are maintained under vendor managed inventory (VMI). Under VMI, the products will rotate through the commercial market. This means that the products will not be stockpiled in the SNS, where they would eventually expire over time, but instead will be in constant rotation and held by the manufacturers, with the USG having access to the product when needed. Additionally BARDA continued investment in the development of biodosimetry assays and devices to measure rapidly the level of radiation exposure for more informed radiation therapies following ionizing irradiation events; from the original 11 candidates, support continued for six (6) remaining candidates.

- *Nerve agent treatments*: In September 2013 a PBS contract was awarded to add a new product to the SNS to treat seizures resulting from exposure to chemical nerve agents. This contract award, valued at $61 million, was made to Meridian Medical Technologies (Columbia, MD) for the late stage development and procurement of 2.3 million doses of

midazolam. Midazolam has been shown to be faster acting and easier to administer than the current anticonvulsant, diazepam. The SNS currently stockpiles diazepam in forward deployed CHEMPACKs. As the diazepam expires, it will be replaced with midazolam at a one-to-one ratio.

- *BAAs*: In July 2013, BARDA reissued its BAA seeking proposals through 2015 for the development of MCMs to treat, prevent, or diagnose the medical consequences of CBRN attacks. In addition, BARDA issued the Strategic Science and Technology Division (SSTD) BAA for the second time. The CBRN and SSTD BAAs reflect the MCM priorities highlighted in the 2012 and current *PHEMCE Strategy and Implementation Plan* and will remain open for two years. These vehicles are the mechanism BARDA uses to build a robust pipeline of candidate products that have the potential to transition to PBS funding for procurement.

Emergency Use Authorization

Section 564 of the FD&C Act, as enacted under the PBS Act and amended under PAHPRA, enables the Commissioner of FDA to issue an EUA to authorize the use of an unapproved medical product, or to authorize an unapproved use of an approved medical product, when the HHS Secretary declares that circumstances exist to justify the issuance of an EUA based on one of four determinations by the Secretary of Homeland Security, Defense or Health and Human Services.

One of the most significant EUA authority changes resulting from PAHPRA in 2013 is that it made it possible for FDA to issue an EUA based on the HHS Secretary's determination that there is a significant potential for a public health emergency.[85] Before an EUA can be issued, one of four specific determinations by the HHS Secretary, Secretary of Homeland Security, or DoD Secretary must be made. Prior to PAHPRA, the HHS determination required the Secretary to declare that a public health emergency exists in accordance with section 319 of the PHS Act. Now, the HHS Secretary's determination is made under section 564 of the FD&C Act, and can be based on either an actual or a potential public health emergency, which provides greater flexibility to issue EUAs in advance of an actual emergency to support preparedness activities. Based on this new flexibility, in 2013 and 2014 FDA issued three EUAs for *in vitro* diagnostic tests for the presumptive detection of the novel influenza A (H7N9) virus, which emerged in 2013. In 2013, FDA also issued one EUA for an *in vitro* diagnostic test for the presumptive detection of Middle East Respiratory Syndrome (MERS-CoV), which emerged in 2012. These EUAs were issued based on a determination by the HHS Secretary that there is a significant

[85] Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) Medical Countermeasure (MCM) Authorities: FDA Questions and Answers for Public Health Preparedness and Response Stakeholders. Washington DC: U.S. Food and Drug Administration. Available at: http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM380269.pdf .

potential for a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad to facilitate preparedness for these emerging threats[86].

SECTION 4: THREAT-BASED APPROACHES

The PHEMCE recognizes the need to address the high-priority threats identified in this document. While the PHEMCE is evolving toward capability-based approaches, it will maintain key threat-based approaches needed to address these threats to national health security. This section describes in detail the threat-based activities and programs that were prioritized based on the PHEMCE prioritization framework to support the approaches described in Section 1 of this document.

ANTHRAX

The HHS PHEMCE anthrax programmatic priorities include:

- Achieving FDA approval for PEP use of the currently approved vaccine[87]
- Pursuing dose- and antigen-sparing approaches for the currently approved vaccine
- Reducing vaccine life cycle costs
- Developing enhanced and next-generation anthrax vaccine candidates
- Providing and maintaining enough vaccine regimens for the SNS to meet the established PHEMCE goal
- Enhancing the sustainability of anthrax vaccines by lowering cost per dose
- Encouraging competition among product sponsors
- Building in redundancy to mitigate risk
- Investing in novel expression and manufacturing platform technologies that are readily transferrable before or after a public health emergency to increase production capacity for anthrax vaccine
- Achieving FDA approval for one or more additional anthrax antitoxins[88]
- Conducting animal model testing to support approval under the Animal Rule of antimicrobials currently approved for other indications for use against inhalation anthrax

Near-term (FY15-16)

Anthrax Clinical Guidance and Communication Materials

[86] In 2014 FDA also issued multiple EUAs for in vitro diagnostics for the detection of Ebola virus following a Secretarial declaration that circumstances exist to justify an EUAs for IVDs for the detection of Ebola virus based on an existing 2006 material threat determination for Ebola virus by DHS.
[87] Supplemental BLA was submitted to the FDA in October 2013 for review and licensure
[88] Raxibacumab, anthrax monoclonal was approved December 2012. AIG, anthrax polycolonal antibody, submitted their BLA to the FDA in July 2014 for review

The Anthrax Management Team (AMT) was established in 2010 to coordinate, consolidate, and integrate all anthrax-related activities at the CDC. When these activities involve MCMs, the activities of this team will align with the PHEMCE prioritization framework described in this Plan. Updated anthrax clinical guidelines for the general population, pregnant women, and the pediatric population have been published by CDC. *(T.A.1)* In the near-term, CDC will also release anthrax clinical guidance for use in the general population during a mass casualty event.

Anthrax Vaccine

(T.A.2) NIH is focusing on improving the currently approved anthrax vaccine through the development and testing of adjuvants that could enhance performance and reduce the number of doses necessary to achieve full immunity in a post-exposure setting. Human clinical Phase 2 testing is underway, with completion anticipated in the near-term. *(T.A.3)* BARDA will support advanced development to expand the vaccine's indications to include PEP, and work to extend product expiry. *(T.A.4)* NIH, CDC, BARDA and FDA, working with the vaccine manufacturer, are supporting research into dose-sparing strategies for PEP vaccine use, with completion anticipated in the near-term. Following the results of these studies, the PHEMCE will re-evaluate the stockpiling targets for anthrax vaccine. *(T.A.5)* Furthermore, BARDA will continue development of existing recombinant anthrax protective antigen (rPA) vaccine candidates in its pipeline and longer-term approaches supporting novel, viral-vectored, vaccine platforms. *(T.A.6)* In addition, BARDA will provide vaccine candidates with advanced development and manufacturing assistance from the CIADMs as appropriate. *(T.A.7)* Early-stage research for enhanced and next-generation anthrax vaccines is in progress at NIH, investigating various technologies for temperature stabilization and alternative routes of delivery. Results from these preliminary studies should be available after FY15. *(T.A.8)* BARDA will support advanced development of anthrax vaccine formulated with more effective adjuvants for antigen- and dose-sparing as compared to the existing licensed anthrax vaccine product.

Anthrax Antitoxins and Antimicrobials

(T.A.9) BARDA will support late-stage development of an additional antitoxin with greater effectiveness and .thermostability. *(T.A.10)* CDC and BARDA are supporting drug manufacturers in fulfilling their post-marketing requirements for approved products. *(T.A.11)* CDC is sharing information with the drug manufacturer regarding patients treated with the investigational antitoxin to date.

(T.A.12) Animal model testing to support approval under the "Animal Rule" for use against inhalation anthrax of antimicrobials currently approved for other indications is in progress at NIH, with FDA review anticipated in FY15. Additional antimicrobial development efforts are also underway at NIH, discussed below as part of the broad-spectrum antimicrobial program. All

such anthrax antimicrobial programs are intended to expand our repertoire of antibiotics that are effective against anthrax.

Anthrax MCM Response Strategy

(3.2.9) By FY15, ASPR will develop a response strategy for the utilization of pharmaceutical anthrax MCMs including vaccines, antimicrobials, antitoxins, and non-pharmaceutical MCMs such as chest tubes and ventilators.

Mid-Term (FY17-18)

Anthrax Vaccine

(T.A.13) BARDA will support expansion of domestic manufacturing capacity for the currently approved anthrax vaccine, including validating new manufacturing processes, conducting additional non-clinical and clinical studies, and pursuing licensure of a new facility. *(T.A.14)* Concurrently, BARDA will continue the development of the existing rPA vaccine candidates in its pipeline, and build on NIH investments to advance a next-generation anthrax vaccine toward licensure through validating manufacturing processes and conducting non-clinical and clinical studies. It is anticipated that as a result of these activities, a next-generation anthrax vaccine may be available for procurement for the SNS by FY17.

Anthrax Antitoxins and Diagnostics

(T.A.15) BARDA anticipates product licensure of one or more additional anthrax antitoxins in this timeframe. The PHEMCE will need to assess the appropriate mix of anthrax antitoxins to maintain in the SNS formulary. *(T.A.16)* The PHEMCE will support efforts to develop more rapid drug susceptibility assays for anthrax under the leadership of CDC and DoD.

Long-Term (FY19 and beyond)

Anthrax Vaccine

NIH long-term research in this area will pursue the development of anthrax vaccines with PEP potential that provide enhancements to the currently available vaccine for more effective utilization in public health emergencies. Ultimately, the objective is an anthrax vaccine for PEP that is effective in one dose and produces a rapid onset of immunity, resulting in a substantially reduced duration of required antimicrobial PEP therapy.

BARDA will continue to support advanced development of next-generation anthrax vaccines. BARDA will also continue to support studies to evaluate vaccines with various adjuvants and altered delivery mechanisms with the goal of reducing the number of doses necessary to obtain protective immunity. Finally, BARDA will continue to provide vaccine candidates with advanced development and manufacturing assistance from the CIADMs.

Anthrax Antitoxins, Antimicrobials, and Diagnostics

Research activities related to novel and simplified forms of antitoxins are underway at NIH and are expected to yield results in the long-term. BARDA will support the advanced development of next-generation, small molecule antitoxins for treatment of antimicrobial-resistant strains of anthrax as they become available. This will include efforts to ensure that appropriate animal models are available for advanced development.

NIH will support research into diagnostic platforms and the identification of biomarkers indicative of anthrax exposure to inform clinical decisions relative to antibiotic PEP administration. Additionally, NIH will support research into a more detailed characterization of symptomatic anthrax disease in order to guide clinical decisions regarding optimal antimicrobial therapy, as well as the need for additional antitoxin therapy. The PHEMCE will continue to support efforts to develop more rapid drug susceptibility assays for anthrax under the leadership of CDC and DoD.

OTHER BACTERIAL THREATS

PHEMCE programmatic priorities for other bacterial threats include:

- Providing additional MCMs for the treatment and/or PEP of diseases caused by biological threat agents through discovery of novel compounds that have the potential to be effective against drug-resistant variants and address bacterial agents for which an MTD has been made;
- Revitalizing the pipeline of antimicrobial drugs to treat hospital- and community-acquired multi-drug resistant (MDR) bacterial infections for use in routine public health applications to advance the President's CARB initiative to address the on-going antimicrobial drug-resistance crisis;
- Establishing public-private partnerships to incentivize companies developing antimicrobials to both continue their commercial development and initiate development for biodefense indications.

Near-Term (FY15-16)

(T.OB.1) NIH maintains *in vitro* and animal model testing services for the infectious disease community, especially for those bacterial threats for which special handling is required (e.g., due to Select Agent status or BSL-3 containment requirements). *(T.OB.2)* In addition, to support product development under the "Animal Rule", NIH and BARDA will seek qualification of animal models of anthrax, plague, and tularemia for PEP and treatment indications, through the FDA's Animal Model Qualification Program[89].

[89] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284078.htm

(T.OB.3) DoD will invest in the development of MCMs against multi-drug resistant (MDR) bacteria that are of interest to the DoD. These efforts will involve leveraging investments in new antibiotics across the government as well as investing in partnerships with industry to repurpose or re-target their existing candidates.

(T.OB.4) NIH will augment antimicrobial efficacy datasets in support of approval of clinical indications for anthrax, plague, and tularemia for off-patent antimicrobials in the SNS and/or in routine use. *(T.OB.5)* Additionally, NIH will support studies to inform utilization policy and response planning for these products.

(T.OB.6) BARDA will support the advanced research and development of novel antimicrobials for PEP and diagnostics for treatment and diagnosis of biological threat agents while addressing the threat of antimicrobial resistance in routine public health settings as part of the CARB initiative. *(T.OB.7)* BARDA, under the animal model network, is establishing key reagents and animal models for testing MCMs against *Burkholderia pseudomallei* and *Burkholderia mallei*. *(T.OB.8)* BARDA will initiate the testing of candidate products against *Burkholderia pseudomallei* and *Burkholderia mallei*.

Mid-Term (FY17-18)

(T.OB.9) NIH will maintain antibiotic efficacy datasets for off-patent antimicrobials within the SNS, as well as for antimicrobials in common routine use. *(T.OB.10)* BARDA will continue advanced development of antimicrobial and diagnostic candidates; pending results of clinical trials, BARDA may procure several of these candidates under PBS. DoD will continue to support the development of new MCMs against MDR bacteria and continue to look for opportunities to leverage existing investments by the USG. *(T.OB.11)* DoD intends to file an IND by FY18 in support of an indication against MDR bacterial agents of interest to the DoD.

Long-Term (FY19 and beyond)

BARDA will support late-stage development activities in support of PEP and treatment of *Burkholderia* infections.

DoD will continue to support the development of new MCMs against MDR bacteria through the pivotal animal trials under Special Protocol Assessments with the FDA and continue to look for opportunities to leverage existing investments by the USG.

SMALLPOX

The PHEMCE smallpox programmatic priorities include:

- Maintaining an adequate stockpile of vaccines and Vaccinia Immune Globulin Intravenous (VIGIV)
- FDA approval of Modified Vaccinia Ankara (MVA) vaccine, intended for use in at-risk populations
- Approval of two smallpox antivirals with different mechanisms of action

Near-Term (FY15-16)

Smallpox Vaccine

Existing smallpox vaccines are mature. *(T.S.1)* In the near-term, the PHEMCE will maintain sufficient quantities of smallpox vaccines in the SNS to provide a response capability to vaccinate every American during a smallpox emergency, if appropriate, including use of a vaccine for at-risk populations. *(T.S.2)* The PHEMCE will also publish the *National Smallpox Vaccine Response Strategy*, which will offer guidance on domestic vaccination strategies, as well as vaccine selection and prioritization for select subgroups, in an emergency triggered by a confirmed clinical case of smallpox. *(3.2.10)* ASPR and CDC, working with FDA, will also focus on the development of a clinical utilization policy to describe the recommended emergency use of all currently stockpiled smallpox vaccines.

(T.S.3) In the near-term, the PHEMCE will address the needs for replacement of expiring doses of the currently approved smallpox vaccine, ACAM2000, and of the stockpile of VIGIV to treat adverse events resulting from smallpox vaccination, as well as developing contingency activities to ensure stockpile maintenance. *(4.2.6)* BARDA, working with CDC, will support activities to achieve FDA approval for the MVA smallpox vaccine, which is intended for use in at-risk populations. *(T.S.4)* BARDA will continue to provide technical support for the manufacture and acquisition of the MVA vaccine for at-risk populations. *(T.S.5)* BARDA will also continue development of a freeze-dried formulation of MVA to allow a longer shelf life and storage at higher temperatures in order to reduce life cycle management costs.

Smallpox Antivirals and Diagnostics

Antivirals for the treatment of smallpox are in advanced development. *(T.S.6)* BARDA will complete delivery to the SNS of the required treatment courses of the smallpox antivirals currently supported under a PBS contract by the end of calendar year (CY) 2014.

(T.S.7) In addition, CDC will continue to evaluate relevant diagnostic assays using both *in vitro* and *in vivo* systems to support FDA regulatory review and ultimately national use of these tests. These assays will include orthopoxvirus-generic and Variola-specific assays to be used in the LRN.

Mid- and Long-Term (FY17 and beyond)

Smallpox Vaccine

In the mid- and long-term, the PHEMCE will continue to maintain smallpox vaccines and VIGIV (as needed) in the SNS. *(T.S.8)* CDC will continue to work in coordination with the PHEMCE to identify research to inform improved VIGIV dosing. *(T.S.9)* The PHEMCE will also develop appropriate animal model(s) to evaluate VIGIV or other therapeutic candidates in treating adverse events associated with the current vaccine.

(T.S.10) BARDA will manage the transition from the present liquid-frozen form of the MVA smallpox vaccine to a freeze-dried formulation with superior life cycle management properties. ASPR, CDC, and FDA will update clinical guidance for smallpox vaccines as needed.

Smallpox Antivirals

(T.S.11) NIH efforts focused on next-generation smallpox antivirals will support those products that emerge from the broad-spectrum antiviral program. Once those candidates have obtained FDA approval for other viral indications, most likely via traditional regulatory pathways, NIH will pursue an orthopox clinical indication under the Animal Rule. *(T.S.12)* BARDA will continue to support approval of one or more antiviral products. *(T.S.13)* CDC will also conduct studies to inform the clinical use of these MCMs.

PANDEMIC INFLUENZA

The HHS PHEMCE pandemic influenza programmatic priorities include:

- Maintain the established comprehensive portfolio approach to develop, acquire, and build an infrastructure for a broad array of MCMs to respond to pandemic influenza, including vaccines, therapeutics, diagnostics, and non-pharmaceutical MCMs
- Sustain a robust domestic pandemic influenza vaccine manufacturing capacity
- Address various aspects of MCM utilization for pandemic influenza, and develop and distribute communication and educational materials before and during an influenza pandemic
- Develop a more effective influenza vaccine using novel antigens with potential “universal” flu vaccine qualities that may eliminate the need for annual modifications to the influenza vaccine or annual boosters and serve as priming doses for future pandemic influenza vaccines

Near-term (FY15-16)[90]

Influenza Antigen-Sparing Technology

NIH maintains an active grant portfolio supporting basic research into novel adjuvants. *(T.PI.1)* NIH and BARDA will continue to collaborate in the clinical evaluation of adjuvants coupled with a variety of influenza vaccines. The goal is to provide antigen-sparing benefits (i.e., decreased amount of viral hemagglutinin antigen needed to provide immunity), broad heterosubtypic immunity (i.e., protection against multiple virus variants), and prime-boost effects (i.e., one dose may be sufficient instead of two or more) for influenza vaccines. In November 2013, the FDA approved a BARDA-supported adjuvanted H5N1 influenza vaccine produced by GlaxoSmithKline, the first approved adjuvanted influenza vaccine in the US.

Communications and Response Planning

(T.PI.2) As called for in the *H1N1 Improvement Plan*[91], CDC will continue to ensure that operational plans for pandemic influenza communication are updated, exercised, evaluated, and improved to facilitate effective communication strategies. *(T.PI.3)* Furthermore, CDC will develop mechanisms to further integrate social media and other communication tools into preparedness activities. *(T.PI.4)* CDC will also improve and share public health emergency messages, including translated and culturally appropriate materials for non-English-speaking communities across the US, and increase the capacity for developing plain language and easily understood materials for public audiences. In addition, CDC will: *(T.PI.5)* (1) develop procedures to ensure that information in future pandemics is provided in accessible and alternative formats; *(T.PI.6)* (2) refine and implement partnership strategies to improve communication with hard-to-reach and at-risk populations; *(T.PI.7)* (3) use partnerships and other information dissemination channels to effectively reach and inform clinicians regarding CDC's policies, guidelines, and recommendations related to pandemic influenza MCMs; and *(T.PI.8)* (4) develop an approach, definitions, tools, and models for a risk communication response plan.

(T.PI.9) ASPR will maintain and continue to promote the use of the Interim Healthcare Coalition Checklist for Pandemic Planning (HCCPP)[92]. In conjunction with other tools, the HCCPP can help healthcare coalitions expand their pandemic influenza emergency response plans to include a diverse mix of partners, including schools, businesses, community organizations, and government agencies. The HCCPP tool outlines recommended actions based on each of the eight preparedness capabilities in ASPR's *Healthcare Preparedness Capabilities: National Guidance for Healthcare System Preparedness*[93].

[90] Information regarding respiratory protective devices for influenza needs is addressed in the capabilities-based approaches section.
[91] Available at http://www.phe.gov/Preparedness/mcm/h1n1-retrospective/Documents/2009-h1n1-improvementplan.pdf
[92] Available at http://www.phe.gov/Preparedness/planning/hpp/reports/Documents/pandemic-checklist.pdf
[93] Found at http://www.phe.gov/Preparedness/planning/hpp/reports/Documents/capabilities.pdf

Influenza Vaccine Stockpiles

(T.PI.10) In the near-term, the PHEMCE will assess the current policy for the pre-pandemic influenza vaccine stockpiles, including the adjuvant stockpile, and guidance for their use.

BARDA collaborates closely with PHEMCE partners, including CDC, NIH, and FDA, to make decisions regarding influenza vaccines suitable for the pre-pandemic vaccine stockpile. Decisions regarding the composition of the pre-pandemic stockpile are informed by the use of the CDC IRAT that assesses the potential pandemic risk posed by influenza A viruses. BARDA in 2013 awarded three-year contracts to five US-approved influenza vaccine manufacturers to produce master vaccine seed stocks for viruses with pandemic potential before a pandemic occurs. The contracts also allow HHS to purchase cell-based vaccine in addition to conventional egg-based vaccine in a pandemic. *(T.PI.11)* BARDA will maintain and update the existing stockpile of novel influenza viruses and pre-pandemic vaccines and adjuvants as needed.

(T.PI.12) CDC, working with BARDA and FDA, will develop rapid methods and biosynthetic technologies to produce candidate vaccine viruses that allow accelerated production of vaccine lots for eventual fill and finish by manufacturers. *(T.PI.13)* In addition, in collaboration with BARDA and FDA, CDC will complete work on the development of rapid laboratory methods to expedite testing to determine the antigen content of influenza vaccine bulk material and enable vaccine formulation prior to product fill and finish.

Influenza Vaccine Development

(T.PI.14) ASPR will lead the PHEMCE in developing a consensus working definition of a "universal influenza vaccine". *(T.PI.15)* NIH is focusing on a wide array of novel viral antigen and universal influenza vaccine concepts, with several candidates entering preclinical development over the next several years. *(T.PI.16)* NIH and BARDA anticipate moving at least one universal influenza vaccine candidate into Phase 1 clinical trials in this timeframe. *(T.PI.17)* NIH is also developing a repository of required influenza-related reagents to support universal influenza vaccine development. *(T.PI.18)* In addition, NIH is working closely with the FDA to develop and refine additional assays to support future vaccine development efforts. *(T.PI.19)* BARDA plans to initiate support in the near-term of one or two promising influenza vaccine candidates through the BAA funding mechanism.

Cell- and recombinant-based influenza vaccine development is a key element in the PHEMCE intermediate and long-term pandemic influenza preparedness strategy in order to provide adequate domestic vaccine manufacturing surge capacity. The first cell-based influenza vaccine was approved in the US in November 2012, and the first recombinant influenza vaccine was approved in the US in January 2013; development of both was supported by BARDA. *(T.PI.20)* BARDA is continuing to support the advanced development of additional recombinant vaccine candidates for both pandemic and seasonal influenza through Phase 3 clinical trials, in this timeframe. *(T.PI.21)* As novel viral antigen or universal influenza vaccine candidates are developed through proof-of-concept Phase 1 clinical trials, BARDA will support the advanced development of these candidates toward approved products. BARDA, working with HHS

colleagues, has developed a plan to produce high yielding / immunogenic influenza vaccine strains for distribution to manufacturers. BARDA and other HHS partners have also developed improved potency assays to replace the current single radial immunodiffusion (SRID) assay calibration technique. *(T.PI.22)* In the near-term, HHS will implement the vaccine strain distribution plan and use of the potency assays to assist in vaccine development for seasonal and pandemic influenza.

Influenza Antivirals

(T.PI.23) NIH will support post-Phase 2a development of an influenza broad-spectrum therapeutic with multi-functional potential. *(T.PI.24)* NIH will also develop both small-molecule drugs and monoclonal antibodies as broad-spectrum influenza therapeutics. These therapeutics will initially be developed as treatments, with the potential for prophylactic use in the future, especially in those individuals for whom vaccine responses are poor.

(T.PI.25) BARDA will support development of existing neuraminidase inhibitor drugs and host-targeted antiviral drug candidates, as well as new combination therapies, monoclonal antibody therapies, and new classes of influenza antiviral drugs. *(T.PI.26)* BARDA will support advanced development of at least two drugs with novel mechanism(s) of action through Phase 3 clinical studies; it is anticipated that two drugs could be approved for use in the US in this timeframe. BARDA continues to seek opportunities to develop new antiviral treatments through the Influenza BAA, with a focus on products with novel mechanisms of actions, and those effective in severely ill, hospitalized patients and suitable for at-risk populations, including pediatrics.

(T.PI.27) DoD will continue the development of a small molecule, broad-spectrum anti-viral targeting pandemic and seasonal influenza. The product is currently in Phase 3 efficacy and safety testing in a worldwide clinical trial in the Northern and Southern hemispheres. NDA filing is expected by the second quarter of FY16.

(T.PI.28) CDC will develop new plans for influenza antiviral distribution and dispensing.

Influenza Diagnostics

(T.PI.29) NIH will sequence and provide genomic data for influenza viral isolates to support current and future diagnostic efforts. In addition, NIH will continue to add representative influenza viral isolates to NIH's NIAID Biodefense and Emerging Infections (BEI) Research Resources Repository in order to make strains available for developing next-generation diagnostic tests.

(T.PI.30) BARDA will continue the development of point-of-care diagnostic devices for detection of influenza and other respiratory pathogens, including intentional biological threat agents. *(T.PI.31)* CDC and BARDA will begin development of new sequencing-based diagnostic assays and prototype device development for diagnosis of influenza viruses and other respiratory pathogens.

Mid-Term (FY17-18)

Communications and Response Planning

(T.PI.32) CDC will refine and expand the use of immunization information systems among all providers, including non-traditional providers.

Influenza Vaccine Stockpiles

(T.PI.33) CDC will continue work to increase the percentage of persons receiving annual influenza vaccinations.[94] *(T.PI.34)* CDC will also work with federal and SLTT partners to implement guidance developed by the USG for situations in which limited vaccine availability requires prioritization of vaccination. *(T.PI.35)* BARDA will continue to maintain and adjust novel influenza virus and pre-pandemic influenza vaccine stockpiles, as warranted, in collaboration with PHEMCE partners and through utilization of the IRAT-derived information as described above.

Influenza Vaccine Development

(T.PI.36) BARDA will support at least one novel viral antigen or universal vaccine candidate expected to be evaluated in Phase 2 clinical studies in the mid-term. *(T.PI.37)* BARDA will continue support for the advanced development of additional recombinant influenza vaccine candidates that are anticipated to complete Phase 3 clinical studies, followed by BLA filings for licensure, in this timeframe.

Influenza Antivirals

(T.PI.38) BARDA will continue support for the advanced development of novel (non-neuraminidase inhibitor) influenza therapeutics, including promising new viral and host-targeting candidates, and monoclonal antibody treatments. *(T.PI.39)* DoD anticipates licensure of a new small molecule broad-spectrum influenza drug by the second quarter of FY17.

Influenza Diagnostics

(T.PI.40) CDC will ensure the implementation of laboratory reference diagnostics for influenza at public health laboratories and refine the methods by which specimens are tested for surveillance purposes. Expansion of capacity to rapidly detect novel influenza viruses and emerging antiviral resistance is also planned. In addition, CDC will improve the timeliness and accuracy of laboratory assays for measuring influenza immunity. *(T.PI.41)* Finally, CDC and BARDA will continue support of the development of sequencing-based diagnostic assays and prototype device development for diagnosis of influenza viruses and other respiratory pathogens.

[94] The target for adults over 18 is 70% with completion projected in 2020. For more information, see http://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives

Long-term (FY19 and beyond)

Influenza Vaccine Stockpiles

BARDA will maintain and update the pre-pandemic stockpile as needed to maintain preparedness, as determined in collaboration with PHEMCE partners. When universal influenza vaccines are approved, the PHEMCE will reexamine the utility of existing pre-pandemic stockpiles.

CDC will work to refine policies and plans related to pre-pandemic vaccine distribution modalities (e.g., pre-pandemic vaccine allocation guidance, utilization strategies, stockpiling goals, and communications plans). This effort will focus on the refinement of the pandemic vaccine prioritization strategy and implementation plans as necessary, including communication plans. In coordination with FDA, CDC will also conduct influenza vaccine safety studies in at-risk populations (e.g., pregnant women) and explore opportunities to improve awareness of vaccine adverse events and increase reporting to the Vaccine Adverse Event Reporting System (VAERS) by clinicians and other vaccine providers.

Influenza Vaccine Development

NIH is focusing on a wide array of universal influenza vaccine concepts, with several candidates entering preclinical development over the next several years. NIH is also developing a repository of required influenza-related reagents to support universal influenza vaccine development. In addition, NIH is working closely with the FDA to develop and refine additional assays, including sterility and potency testing, to support future vaccine development efforts.

In close coordination with NIH, CDC, and FDA, BARDA will support the advanced development and licensure of new influenza vaccines with improved effectiveness. These vaccines will use recombinant and antigen sparing/immunomodulatory approaches to create better vaccines that provide greater protection against seasonal and pandemic influenza viruses.

Influenza Antivirals

In this time frame, it is anticipated that at least four additional influenza therapeutics supported by BARDA will be approved for use in the US.

VIRAL HEMORRHAGIC FEVER AND OTHER VIRAL THREATS

For EIDs, viral agents remain a dominant source of likely novel outbreaks. PHEMCE programmatic priorities for other viral threats include:

- Addressing existing viral threats
- Strengthening the capability to respond to emerging viral threats through a broad-spectrum antiviral program

Near-Term (FY15-16)

(T.OV.1) NIH anticipates moving broad-spectrum antiviral candidates into clinical testing in this time frame. Initial targeted clinical indications include influenza, smallpox, and certain viral hemorrhagic fevers. *(T.OV.2)* In addition, NIH will offer *in vitro* and *in vivo* screening of newly discovered candidates. *(T.OV.3)* NIH will also continue its lead role in a USG-wide interagency working group developing specific reagents, assays, and animal efficacy models to support filovirus vaccine and therapeutic MCMs approval. More than 30 different filovirus vaccine formulations have been evaluated through the NIH's preclinical services since 2011 using animal models and assays that NIH has developed over many years. Several of these candidates qualified for further testing and a number are currently in the product development pipeline. *(T.OV.4)* BARDA is currently supporting advanced development and manufacturing activities for three Ebola vaccine candidates (Profectus, BioProtection/Newlink (now partnered with Merck), and GlaxoSmithKline). *(T.OV.5)* BARDA anticipates additional awards based on supplemental funding for other vaccine candidates. *(T.OV.6)* BARDA is utilizing its Fill-Finish and Manufacturing Network to assist vaccine manufacturers in filling their vaccine candidates for clinical trials. *(T.OV.7)* BARDA will also employ its Clinical Studies Network to assist the CDC in managing vaccine trials in West Africa. *(T.OV.8)* CDC will conduct evaluations of Ebola vaccine clinical trials in affected countries to assess safety and efficacy of vaccine candidates.

Two examples of NIH's filovirus therapeutics development are ZMapp and BCX-4430. DoD funded the initial development of ZMapp, which is a combination of three recombinant antibodies directed against the Ebola virus, manufactured in tobacco plants. *(T.OV.9)* NIH is collaborating with partners at DoD, BARDA, and FDA to advance development and testing of ZMapp to determine whether it is safe and effective. BARDA is now providing support for all manufacturing activities for ZMapp including utilization of BARDA's Fill-Finish and Manufacturing Network to assist the manufacturer in filling the product. *(T.OV.10)* The pivotal ZMapp preclinical safety data supported by NIAID is being delivered in February 2015 to allow for a NIAID-supported Phase 1 trial to begin in the first quarter of 2015. *(T.OV.11)* ZMapp is also expected to be included in the master randomized control trial (RCT) protocol expected to begin in the U.S. and West Africa in early 2015.

BCX-4430 is a novel drug that interferes with the replication process of the Ebola virus and has shown activity against a broad spectrum of viruses. *(T.OV.12)* NIAID is supporting efficacy studies in NHPs, manufacturing and formulation activities for both intramuscular and IV administration, and IND-enabling preclinical studies. BioCryst Pharmaceuticals, Inc., began Phase 1 testing of BCX-4430 in December 2014.

A number of Ebola vaccine candidates are currently undergoing Phase 1 clinical testing with PHEMCE agency support. NIH played a critical role in advancing one of these candidates, ChAd3, in partnership with GSK. *(T.OV.13)* NIH is conducting Phase 1 trials of this candidate and partnering with DoD to conduct trials of an additional vaccine candidate, an rVSV-vectored EBOV in development by NewLink Genetics Corp with funding from the DoD. *(T.OV.14)* In partnership with GSK, the DoD, and NewLink plans are underway to advance these candidate

vaccines to Phase 2/3 efficacy testing. *(T.OV.15)* BARDA is also supporting development of an additional vaccine with Profectus BioSciences Inc through animal safety studies to support a future IND application.

NIH also has supported a number of Ebola virus vaccine candidates that are currently earlier in development. *(T.OV.16)* NIH and DoD are supporting Profectus BioSciences, Inc., to investigate a second rVSV-vectored vaccine candidate against Ebola and Marburg viruses. NIH also funded Crucell to develop a recombinant adenovirus-vectored Ebola vaccine. In animal studies, this vaccine candidate protected against filovirus infection, including Ebola virus infection. NIH has played an instrumental role in the recent announcements by Johnson & Johnson (parent company of Crucell) and Bavarian Nordic that they will collaborate on a two-dose (prime-boost) vaccination regimen that will begin Phase 1 testing in 2015.

(T.OV.17) NIAID also is engaged in screening licensed drugs for anti-filovirus activity and is collaborating with federal and non-profit agencies to gain the data necessary to establish safety and efficacy to support using the drugs to treat Ebola patients. *(T.OV.18)* NIAID is also collaborating with the NIH National Center for Advancing Translational Sciences and pharmaceutical industry partners to screen antiviral candidates in development in order to accelerate any promising therapies that have not been previously identified

(T.OV.19) BARDA will expand platform programs with the potential to address more threats, such as the filoviruses. In addition, BARDA has established core services to include: animal models network, CIADM, Fill-Finish network, and Clinical Studies network that complement the already existing networks established at the NIH to potentially allow the PHEMCE to respond quickly to emerging threats. BARDA awarded its first task order to a Fill-Finish Network performer to support the manufacture of Ebola therapeutics.

DoD has tested and shown that the broad-spectrum anti-viral candidate favipiravir, currently in Phase 3 clinical trials for influenza, is active against other members of RNA virus families. These currently include Filovirus, Alphavirus, Bunyavirus, Flavivirus, Togavirus, Orthomyxovirus, and Coronavirus. *(T.OV.20)* DoD is funding a Phase 2 clinical trial of favipiravir in West Africa in early 2015. *(T.OV.21)* Favipiravir and another potential therapeutic in development by Tekmira, TKM-Ebola, are also under consideration for inclusion in the master RCT protocol slated to begin in early 2015.

Mid-Term (FY17-18)

(T.OV.22) NIH will continue pre-clinical and early clinical development of therapeutics and vaccines to establish a pipeline of potential medical countermeasures for established or emerging viral disease threats. *(T.OV.23)* NIH will undertake animal efficacy model studies to evaluate these agents' broad-spectrum activity and examine their potential to replace existing stockpiled MCMs once they gain approval. *(T.OV.24)* BARDA will continue advanced development of existing and new Ebola vaccine and therapeutic candidates that meet PHEMCE product specific requirements towards FDA licensure and approval. Provided sufficient maturity

of Ebola vaccine and therapeutic candidates is reached, BARDA may procure initial products utilizing the SRF for stockpiling. *(T.OV.25)* BARDA also plans to support expanded formulations of existing and proven antiviral drugs and therapeutics. *(T.OV.26)* DoD will continue the testing and evaluation of small molecule broad-spectrum anti-viral against additional members of the Filovirus and Alphavirus families.

Long-Term (FY19 and beyond)

Mid- to late-stage development activities for a filovirus therapeutic(s) are anticipated to require continued support by BARDA. DoD will continue testing the small molecule, broad-spectrum anti-viral in non-human primate (NHP) models of Filovirus disease and will file a supplemental New Drug Application by FY19.

BOTULISM

PHEMCE botulism programmatic priorities include:

- Establishing and maintaining a long-term supply of heptavalent botulism antitoxin (BAT)
- Developing next-generation botulism therapeutics that offer reduced manufacturing and storage costs
- Transitioning to a sustainable platform for long-term production

Near-Term (FY15-16)

(T.B.1) NIH will continue to evaluate a collection of next-generation botulism antitoxin monoclonal antibodies. A botulism serotype A cocktail has completed Phase 1 trials, while botulism serotype B&E cocktails will be in Phase 1 trials during this period. Serotypes C&D may also advance to clinical testing during this period. Serotype F&G candidates are undergoing final selection. *(T.B.2)* In conjunction with CDC or other PHEMCE partners, the recently described botulism type “H” strain will be evaluated for sensitivity to the currently approved BAT as well as to appropriate candidate monoclonal antibodies. *(T.B.3)* Following FDA approval of the BAT product in 2013, including for use in pediatric patients, BARDA will continue work with the product sponsor, CDC, and FDA on satisfying Phase 4 post-marketing requirements.

Mid- and Long-Term (FY17 and beyond)

(T.B.4) Presuming successful testing of the next-generation serotype A and serotype B&E monoclonal antibody cocktails, serotypes A, B, and E will be combined into one product by NIH to investigate the effectiveness of a cocktail that would address more than 95% of naturally occurring botulism. *(T.B.5)* BARDA will support the advanced development of the next-generation monoclonal antibody product(s) as they become eligible for transition from NIH to ensure that the MCM meets the PHEMCE requirement for a large-scale foodborne scenario.

RADIOLOGICAL AND NUCLEAR THREATS

PHEMCE programmatic priorities for radiological and nuclear threats include:

- Elucidating mechanisms of radiation injury at the system, organ, cell, and molecular levels, with special focus on the hematopoietic, gastrointestinal, immune, pulmonary, renal, skin, neurological, and vascular systems
- Identifying and characterizing MCM approaches to minimize the short- and long-term adverse health effects of radiation exposure, including cytokines, growth factors, anti-apoptotics, anti-inflammatory agents, and antioxidant candidates, as well as products with other novel mechanisms of action
- Emphasizing candidates that have routine medical/clinical indications and can be administered effectively under current or anticipated CONOPs
- Developing definitive-care treatments for thermal burns, as well as providing incentives, through public-private partnerships, for companies developing thermal burn and other nuclear and radiological exposure treatments to continue commercial development while meeting civilian emergency preparedness requirements

Near-Term (FY15-16)

(T.RN.1) The PHEMCE will conduct market analyses on antimicrobials and other products needed to respond to the public health and medical consequences of radiological or nuclear threats. These analyses will include gap analyses and determination of market capacities to inform strategic national stockpiling.

Medical Countermeasures for ARS and the Delayed Effects of Acute Radiation Exposure (DEARE)

NIH has identified more than 75 candidate MCMs in the early discovery phase for hematopoietic ARS. NIH has also identified more than fifteen candidates in the early discovery phase for gastrointestinal ARS and more than five candidates in the early discovery phase for the treatment of pulmonary radiation injuries. *(T.RN.2)* These candidates will continue to be evaluated and developed toward IND submission. Successful candidates will be identified that can move forward to BARDA for potential advanced development.

(T.RN.3) BARDA will support evaluation of a number of commercial drugs for repurposing to enable use in the treatment of exposure to radiological and nuclear agents, ensuring that at-risk population needs are considered. *(T.RN.4)* BARDA will also support the advanced research and development of novel compounds for PEP and treatment of blood, gastrointestinal, lung, and skin exposures from radiological and nuclear insults.

(T.RN.5) ASPR, with the support of VA, will conduct exercises to pilot different cytokine distribution and dispensing models to address ARS-associated neutropenia. *(T.RN.6)* ASPR

has conducted, and will continue to conduct, user engagements to determine the needs of the end-users and their ability to administer products after an incident.

Thermal Burn Therapeutics

(T.RN.7) BARDA will assess results from the current proof-of-concept studies for promising candidates for thermal burn injuries and continue to support the development of thermal burn definitive care products.

Decorporation and Blocking Agents

(T.RN.8) NIH will explore new decorporation agents for radionuclides of current interest and explore candidate MCMs that increase the mucociliary clearance of particulates from the lung. *(T.RN.9)* BARDA will continue to support advanced research and development of Prussian blue dosage forms appropriate for children under the age of two years. *(T.RN.10)* The PHEMCE will complete a re-evaluation of the existing armamentarium of decorporation and blocking agents in light of the current Integrated Terrorism Risk Assessment to determine whether additional research and development of novel MCMs is warranted. *(T.RN.11)* The PHEMCE will also annually re-evaluate the prioritization, with the PHEMCE Prioritization Framework, of resources to support additional national radiobioassay capabilities that would be critical to informing the appropriate use of decorporation agents following a radiological incident.

Mid-Term (FY17-FY18)

Medical Countermeasures for ARS and DEARE

(T.RN.12) NIH will continue to evaluate additional candidates for hematopoietic ARS, gastrointestinal ARS, and pulmonary radiation injuries in rodent and non-human primate animal models, and in IND-enabling studies. Successful candidates will be identified that can move forward to BARDA for potential advanced development. *(T.RN.13)* Rodent and NHP animal models are being further developed and will be submitted to the FDA for qualification, for use under the Animal Rule, to be used as available models for the adequate and well-controlled animal efficacy studies.

Long-Term (FY19 and beyond)

In the long term, BARDA will emphasize achieving regulatory approval of MCMs for use in treating injuries from radiation exposure.

Medical Countermeasures for ARS and DEARE

BARDA will work to maintain the current inventory of anti-neutropenic products for the SNS and work toward procurement of additional products as they mature to address other sub-syndromes of DEARE. Using appropriate animal models, BARDA will support studies to obtain additional data to support pre-EUA applications and ultimately regulatory approval for these products.

Decorporation and Blocking Agents

BARDA will monitor programs under development at NIH to determine if and when they may be eligible for transition to BARDA.

CHEMICAL THREATS

The HHS PHEMCE chemical programmatic priorities include:

- Developing *in vitro* and animal models for efficacy screening of novel therapeutics
- Developing MCMs for the treatment of injuries caused by exposure to chemical threats, with an emphasis on products that can be administered effectively under current or anticipated CONOPs
- Maintaining public-private partnerships with companies developing chemical agent treatments

Near- and Mid-Term (FY15-18)

(T.C.1) In the near-term the PHEMCE is developing an approach to prioritize chemical agents from the DHS Chemical TRA for MCM research, development, and procurement efforts. *(T.C.2)* NIH is supporting investments against classical chemical agents (e.g., nerve agents and vesicants), and toxic industrial chemicals (TICs). Included are compounds that can damage the nervous system, respiratory tract, skin, mucous membranes, and other organs. *(T.C.3)* Other research thrusts include more effective and more easily administered MCMs against cyanide.

(T.C.4) BARDA and DoD are supporting advanced development of promising anticonvulsants, such as midazolam, as potential replacements for diazepam for the treatment of nerve agent-induced seizures. *(T.C.5)* BARDA will continue to support the ARD of novel compounds for treatment or PEP following exposure to chemical agents, including patient decontamination solutions for use on intact or injured human skin.[95] *(T.C.6)* BARDA will also evaluate commercially available drugs using animal models to determine if their approved use can be expanded to the treatment of chemical exposures. *(T.C.7)* In addition, BARDA will continue to support the regulatory approval process for products treating injuries due to exposure to chemical agents. *(T.C.8)* The DoD will conduct clinical trials to evaluate the effectiveness of its Improved Nerve Agent Treatment System (INATS). INATS is intended to replace the current Antidote Treatment -– Nerve Agent, Auto-Injector (ATNAA). It is being developed to be more efficacious, requiring fewer treatments than ATNAA, and to be effective against a broader range of nerve agent threats. *(T.C.9)* The DoD will also continue advanced development of its Bioscavenger, a novel prophylactic treatment against the effects of nerve agents.

[95] More information on patient decontamination efforts is described in the Capabilities-Based Approaches section below as a non-pharmaceutical MCM.

Long-Term (FY19 and beyond)

NIH will focus research efforts on highly toxic chemicals of greatest public health concern. This will include an emphasis on TIC exposures, such as industrial chemicals and pesticides. Planned activities include: (1) integrating research of potential products into evolving standards of emergency care; (2) assessing products already approved for use in the US for applicability to chemical casualty care; (3) assessing products from military applications for civilian use; and (4) developing and/or improving medical diagnostic tests and assays to detect the presence of specific chemicals or their metabolites in bodily fluids.

BARDA will support the advanced research and development of novel compounds for PEP and treatment following exposure to chemical agents. Emphasis will be placed on achieving regulatory approval of products for use in treating injuries due to chemical agent exposures. BARDA will also support the repurposing of commercial products approved for other uses for potential use as treatments for exposure to chemical agents.

SECTION 5: CAPABILITIES-BASED APPROACHES

The PHEMCE is increasingly emphasizing programs that will provide more flexible and sustainable capabilities over the long term. This is best reflected in the promotion of technologies that have more than one application, and/or of infrastructures that can be rapidly adjusted to surge to new demands and respond to new threats. This evolution is highly dependent on early-stage research and early identification of biotechnologies that may already be applied in routine product development. NIH and DoD programs on platform technologies and broad-spectrum approaches are thus key to fueling this early pipeline. Similarly, efforts underway at BARDA and DoD are critical in advancing the nation's capability to build and sustain a flexible manufacturing and development infrastructure, as well as in identifying products that may be repurposed or altered to meet PHEMCE needs. In addition to the many cross-cutting capabilities described in Section 1 with respect to the strategic goals and objectives they address, this section highlights several specific examples of these capabilities-based approaches.

BROAD-SPECTRUM ANTIMICROBIALS

(C.A.1) NIH and BARDA are continuing to expand their broad-spectrum antimicrobial programs to address both biothreat indications and the more general public health concern of antimicrobial resistance. BARDA currently supports six different programs and has utilized the OTA authority provided under the PHS Act to partner with a large pharmaceutical company in the development of novel antimicrobial drugs. In 2014 the White House announced an effort to combat antimicrobial resistance in bacteria, and multiple PHEMCE partners are participating in those discussions to ensure that PHEMCE priorities and efforts align with these recommendations. *(C.A.2)* The Executive Order, "Combatting Antibiotic-Resistant Bacteria" (Sept.18, 2014), specifically calls upon BARDA, in addition to targeting biodefense threats, to

develop new and next-generation countermeasures that target antibiotic-resistant bacteria that present a serious or urgent threat to public health.

CBRN DIAGNOSTICS

PHEMCE programmatic priorities for CBRN diagnostics include:

- Developing both high-throughput and POC diagnostics that will inform the use of MCMs for the treatment of conditions or diseases caused by radiological agents, biological pathogens, or chemical agents/toxins
- Developing platform technologies that offer the capacity for a multiplexed capability, so that as additional threats are encountered, they can be seamlessly integrated into existing systems
- Developing and advancing diagnostic policies to prevent, detect, and control public health security threats from CBRN agents

Near-Term (FY15-16)

(C.D.1) NIH and BARDA will continue support for the development of biological agent diagnostic systems, chemical agent diagnostic systems, and systems to identify and characterize unknown threats, including development of assays and instrumentation to address PHEMCE requirements for high-throughput and POC usage. *(C.D.2)* NIH will also work in conjunction with FDA to define alternative methodologies for the generation of requisite datasets for specific threat agents for which traditional clinical specimens are insufficient to support approval.

(C.D.3) BARDA will fund development of biodosimetry assays and devices and integrate the development of both POC and high-throughput biodosimetry assays with commercial off-the-shelf (COTS) diagnostic instrumentation to achieve high-throughput biodosimetry diagnostic systems. The programs to date have moved from proof-of-concept to biomarker feasibility and some have developed prototype devices. *(C.D.4)* BARDA will continue working with the developers to ensure they partner, where possible, with manufacturers of existing platforms. *(C.D.5)* BARDA will also work closely with interagency partners to develop an appropriate stockpiling strategy for each product and transition candidates to procurement as they mature.

(C.D.6) In collaboration and coordination with CDC and with support from other agencies (i.e., FDA, Federal Bureau of Investigation, BARDA), DHS will develop highly sensitive, specific, and robust Public Health Actionable Assays for high-priority biological threat agents (i.e., bacterial, viral, and toxins) for deployment and employment through the CDC LRN to support rapid detection, diagnosis, event characterization, and epidemiological investigations. These assays may serve as the confirmatory assays for public health actions and decisions.

DoD will continue support for two diagnostics programs in the near term; the Joint Biological Agent Identification and Diagnostic System (JBAIDS) and the Next Generation Diagnostics System (NGDS) Increment 1. The JBAIDS program has eight pre-EUA data packages for *in*

vitro diagnostic (IVD) assays that can be deployed in the event of a health emergency for the identification of low probability, high consequence pathogens in clinical samples. *(C.D.7)* Additional pre-EUA assays for Pan-Burkholderia and Ebola Bundibugyo will be developed for JBAIDS by FY16. The JBAIDS also has surveillance kits to detect anthrax and smallpox in the environment as well as an FDA-approved IVD anthrax kit.

The NGDS system is meant to provide chemical, biological and radiological diagnostic capabilities that are suitable for use as far forward as possible, dependent upon the availability of medical manpower and treatments, to maximize patient outcomes and inform the use of force health protection countermeasures. *(C.D.8)* DoD will develop FDA-approved IVD capabilities for anthrax and smallpox as part of the NGDS Increment 1 platform. *(C.D.9)* DoD will also develop an environmental assay for smallpox as part of this platform.

Mid-Term (FY17-18)

(C.D.10) NIH will develop reference profile panels of threat agents that will support generation of requisite datasets required for approval of a next-generation diagnostic platform.
(C.D.11) CDC will develop and validate additional radionuclide bioassay diagnostic tests to allow rapid detection and measurement of radionuclides in clinical specimens. The goal is to develop a suite of assays capable of rapidly detecting the radionuclides identified by an HHS-led interagency workgroup as most likely to be used in radiological terrorism. These assays can be used to identify who was internally contaminated in an incident, and to assess the need for, and efficacy of, decorporation therapies.

(C.D.12) NGDS Increment 1 will replace the JBAIDS diagnostic platform starting in FY17. NGDS Increment 1 improvements over JBAIDS include: 1) availability of FDA-approved COTS assays with military utility (e.g., Respiratory and Blood Culture Identification panels), the screening capability to simultaneously interrogate one specimen for multiple different analytical targets (i.e., up to 30 targets) in one run, and a robust COTS IVD Assay Pipeline (Gastrointestinal, Meningococcal, Sexually Transmitted Infections, and Tropical Disease panels).

Long-Term (FY19 and beyond)

In the long term, BARDA will support activities that include development, implementation, agency approval, manufacturing preparation, and appropriate stockpiling for CBRN diagnostic systems, including both assays and instrumentation, for identifying and characterizing unknown threats in both high-throughput and POC systems.

NGDS Increment 2 is being developed by the DoD to expand the breadth of chemical, biological, radiological, infectious disease, and emerging disease agent diagnostics to support those diseases/toxins that are not able to be detected with NGDS Increment 1. It will provide potential far-forward capability to rapidly process and analyze remotely collected human clinical samples with FDA-approved immunoassay diagnostic systems and qualified assays for diagnostic and surveillance applications.

DHS and CDC will develop highly sensitive, specific and robust Public Health Actionable Assays for moderate to high-priority biological threat agents (i.e., bacterial, viral (including Ebola Virus Disease), and toxins) for deployment and employment through the CDC LRN.

NON-PHARMACEUTICAL MEDICAL COUNTERMEASURES

Near-Term (FY15-16)

Respiratory Protective Devices (RPDs)

(C.NP.1) CDC certifies RPDs and maintains a "Trusted Sources Webpage" so that informed RPD selection decisions can be made.[96] *(C.NP.2)* To shepherd new respirators to market that meet the standards of both FDA and the National Institute for Occupational Safety and Health (NIOSH), VA will continue to chair an interagency effort known as Project BREATHE (Better Respiratory Equipment using Advanced Technologies for Healthcare Employees). *(C.NP.3)* In addition, CDC will strengthen RPD design, use, testing, and certification for the occupational setting. *(C.NP.4)* The PHEMCE will also reassess the quantity and composition of respiratory protective device (RPD) stockpiles for pandemic influenza and other threats, taking fiscal constraints into account, to determine whether the stockpiling of RPDs in the SNS should be continued. If so, the PHEMCE will develop RPD stockpiling goals for critical infrastructure and key resources personnel. *(C.NP.5)* In addition, beginning in the near-term and extending beyond 2018, CDC will conduct research to better understand influenza transmission and determine when the use of N95 respirators or other devices may be more appropriate.

Mechanical Ventilators

(C.NP.6) BARDA will identify opportunities to promote ventilator standardization and interchangeable components.

Patient Decontamination

(3.2.13) A national planning guidance for conducting mass patient decontamination in a chemical incident, an effort co-led by HHS and DHS, was published in December 2014. *(C.NP.7)* HHS and DHS will begin work with appropriate organizations to integrate the planning guidance into emergency response training curricula.

Mid-Term (FY17-18)

Respiratory Protective Devices

(C.NP.8) CDC will work with standard-setting organizations to incorporate health care worker RPDs research project findings on improving respirator compliance, comfort, and tolerability into

[96] See http://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/RespSource.html

industry and consensus standards. *(C.NP.9)* HHS will develop systems to monitor the safety, effectiveness, and shortages of RPDs after deployment.

Mechanical Ventilators

(C.NP.10) CDC will reassess strategies for distributing SNS ventilators to the states to help ensure federal assets will be used equitably.

Long-Term (FY19 and beyond)

Respiratory Protective Devices

CDC will fund research to better understand benefits of using re-usable respirators in the health care setting.

CENTERS FOR INNOVATION IN ADVANCED DEVELOPMENT AND MANUFACTURING

PHEMCE programmatic priorities for the CIADMs include:

- Expanding the nation's domestic ability to respond rapidly and nimbly to bioterrorism threats, pandemic influenza, and other emerging infectious disease threats
- Providing experienced biopharmaceutical developers to aid CBRN MCM developers, resulting in a more robust, timely, and successful product development pipeline and stockpile
- Incorporating innovative technologies that will provide a more efficient model for MCM product development relative to cost and time
- Providing domestic manufacturing surge capacity for pandemic influenza vaccine[97]

Near-Term (FY15-16)

(C.CIADM.1) BARDA will support completion of the construction of critical infrastructure within the CIADMs. It is anticipated that some of these centers may have limited capability to provide certain advanced development and manufacturing core services during this time frame, if required by the USG. The Centers will provide MCM development and manufacturing capabilities to address public health threats as needed. *(C.CIADM.2)* The Centers will also be initiating the activities required for the licensing of pandemic influenza vaccine candidates, including in-licensing as needed, and process development related to the eventual technology transfer of the candidate into the facility. (*C.CIADM.3*) BARDA will also support, through the CIADM governance board, the issuance, evaluation, and task orders for advanced development and manufacturing core services as programs flow from HHS and DoD programs. *(C.CIADM.4)* BARDA will support activities towards licensure of pandemic influenza vaccine candidates in the

[97] For more information, see https://www.medicalcountermeasures.gov/barda/core-services/ciadm.aspx

CIADMs and will provide for the appropriate framework to maintain a state of readiness in the event of a pandemic or other national public health emergency. *(C.CIADM.5)* Center academic partners will offer advanced training for the next generation of biotechnology workers.

Mid-Term (FY17-18)

BARDA will continue to provide assistance to CBRN MCM developers through the CIADM governance board.

Long-Term (FY19 and beyond)

The CIADMs will continue to support advanced development of CBRN MCM candidates, as needed from HHS and DoD development programs.

CROSS-CUTTING CAPABILITIES

The PHEMCE has developed a range of capabilities that could address multiple potential national health security threats, as well as the multiple PHEMCE goals and objectives. This subsection summarizes some of these cross-cutting capabilities; many of these are described in greater detail in Section 1 with respect to the strategic goals and objectives they address.

PHEMCE programmatic priorities for Product Development Core Services include:

- Developing a suite of preclinical and advanced development core service capabilities to improve the efficiency of public-private partnerships in delivering needed MCMs
- Qualifying an array of animal models to support product development under the Animal Rule
- Building and maintaining a world-class workforce of subject matter experts in the management of clinical trials, clinical medicine, regulatory and quality affairs, pharmacology and toxicology, manufacturing and bioprocessing, analytic decision support, and modeling

As described in greater detail in previous sections, NIH and BARDA provide a range of core services in support of MCM development and manufacturing. *(C.CC.1)* As part of these core services, NIH will continue to maintain its Vaccine and Treatment Evaluation Units (VTEUs) for vaccine testing capacity during clinical trials in support of public health emergencies. NIH will also continue to manage the Concept Acceleration Program, which is designed to accelerate development of promising MCMs.

BARDA, in conjunction with NIH, will support the development of new animal models for *Burkholderia*, tularemia, ARS, and other threats as needed. *(C.CC.2)* BARDA will also establish an Innovation Hub to provide analytic decision support and access to real-time modeling capabilities to senior decision-makers within ASPR and the PHEMCE. BARDA has already established core services for non-clinical evaluation, CIADMs, a Fill-Finish network, and a Clinical Studies network that are complementary to the core services established at the NIH.

BARDA will continue to adapt its business model and its provision of core services to complement the capabilities and strengths of its private sector partners, reducing redundant efforts and streamlining the product development pathway.

In the mid-term, NIH, BARDA, and FDA will expand the number of qualified animal models, focusing on models for the highest-priority threats and those needed for maturing product development initiatives. BARDA will fully integrate the provision of core services into its public-private partnerships, adapting increasingly flexible models of partnership to expedite product development and facilitate long-term strategic relationships. NIH's infrastructure services will continue to provide appropriate *in vitro* and *in vivo* testing for candidate MCMs, especially those requiring adequate biocontainment facilities, as well as product-specific services, in support of overall anti-infective development capabilities.

FDA plays a critical role in supporting the MCM mission from discovery through development to deployment and use. As described under Goal 2, FDA works with PHEMCE partners to identify and resolve regulatory and scientific challenges that impede MCM development and use across all PHEMCE priorities. Through its MCMi, FDA has established multidisciplinary Public Health and Security Action Teams to identify and help resolve regulatory and scientific challenges for high-priority MCMs and related technologies; an MCM Regulatory Science Program to build the science base necessary to support MCM development and regulatory assessment; and a policy team that works to ensure that FDA laws, regulations, and policies adequately support MCM development, distribution, and use. FDA also works directly with both individual product developers and the MCM development community to clarify regulatory requirements and provide scientific and technical expert review of MCM product applications, with the ultimate goal of approving MCMs. In addition, FDA fosters preparedness and effective, timely responses to public health emergencies with MCMs that are available but not yet FDA-approved for the intended use through a variety of regulatory mechanisms that allow for emergency use of such products. *(C.CC.3)* FDA and BARDA are also working on developing a matrix to determine high-priority programs for inclusion in the Regulatory Management Plan mandated under the Federal Food, Drug, and Cosmetic Act, as amended by PAHPRA.[98]

CDC maintains several cross-cutting capabilities that can be drawn upon to help guide the best use of MCMs, provide MCMs in a timely manner and reduce the adverse health impacts during an emergency. CDC's scientific expertise and core laboratory science, epidemiology, and surveillance functions provide public health authorities with timely, accurate, and interpretable information that enables health officials to make informed decisions – such as placement and use of MCMs, and social distancing measures – needed for saving lives and protecting the public.

(C.CC.4) Within CDC there is a core laboratory capacity to detect, identify, confirm, and quantify the vast majority of the high-priority biological, chemical, and radiological threat agents. *(C.CC.5)* In addition, CDC manages the LRN, a group of local, state, federal, and international

[98] 21 U.S.C. 360bbb-4.

laboratories with unique testing capabilities for detecting high-priority biological and chemical threat agents. LRN labs play a critical role in our nation's ability to detect, characterize, and communicate confirmed threat agents.

(C.CC.6) CDC also supports some 280 surveillance-related activities to monitor and assess the population's health, including ILINet, and PulseNet, which may help authorities detect and characterize or confirm an attack. In addition, CDC supports the development, evaluation, and improvement of state and local capabilities for MCM distribution and dispensing through programs providing guidance, training, exercise, and evaluation for MCM preparedness and response functions.

Finally, the DSNS maintains partnerships for priority access to ground and air transportation to deliver medicines and supplies for state and local emergency response. Similarly, CDC's Vaccines for Children (VFC) infrastructure offers a mechanism for ordering and shipping routine childhood vaccines as well as pandemic influenza vaccine to health departments and other vaccine providers in the event of a disease outbreak.

The DoD's cross-cutting initiatives that support the PHEMCE include laboratory facilities located both within and outside the contiguous US *(C.CC.7)* and a soon-to-be-established advanced development and manufacturing (ADM) facility. The ADM facility, when fully established, will support the manufacture, advanced testing, and evaluation of MCMs against agents of interest. The capability will be able to work cooperatively with analogous facilities established by HHS. Current DoD laboratory capabilities include dedicated space to conduct studies at all biological safety levels; facilitate the discovery, early development, and testing of vaccines, therapeutics, and diagnostics and the associated relevant animal models for the evaluation of new MCMs; and provide the infrastructure and personnel to characterize emerging chemical and biological threats.

(C.CC.8) The DoD has embarked on a long-term stewardship effort to maintain its MCM capabilities and is currently refurbishing its chemical and biological flagship laboratories. These efforts, critical to DoD, are also integral to the nation by providing a sustained set of assets and scientific expertise necessary for MCM development. Specifically, the DoD is establishing a dedicated BSL-4 laboratory capable of conducting tests that meet GLP requirements and evaluation of MCMs, and is also investing in state of the art laboratory facilities. The overall cooperative efforts between HHS and DoD with regard to advanced development and manufacturing provide an agile and responsive capacity for the nation to manufacture MCMs. *(C.CC.9)* Along with MCM development, the DoD continues to develop programs such as biosurveillance and support of diagnostics to aid the interagency in the use of MCMs to protect the population.

CONCLUSION

This *2014 PHEMCE Strategy and Implementation Plan* identifies the top priorities and projected timelines for federal MCM research, development, acquisition, stockpiling, distribution, dispensing, and monitoring programs, as well as initiatives that HHS has determined, in collaboration with interagency partners throughout the PHEMCE, will make the best use of existing resources to improve public health emergency preparedness and advance national health security. ASPR has established the necessary management processes and tools to track, monitor, and evaluate execution of these priorities. Periodic updates will continue to be provided through the PHEMCE governance structure, and annually, as appropriate, to external stakeholders. This tracking system will facilitate accountability, foster coordination, and identify and address potential challenges in pursuit of these important goals and objectives.

APPENDIX 1: ACRONYMS

ABA	American Burn Association
ACF	Administration for Children and Families
ACIP	Advisory Committee on Immunization Practices (CDC)
ACOG	American Congress of Obstetricians and Gynecologists
ADM	advanced development and manufacturing
AMCG	Office of Acquisition Management, Contracts, and Grants (ASPR)
AMT	Anthrax Management Team (CDC)
ARD	advanced research and development
ARS	acute radiation syndrome
ASPR	Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officials
BAA	broad agency announcement
BARDA	Biomedical Advanced Research and Development Authority
BEI	Biodefense and Emerging Infections
BIO	Biotechnology Industry Organization
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BREATHE	Better Respiratory Equipment using Advanced Technologies for Health Care Employees
BSC	Board of Scientific Counselors
BSL	biosafety level
CAP	Concept Acceleration Program (NIH)
CBR	chemical, biological, and radiological
CBRN	chemical, biological, radiological, and nuclear
CDC	Centers for Disease Control and Prevention
CERC	Crisis and Emergency Risk Communication
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CHILD	Children's HHS Interagency Leadership on Disasters
CIADM	Centers for Innovation in Advanced Development and Manufacturing
CNAS	Center for a New American Security
CONOP	concept of operation
COTS	commercial off-the-shelf
CRI	Cities Readiness Initiative
CRO	Clinical Research Organization
CY	calendar year
DARPA	Defense Advanced Research Projects Agency
DDT	Drug Development Tool (FDA)
DEARE	delayed effects of acute radiation exposure
DHS	Department of Homeland Security
DHSP	Division of Health System Policy (ASPR)

DLG	Disaster Leadership Group (ASPR)
DoD	Department of Defense
DSNS	Division of the Strategic National Stockpile (CDC)
DTRA	Defense Threat Reduction Agency (DoD)
EEC	Enterprise Executive Committee (PHEMCE)
EID	emerging infectious disease
ESC	Enterprise Senior Council (PHEMCE)
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency (DHS)
FMS	Federal Medical Station
FY	fiscal year
GABA	gamma aminobutyric acid
GHSI	Global Health Security Initiative
GLP	Good Laboratory Practices
HBAT	heptavalent botulinum antitoxin
HCCPP	Healthcare Coalition Checklist for Pandemic Planning
HHS	Department of Health and Human Services
HPP	Hospital Preparedness Program
IAA	interagency agreement
ICD	integrated capabilities document
IDSA	Infectious Diseases Society of America
IGSP	Influenza Genome Sequencing Project
IND	Investigational New Drug
IP	implementation plan
IPT	integrated program team (PHEMCE)
IRAT	Influenza Risk Assessment Tool (CDC)
IV	intravenous
IVD	in vitro diagnostic
JPEO-CBD	Joint Program Executive Office for Chemical and Biological Defense (DoD)
LRN	Laboratory Response Network
MCM	medical countermeasure
MCMi	Medical Countermeasures Initiative (FDA)
MCMSI	medical countermeasure strategic investor
MDR	multi-drug resistant
MERS-CoV	Middle East Respiratory Syndrome coronavirus
MOA	memorandum of agreement
MOU	memorandum of understanding
MSA	metropolitan statistical area
MTA	material threat assessment
MTD	material threat determination
MVA	modified vaccinia Ankara
NACCHO	National Association of County and City Health Officials
NAPAPI	North American Plan for Animal and Pandemic Influenza

NBSB	National Biodefense Science Board
NCBI	National Center for Biotechnology Information
NCDMPH	National Center for Disaster Medicine and Public Health
NDA	new drug application
NGO	non-governmental organization
NHSS	National Health Security Strategy
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NPM	National Postal Model
ODASD(CBD)	Office of the Deputy Assistant Secretary of Defense for Chemical and Biological Defense
OEM	Office of Emergency Management (ASPR)
OGA	Office of Global Health Affairs (HHS)
OPHPR	Office of Public Health Preparedness and Response (CDC)
OPP	Office of Policy and Planning (ASPR)
OPT	Office of Pediatric Therapeutics (FDA)
ORR	Operational Readiness Review
OTA	other transactional authority
PAC	Portfolio Advisory Committee
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act
PBS	Project BioShield
PCT	project coordination team (PHEMCE)
PedsOB IPT	Pediatric and Obstetric Integrated Program Team (PHEMCE)
PEP	post-exposure prophylaxis
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PHEP	Public Health Emergency Preparedness
PI	pandemic influenza
PK	pharmacokinetics
POC	point of care
POD	point of dispensing
PPE	personal protective equipment
PREA	Pediatric Research Equity Act
PSR	product-specific requirement
PTCI	Portfolio Tracking and Coordination Initiative
Quad-MCMC	Quadrilateral Medical Countermeasures Consortium
RAC	Regional Area Council
RDD	radiological dispersal device
REC	Regional Emergency Coordinator (ASPR)
RFA	request for applications
RMP	Regulatory Management Plan
rPA	recombinant (anthrax) protective antigen
RPD	respiratory protective device

RR	research requirement
SBA	scenario-based analysis
SIP	Strategy and Implementation Plan
SLEP	Shelf Life Extension Program
SLTT	state, local, tribal, and territorial
SNS	Strategic National Stockpile
SRF	Special Reserve Fund (Project BioShield)
TAR	Technical Assistance Review
TBD	to be determined
TELL	Training, Exercises and Lessons Learned (ASPR)
TETS	tetramethylenedisulfotetramine
TIC	toxic industrial chemical
TRA	Terrorism Risk Assessment
TRL	Technology Readiness Level
UASI	Urban Areas Security Initiative
US	United States
USC	United States Code
USDA	Department of Agriculture
USG	United States Government
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VIGIV	Vaccinia Immune Globulin Intravenous
VMI	vendor-managed inventory
VTEU	Vaccine and Treatment Evaluation Unit
WG	working group
WHO	World Health Organization

APPENDIX 2:
PHEMCE ORGANIZATIONAL STRUCTURE

In July 2006, HHS established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE or Enterprise). The PHEMCE's mission is to advance national preparedness against CBRN and EID threats, including pandemic influenza, by coordinating MCM-related efforts within HHS and in cooperation with interagency PHEMCE partners. The forum for cooperation and overall mission fulfillment is the Enterprise Senior Council (ESC) and its supporting infrastructure (Figure 1). Structurally, the ESC is led by the ASPR and comprised of the senior leadership of NIAID, CDC, and FDA with comparable senior level representatives from DoD, DHS, VA, and USDA. Additional HHS components participate in a non-voting capacity, including the Office of the General Counsel, Office of the Assistant Secretary for Health, Office of the Assistant Secretary for Legislation, and the Office of the Assistant Secretary for Planning and Evaluation. The PHEMCE activities are organized and governed using the hierarchy shown in Figure 1.

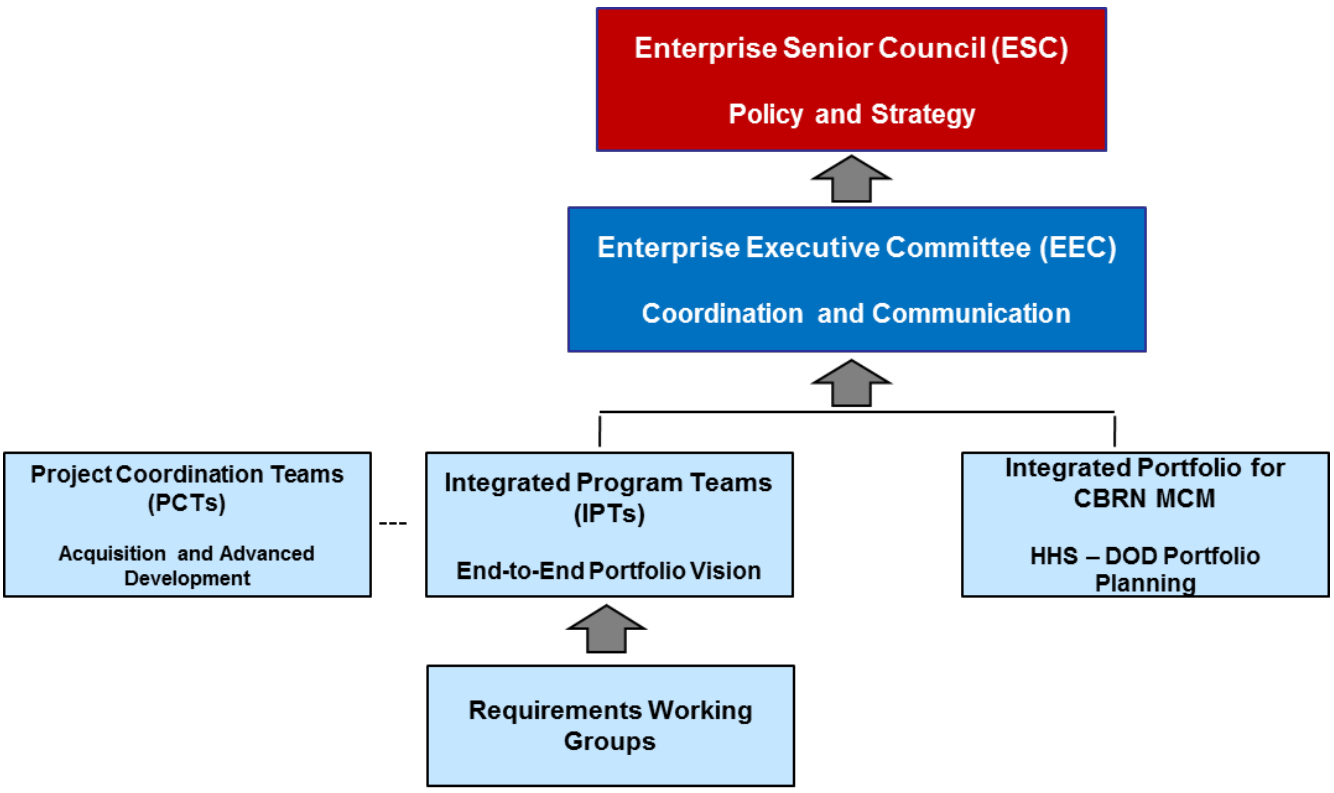

Figure 1. PHEMCE Governance Structure

Enterprise Senior Council (ESC) – It is the mission of the ESC to provide, on behalf of the HHS Secretary, coordinated, strategic direction and policy oversight for HHS "end-to-end" MCM preparedness activities, defined as requirements generation, research, early- and late-stage product development, procurement, and utilization planning activities for all threats including CBRN, pandemic influenza, and EID. The ESC is a consensus interagency body chaired by the HHS ASPR, as the HHS Secretary's principal advisor on federal public health and medical preparedness and response for public health emergencies. The HHS principal members are the Director of the CDC, the Director of the NIAID within the NIH, and the Commissioner of the FDA. The principal interagency members are the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs, Office of the Under Secretary of Defense for Acquisition, Technology, and Logistics from DoD; the Assistant Secretary for Health Affairs and Chief Medical Officer from DHS; the Assistant Secretary for Operations, Security, and Preparedness from VA; and the Undersecretary for Food Safety from USDA. As the most senior level in the PHEMCE structure, this group provides recommendations to the HHS Secretary, approves major policies, MCM requirement quantities (i.e., need-based quantity, operational quantity, stockpiling goal), and large-scale procurement actions. It also oversees strategic reviews of the activities in each of the major threat portfolios (e.g., anthrax, smallpox, radiological/nuclear) and is the final reporting body for high-priority actions identified as gaps in these reviews.

Enterprise Executive Committee (EEC) – The EEC is an operational-level decision and coordination body for all policy and product-level issues in the Enterprise. The EEC is comprised of senior program managers across the partner agencies. It provides the critical interface and organizing capability between the strategic focus of the ESC and the tactical-level efforts conducted within the subordinate IPTs and Working Groups (WGs). The EEC reports directly to, and receives guidance from, the ESC. The Executive Committee is co-chaired by two senior management officials appointed by the ASPR. The EEC is composed of senior staff from each PHEMCE agency selected by the ESC members. The EEC is responsible for assuring that important programmatic, procurement, requirements, and portfolio actions are fully vetted and that the solutions and recommended actions requiring approval at higher levels are well delineated for decisions. Additionally, the EEC manages the work at the lower IPT and subgroup levels, directly manages the annual assessment of the SNS, and composes PHEMCE-level documents, such as this SIP.

Integrated Program Teams (IPTs) – The IPTs provide an end-to-end vision of MCMs against a particular threat type (e.g., anthrax, smallpox) or capability (e.g., diagnostics) that ranges from requirements-setting (i.e., stockpiling targets and product characteristics) through to stockpiling, delivery and dispensing, and monitoring and evaluating MCM effectiveness. The IPTs develop strategies for addressing key cross-cutting issues, in consideration of available programmatic resources at the federal and SLTT levels. IPTs serve as subject matter expert communities of practice for interagency vetting and input on issues within their purview. They report to the EEC.

Requirements Working Groups (WGs) – The Requirements WGs are established by the EEC to assist the IPTs in determining which types of MCMs are needed for response to public health

emergencies and other threats to national health security. The WGs provide their products to the appropriate IPT(s) for further development and/or passing along to the EEC.

Project Coordination Teams (PCTs) – PCTs are established by the BARDA Director to support the development and administration of each MCM acquisition or advanced development program managed by BARDA.

Integrated Portfolio for CBRN Medical Countermeasures/Portfolio Advisory Committee (PAC) – The PAC seeks to maximize national preparedness to respond to CBRN threats by aligning HHS and DoD MCM development and related infrastructure resources. The PAC reports to the EEC. The activities of the PAC enhance intra- and inter-departmental collaboration in CBRN MCM development, establish a shared understanding of each agency's programmatic requirements, and develop an integrated set of goals. The PAC is co-chaired by the BARDA Principal Deputy Director and by the Medical Director of the Office of the Deputy Assistant Secretary of Defense for Chemical and Biological Defense (ODASD(CBD)).

Specific PHEMCE mission components – and organizations with lead responsibilities and capabilities in these areas – are depicted in Figure 2[99], which shows the complex interconnectedness of the PHEMCE organizations and mission space.

[99] While capabilities from across the PHEMCE are utilized in many of these areas, the organizations with lead responsibility in particular areas are specifically depicted here.

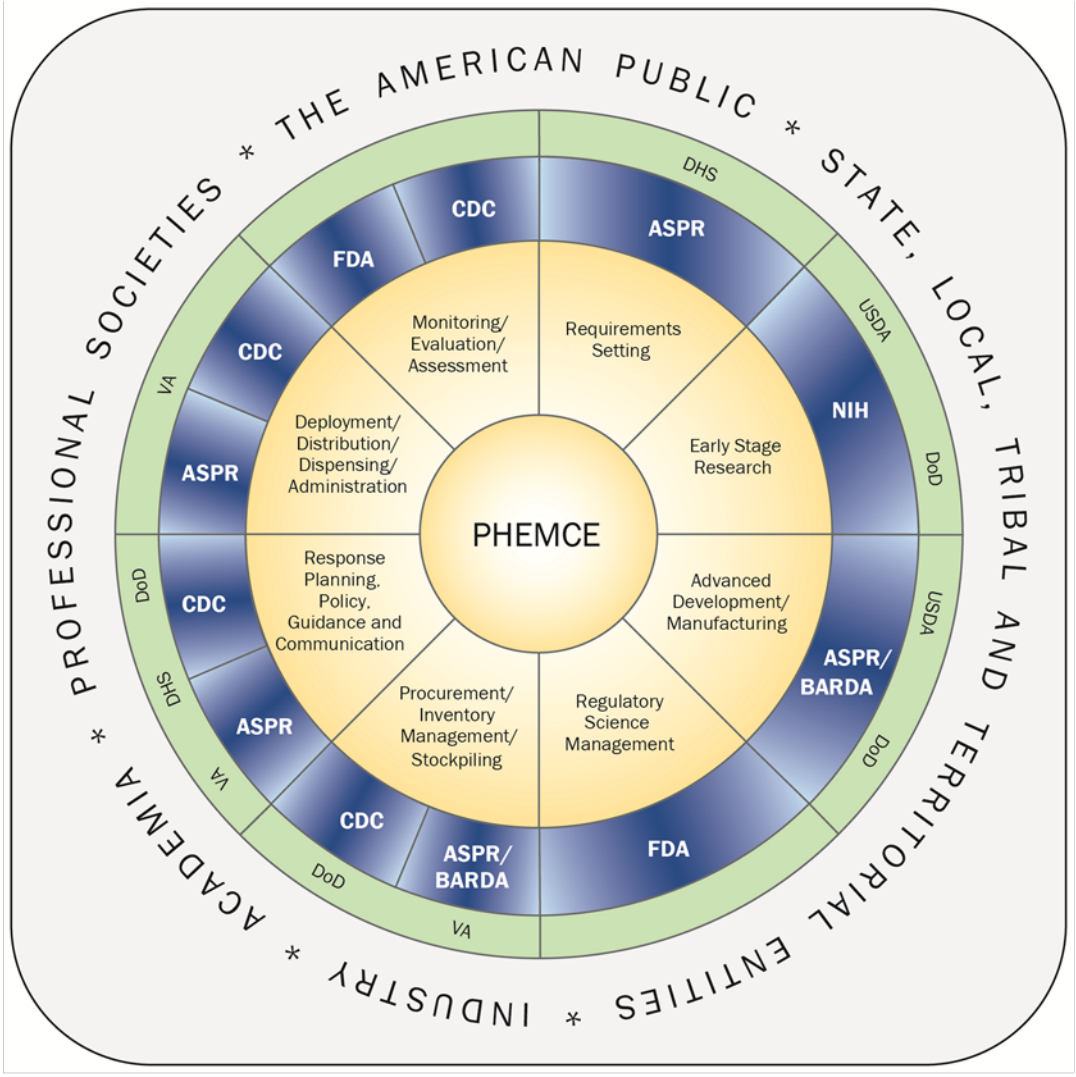

Figure 2: PHEMCE Agency Lead Roles

Key

- PHEMCE Mission Components
- HHS PHEMCE Agencies
- Non-HHS PHEMCE Agencies
- Non-Federal Stakeholders

Acronyms

PHEMCE: Public Health Emergency Medical Countermeasures Enterprise
DHS: Department of Homeland Security
DoD: Department of Defense
USDA: U.S. Department of Agriculture
VA: Department of Veterans Affairs
HHS: Department of Health and Human Services
ASPR: Assistant Secretary for Preparedness and Response
BARDA: Biomedical Advanced Research & Development Authority
CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
NIH: National Institutes of Health

APPENDIX 3:
PROGRESS IN ADDRESSING AT-RISK POPULATION MEDICAL COUNTERMEASURE NEEDS

Since the release of the *2012 PHEMCE Strategy* and *Implementation Plan*, significant progress has been made in addressing the MCM needs of at-risk populations. As required by section 2811(d) of the PHS Act[100] selected highlights of this progress are listed below.

Table 5. Progress in Addressing At-Risk MCM Needs

PHEMCE Mission Component[101]	Progress
Advanced Development / Manufacturing	• BARDA is supporting the development of a safe and effective pediatric dosage form of Radiogardase® (Prussian blue) for treatment of children younger than two years of age following radiation poisoning with radioactive cesium and/or radioactive or non-radioactive thallium. • BARDA is supporting the development of a low-cost, portable ventilator that will be suitable for neonate, infant, and pediatric populations. • BARDA supported clinical studies to evaluate the safety and immunogenicity of adjuvanted and antigen-alone pandemic influenza vaccines in both pediatric and elderly populations. • NIH established the Pediatric Trials Network in 2010 to create an infrastructure to study critical drugs and diagnostic devices in children with the goal of improving their labeling for pediatric use. The Network plans to conduct 16 trials over the next five years that might enhance pediatric labeling. • NIH and FDA manage the implementation of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), which address obstacles that hinder the adequate study and labeling of drugs and biologics for the pediatric population and identify and prioritize drugs needing study. As a result of these efforts, more than 425 drug labels have been revised with important pediatric information. • NIH, BARDA, and DoD funded clinical studies to support a seizure (i.e., status epilepticus) pediatric indication for midazolam, which would include pediatric use. DoD also funded animal model studies to test midazolam's efficacy against nerve agent-induced seizures. These studies are intended to support FDA approval of a midazolam auto-injector for both children and adult populations, as well as approval of midazolam for use in treating common prolonged seizures. • NIH's National Institute of Child Health and Human Development launched several studies to obtain additional doxycycline pharmacokinetic data to support improved dosing recommendations for the treatment of *Bacillus anthracis* spore exposure in young children, including palatability studies for crushing and mixing antibiotics.

[100] 42 U.S.C. 300hh-10(d)
[101] As listed in the *2012 PHEMCE Strategy*

	• NIH supported chart reviews and clinical trials of influenza antivirals in neonates that led to Emergency Use Authorization by FDA of oseltamivir for use in children under one year of age during the 2009 pandemic and subsequently led to FDA full approval of oseltamivir for use in children down to 2 weeks of age. • NIH has supported trials of pandemic and seasonal influenza vaccines in at-risk populations.
Regulatory Science Management	• FDA expanded the approved use of the influenza antiviral Tamiflu® (oseltamivir) to treat children as young as two weeks old who have shown symptoms of influenza for no longer than two days. • In December 2012, FDA approved Raxibacumab, under the Animal Rule, to treat inhalation anthrax in combination with appropriate antibacterial drug(s) as well as to prevent inhalation anthrax when alternative therapies are not available or not appropriate, including in pediatric populations. • FDA established a Pediatric and Maternal Public Health and Security Action Team through its MCMi. Among its activities, this group worked with CDC to complete an inventory of the SNS to identify data gaps that could inhibit the effective use of stockpiled MCMs in children and other at-risk individuals. • In March 2013, FDA approved Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine) to treat adult and pediatric patients showing signs of botulism following exposure to botulinum neurotoxin. • FDA held a meeting of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee to discuss ethical issues in pediatric product development, including MCMs.[102] • FDA held a public workshop on *Complex Issues in Developing Medical Devices for Pediatric Patients Affected by Rare Diseases*. • In April-May 2012, FDA held a public workshop[103] on *Development of Animal Models of Pregnancy To Address Medical Countermeasures for Influenza in the 'At Risk' Population of Pregnant Women: Influenza as a Case Study*, which provided a forum to carefully consider scientific issues related to selecting animal models for use in evaluating anti-influenza drugs that may be given during pregnancy. Specifically, the workshop addressed experimental design issues in selecting the most appropriate animal model that mimics human pregnancy.
Procurement / Inventory Management / Stockpiling	• Subject matter experts determined and prioritized pediatric MCM gaps in the SNS as part of the 2012 and 2013 SNS Annual Reviews. These recommendations were considered as part of the annual HHS budget formulation process. • CDC established a child health team and procured pediatric doses of influenza antivirals for the SNS.
Deployment / Distribution / Dispensing / Administration	• The US Public Health Service Commissioned Corps established a Pediatric Care Coordinator for emergency responses and includes pediatric specialists on its Rapid Deployment Force teams. • CDC funded the National Center for Birth Defects and Developmental

[102] For more information, see http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm367054.htm
[103] https://www.signup4.net/public/ap.aspx?EID=FDAA10E&OID=50

Disabilities to spearhead an initiative to coordinate CDC activities related to children's preparedness and response.

- CDC translated doxycycline fact sheets into 56 languages (i.e., other than English) to assist with mass dispensing to non-English speaking populations.
- CDC worked with FDA to simplify and enhance clarity on the doxycycline crushing instructions and dosing to further ease administration of this MCM at the time of an emergency.
- CDC created an instructional video to supplement the doxycycline crushing instructions to provide families another way to comply with anthrax post-exposure prophylaxis recommendations. The video is currently being revised pursuant to the simplified dosing strategies referenced above.
- CDC held a meeting in March 2014, to outline allocation strategies in the event of MCM and critical care resource shortages during a mass exposure anthrax incident and develop resultant clinical guidance. Meeting attendees included significant pediatric medicine representation.
- The CDC's Children's Preparedness Team worked with the American Academy of Pediatrics to formalize clinical guidance for the treatment and prophylaxis of children against anthrax.
- CDC incorporated expanded pediatric content into SNS mass antibiotic dispensing courses for state and local health departments.
- The CDC Anthrax Management Team (AMT) was established to better coordinate and integrate preparedness and response activities for anthrax related issues.[104] The AMT has a Pregnant and Postpartum Women Team that focuses on how approaches to prophylaxis and treatment for anthrax may require modification due to the unique needs of pregnant women.
- Data from seasonal and pandemic influenza show that pregnant women are at increased risk for influenza-associated complications. The importance of collaborations among experts in influenza, vaccine safety, vaccine coverage, and reproductive and infant health has increased in recent years. CDC created the Influenza and Pregnancy Collaborative Workgroup in support of its various activities related to influenza prevention and treatment among pregnant women. The Workgroup meets quarterly to promote coordination at CDC regarding issues related to influenza and pregnancy.
- CDC conducted a systematic review[105] of antibiotic safety and pharmacokinetics (PK) in pregnant and lactating women for antimicrobials recommended for anthrax prophylaxis and treatment.
- CDC has held four anthrax-related meetings: the first on clinical management (October 2011), the second on anthrax antitoxin and PEP (March 2012), the third to specifically address pregnant, post-partum, and newborn issues (August 2012), and the fourth to develop pediatric clinical guidelines (November 2012). The third outreach meeting focused on the integration of the needs of pregnant and post-partum women into the nation's overall capability for anthrax MCMs. Participants included state and

[104] CIDRAP and the University of Minnesota Online. Accessed 12/27/12. http://www.cidrap.umn.edu/cidrap/content/bt/bioprep/news/sep0711prepared.html
[105] http://www.ncbi.nlm.nih.gov/pubmed/24084549

	local officials, academicians, the American Congress of Obstetricians and Gynecologists (ACOG), as well as officials from the DHS and DoD. The effort responded to one of the high-priority action items that emerged from the ASPR-led MCM portfolio review process. The final guidance was published in October 2013.[106]
Partner efforts	• The new National Advisory Committee on Children and Disasters convened on August 8, 2014.

Additionally, the PHEMCE has coordinated with the FDA Office of Pediatric Therapeutics (OPT) through FDA's Pediatrics and Maternal Action Team that includes members from OPT and that works to identify and address the needs of pediatric and maternal populations. This Action Team is assessing MCMs in the SNS to identify outstanding issues that may prevent or impede their availability and usability for the pediatric population during public health emergencies. The Action Team will work with the PHEMCE's PedsOB IPT to develop action steps to address the gaps identified in the analysis.

OPT also works closely with the FDA review divisions to help facilitate the development and availability of MCMs for pediatric populations. For example, OPT works with FDA scientists and reviewers to provide regulatory advice and guidance to product developers and PHEMCE partners to assure that children are only enrolled in clinical studies that are both scientifically necessary and ethically appropriate and that any pediatric studies conducted for MCMs are rigorously designed and conducted in accord with current scientific understanding of issues such as exposure-response and extrapolation.

[106] http://www.ncbi.nlm.nih.gov/pubmed/24084549

APPENDIX 4:
STRATEGIC ALIGNMENT[107]

Table 6. Strategic Alignment with Other Strategic Documents

PHEMCE Goals	PHEMCE Mission Components[108]	HHS Strategic Plan[109]	Secretary's Strategic Initiatives[110]
Goal 1: Identify, create develop, manufacture, and procure critical medical countermeasures	Requirements	Goal 2: Advance Scientific Knowledge and Innovation, Objective A: Accelerate the process of scientific discovery to improve health	Accelerate the Process of Scientific Discovery to Improve Health
Goal 2: Establish and communicate clear regulatory pathways to facilitate medical countermeasure development and use.	Regulatory Science Management	Goal 2: Advance Scientific Knowledge and Innovation, Objective C: Advance the regulatory sciences to enhance food safety, improve medical product development, and support tobacco regulation	Accelerate the Process of Scientific Discovery To Improve Health
Goal 3: Develop logistics and operational plans for optimized use of medical countermeasures at all levels of response	Procurement / Inventory Management / Stockpiling; Response Planning, Policy, Guidance, and Communication; Deployment / Distribution / Dispensing / Administration; Monitoring / Evaluation / Assessment	Goal 3: Advance the Health, Safety, and Well-being of the American People, Objective F: Protect Americans' health and safety during emergencies, and foster resilience to withstand and respond to emergencies	Protect Americans' Health and Safety during Emergencies, and Foster Resilience in Response to Emergencies

[107] Future iterations of the *PHEMCE SIP* will include alignment with the 2014 National Health Security Strategy following its release.
[108] As detailed in the *2012 PHEMCE Strategy*
[109] HHS Strategic Plan FY 2014 – 2018; available at http://www.hhs.gov/strategic-plan/priorities.html
[110] Available at http://www.hhs.gov/strategic-plan/priorities.html

PHEMCE Goals	PHEMCE Mission Components[111]	HHS Strategic Plan[112]	Secretary's Strategic Initiatives[113]
Goal 4: Address medical countermeasure gaps for all sectors of the American population	Requirements Setting; Early Stage Research; Advanced Development / Manufacturing; Regulatory Science Management; Procurement / Inventory Management / Stockpiling; Response Planning, Policy, Guidance, and Communication; Deployment / Distribution / Dispensing / Administration; Monitoring / Evaluation / Assessment	Goal 1: Strengthen Health Care, Objective E: Ensure access to quality, culturally competent care, including long-term services and supports, for vulnerable populations; Goal 2: Advance Scientific Knowledge and Innovation, Objective A: Accelerate the process of scientific discovery to improve health and Objective C: Advance the regulatory sciences to enhance food safety, improve medical product development, and support tobacco regulation; Goal 3: Advance the Health, Safety, and Well-being of the American People, Objective F: Protect Americans' health and safety during emergencies, and foster resilience in response to emergencies	Eliminate Health Disparities; Accelerate the Process of Scientific Discovery To Improve Health; Protect Americans' Health and Safety during Emergencies, and Foster Resilience in Response to Emergencies

[111] As detailed in the *2012 PHEMCE Strategy*
[112] HHS Strategic Plan FY 2014 – 2018; available at http://www.hhs.gov/strategic-plan/priorities.html
[113] Available at http://www.hhs.gov/strategic-plan/priorities.html

APPENDIX 5:
NEAR-TERM DELIVERABLES

This table summarizes near-term deliverables, identified in this *Strategy and Implementation Plan*, which are projected at the time of this writing for completion by the end of fiscal year 2016.

Table 7. Near-Term Deliverables

2014 Activity Number	Milestone Description	Lead Agency	Projected Completion Date
1.1.2	Submit 2014 Multi-Year Budget report to Congress	ASPR	FY15
1.1.3	Implement PHEMCE-wide portfolio tracking tools to further enable coordinated planning and management of CBRN MCM development	ASPR	FY15
1.1.6	Develop measures for the PHEMCE preparedness goal framework	ASPR	FY14[114]
1.1.7	Interagency IPTs will implement the framework and associated metrics to assess current and target levels of MCM preparedness against five preparedness determinants	ASPR	FY16
1.2.1	Update initial anthrax MTA	DHS	FY15
1.2.3	Coordinate modeling efforts to ensure that the models and parameters are consistent to bring the TRAs and MTAs into alignment in support of MCM planning	BARDA / DHS	FY16
1.2.4	Update the TRA development process in accordance with the *TRA Stakeholder Engagement Strategy*	DHS	FY15
1.2.5	Produce a TRA program implementation plan	DHS	FY16
1.2.9	Lead development of a risk assessment methodology and process through which the PHEMCE will determine which EID threats require PHEMCE response	ASPR	FY16
1.2.11	Develop or update MCM requirement documents for CBRN threats, as well as requirements that address multiple threats, as detailed in Objective 1.2, Table 2	ASPR	FY16

[114] This has been completed

2014 Activity Number	Milestone Description	Lead Agency	Projected Completion Date
1.3.5	Make awards under a BAA entitled *Targeting Therapeutics Development to Relieve Bottlenecks in Translational Research*	NIH	FY15
1.3.6	In CY15 NIH plans to release a BAA entitled "Development of Therapeutic Medical Countermeasures for Biodefense and Emerging Infectious Diseases" with awards to be made in FY16.	NIH	FY16
1.3.8	Re-evaluate the medical consequences of the threat posed by radiological dispersal devices (RDDs) and develop recommendations for further research, development, and procurement of MCMs to address these threats	BARDA	FY16
1.3.10b	Acquire or maintain critical medical countermeasures as detailed in Table 4	BARDA / CDC	FY14
2.1.7	Update the 2007 *Guidance on the Emergency Use Authorization of Medical Products* to be consistent with the amendments to FDA's EUA authorities under PAHPRA	FDA	FY16
3.1.1	Submit to Congress the SNS Annual Review report	HHS	FY14-FY16
3.1.2	Develop a risk-based analysis of investment needs by using perspectives from the intelligence community and DHS risk assessment processes	CDC / DHS	FY15
3.2.6	Implement a new method of reviewing state and local MCM operational readiness through the use of the Operational Readiness Review (ORR), which replaces the legacy Technical Assistance Review (TAR) assessment tool	CDC	CY14
3.2.9	Develop national response strategies for anthrax (FY15), botulism, glanders and melioidosis, and smallpox	ASPR / CDC	FY16
3.2.10	Develop clinical practice guidelines for MCMs to address chemical agents, smallpox, anthrax, and botulism	ASPR / CDC	FY16
3.2.11	Develop an assessment of state and local capacity to utilize cytokines for ARS-associated neutropenia following use of an improvised nuclear device	ASPR / CDC	FY15
3.2.13	Develop planning guidance for patient decontamination in a mass exposure chemical incident	ASPR / CDC	FY15
3.2.15b	The PHEMCE, through collaboration with finance, budget, and contract management partners, will identify strategies to accelerate the MCM-related administrative decision-making processes	ASPR	FY16

2014 Activity Number	Milestone Description	Lead Agency	Projected Completion Date
3.2.29	Work with Canada and Mexico to address barriers to providing mutual assistance and harmonizing utilization policies for MCMs during international public health emergencies under the framework of the US-Canada Beyond the Border Initiative, and as called for in the North American Plan for Animal and Pandemic Influenza	ASPR	FY16
3.3.3	Update the Crisis and Emergency Risk Communication (CERC) manual and materials as needed, coordinate sponsored training for government leaders and partners, and maintain a trained cadre of people able to give CERC trainings	CDC	FY15
4.2.1	Develop rodent and porcine juvenile models of ARS	NIH / BARDA / DoD	FY16
4.2.6	Support efforts to achieve FDA approval (in healthy populations) for a smallpox vaccine that is ultimately intended for use in immunocompromised individuals in an emergency	BARDA / CDC	FY16
4.3.9	The PedsOB IPT will work with ASPR on incorporating at-risk individual needs into the new HHS All-Hazards Plan and threat-specific annexes that outline key options and actions to aid the HHS Secretary and the ASPR in making necessary decisions in an emergency	ASPR	FY16
T.A.1	Publish anthrax clinical guidance for use in the general population during a mass casualty event	CDC	FY16
T.A.2	Complete human clinical Phase 2 testing of adjuvants that could enhance performance of the approved anthrax vaccine and reduce the doses necessary to achieve full immunity in a post-exposure setting.	NIH	FY15
T.A.4	Work with the anthrax vaccine manufacturer to support research into dose-sparing strategies for PEP vaccine use	NIH / CDC / FDA / BARDA	FY15
T.A.7	Obtain results from preliminary studies into various technologies for temperature stabilization and alternative routes of delivery for next-generation anthrax vaccines	NIH	FY15
T.A.12	FDA review of animal model studies to support approval under the Animal Rule for use against inhalation anthrax of antimicrobials currently approved for other indications	NIH / FDA	FY15
T.OB.2	Qualify animal efficacy models for anthrax, plague, and tularemia in support of PEP and treatment indications, through the FDA's Animal Model Qualification Program	NIH / BARDA	FY16

2014 Activity Number	Milestone Description	Lead Agency	Projected Completion Date
T.OB.8	Initiate the testing of candidate products against *Burkholderia pseudomallei* and *Burkholderia mallei*	BARDA	FY16
T.S.2	Publish the National Smallpox Vaccine Response Strategy, which will offer guidance on domestic vaccination strategies, as well as vaccine selection and prioritization for select subgroups, in an emergency triggered by a confirmed clinical case of smallpox.	CDC / ASPR	FY16
T.S.3	Address the needs for replacement of expiring doses of the currently approved smallpox vaccine, ACAM2000, and of the stockpile of VIGIV to treat adverse events resulting from smallpox vaccination, as well as developing contingency activities to ensure stockpile maintenance	CDC / ASPR	FY16
T.S.6	Complete delivery to the SNS of the required treatment courses of the smallpox antivirals currently under contract	BARDA	CY14
T.PI.3	Develop mechanisms to further integrate social media and other communication tools into preparedness activities	CDC	FY16
T.PI.5	Develop procedures to ensure that public information in future pandemics is provided in accessible and alternative formats	CDC	FY16
T.PI.6	Refine and implement partnership strategies to improve communication with hard-to-reach and at-risk populations	CDC	FY16
T.PI.8	Develop an approach, definitions, tools, and models for a risk communication response plan	CDC	FY16
T.PI.10	Assess the current policy for the pre-pandemic influenza vaccine stockpiles, including the adjuvant stockpile, and guidance for their use	CDC / BARDA	FY16
T.PI.11	Maintain and update the existing stockpile of novel influenza viruses and pre-pandemic vaccines and adjuvants as needed	BARDA	FY16
T.PI.12	Develop rapid methods and biosynthetic technologies to produce candidate vaccine viruses that allow accelerated production of vaccine lots for eventual fill and finish by manufacturers	CDC / BARDA / FDA	FY16
T.PI.13	Develop rapid laboratory methods to expedite testing to determine the antigen content of influenza vaccine bulk material and enable vaccine formulation prior to product fill and finish	CDC/ FDA/BARDA	FY16
T.PI.14	Develop a consensus working definition of a “universal influenza vaccine”	ASPR	FY16

2014 Activity Number	Milestone Description	Lead Agency	Projected Completion Date
T.PI.16	Move at least one universal influenza vaccine candidate into Phase 1 clinical trials	NIH / BARDA	FY16
T.PI.19	Initiate support of one or two promising influenza vaccines through the BAA funding mechanism	BARDA	FY16
T.PI.22	Implement plan for production of high yielding/immunogenic influenza vaccine strains for distribution to manufacturers and use of the improved potency assays to assist in vaccine development for seasonal and pandemic influenza	BARDA	FY16
T.PI.26	BARDA will support advanced development of at least two drugs with novel mechanism(s) of action through Phase 3 clinical studies; two drugs could be approved for use in the US in this timeframe	BARDA / FDA	FY16
T.PI.27	NDA filing for a small molecule, broad-spectrum anti-viral targeting pandemic and seasonal influenza	DoD	FY16
T.PI.28	Develop new plans for antiviral distribution and dispensing	CDC	FY16
T.PI.31	Commence development of new sequencing-based diagnostic assays and prototype device development for detection of influenza viruses and other respiratory pathogens	CDC / BARDA	FY16
T.OV.1	Move broad-spectrum antiviral candidates into clinical testing	NIH	FY16
T.OV.5	Make additional awards for vaccine candidates based on supplemental funding.	BARDA	FY16
T.OV.10	The pivotal ZMapp preclinical safety data supported by NIAID will be available in February 2015 to allow for a NIAID-supported Phase 1 trial to begin in the first quarter of 2015.	NIH	FY15
T.OV.11	ZMapp is also expected to be included in the master randomized control trial (RCT) protocol expected to begin in the U.S. and West Africa in early 2015.	NIH	FY15
T.OV.14	Advance Ebola candidate vaccines to Phase 2/3 efficacy testing	NIH / DoD	FY16
T.OV.21	Favipiravir, and another potential therapeutic, Tekmira, may undergo Phase 2 trials in West Africa in early 2015	DoD	FY16
T.B.1	NIH will continue to evaluate a collection of next-generation botulism antitoxin monoclonal antibodies. Botulism serotype B&E cocktails will be in Phase 1 trials during this period. Serotypes C&D may also advance to clinical testing during this period. Serotype F&G candidates are undergoing final selection.	NIH	FY16

2014 Activity Number	Milestone Description	Lead Agency	Projected Completion Date
T.B.2	Evaluate botulism type "H" strain for sensitivity to the currently approved BAT as well as appropriate candidate monoclonal antibodies	NIH	FY16
T.RN.1	Conduct market analyses on antimicrobials and other products needed to respond to the public health and medical consequences of radiological or nuclear threats	HHS	FY16
T.RN.5	Conduct exercises to pilot different cytokine distribution and dispensing models to address ARS-associated neutropenia	ASPR / VA	FY16
T.RN.6	Conduct user engagements to determine the needs of the end-users and their ability to administer products after an incident	ASPR	FY16
T.RN.10	Complete a re-evaluation of the existing armamentarium of decorporation and blocking agents in light of the current Integrated Terrorism Risk Assessment to determine whether additional research and development of novel MCMs is warranted.	BARDA / NIH	FY16
T.RN.11	Re-evaluate (annually) the prioritization, with the PHEMCE Prioritization Framework, of resources to support additional national radiobioassay capabilities that would be critical to informing the appropriate use of decorporation agents following a radiological incident	CDC	FY15-16
T.C.1	Develop an approach to prioritize chemical agents from the DHS Chemical TRA for MCM research, development, and procurement efforts	ASPR	FY16
C.D.2	Define alternative methodologies for the generation of requisite datasets for specific threat agents for which traditional clinical specimens are insufficient to support approval	NIH / FDA	FY16
C.D.6	Develop highly sensitive, specific, and robust Public Health Actionable Assays for high-priority biological threat agents (i.e., bacterial, viral, and toxins) for deployment and employment through the CDC LRN	DHS / CDC	FY16
C.D.7	Develop additional pre-EUA assays for JBAIDS for Pan- Burkholderia and Ebola Bundibugyo	DoD	FY16
C.D.8	Develop FDA-approved IVD capabilities for anthrax and smallpox as part of the NGDS Increment 1 platform	DoD	FY16
C.D.9	Develop an environmental assay for smallpox as part of the NGDS Increment 1 platform	DoD	FY16
C.NP.4	Reassess the quantity and composition of RPD stockpiles for pandemic influenza and other threats, taking fiscal constraints into account, to determine whether the stockpiling of RPDs in the SNS should be continued	CDC / ASPR	FY16
C.NP.7	Begin work with appropriate organizations to integrate the patient decontamination planning	HHS / DHS	FY16

2014 Activity Number	Milestone Description	Lead Agency	Projected Completion Date
	guidance into emergency response training curricula		
C.CIADM.1	BARDA will support completion of the critical infrastructure within the CIADMs. It is anticipated that these centers will have limited capability to provide certain advanced development and manufacturing core services during this time frame, if required by the USG.	BARDA	FY16
C.CIADM.2	Centers will initiate the activities required for the licensing of pandemic influenza vaccine candidates, including in-licensing as needed, and process development related to the eventual technology transfer of the candidate into the facility	BARDA	FY16
C.CC.2	Establish an Innovation Hub to provide analytic decision support and access to real-time modeling capabilities to senior decision-makers within ASPR and the PHEMCE	BARDA	FY16
C.CC.3	Develop a matrix to determine high-priority programs for inclusion in the Regulatory Management Plan mandated under PAHPRA	FDA / BARDA	FY16
C.CC.7	Establish an MCM advanced development and manufacturing facility	DoD	FY16

APPENDIX 6:
ADVANCED RESEARCH AND DEVELOPMENT AND PROCUREMENT:
PAST AND CURRENT FUNDING

Advanced Research and Development and Procurement Contracts

Per the requirements of the PHS Act, the advanced research, development, and procurement contracts awarded since the passage of PAHPRA, and those costs associated with replenishment of the SNS holdings are summarized by threat below.

Table 8a. Advanced Research and Development Contracts

Threat Area	Time from Submission to Award	Current Award Amount[115]($M)	Benchmarks / Milestones
Anthrax	--	-	--
Botulism	--	-	--
Broad-Spectrum Antimicrobials	• Solithromycin development (Cempra) – 6 months • Portfolio of new antimicrobials (GSK) – 6 months • BAL 30072 development (Basilea) – 7 months • Carbavance (TM) development (Rempex) – 7 months	17.7 40.0 16.8 19.8[116]	Data to support potential use during an emergency and transition to procurement as product achieves this milestone
Chemical	--	-	--

[115] This is reported from March 2013 (at the time of passage of PAHPRA) through February 2014.
[116] BARDA obligated a total of approximately $19.8M in the initial award to Rempex. The award included funding for the base period of performance and the immediate exercise of one option. The contract includes another six options, which could bring the total contract value (including both the base period and all options) to $89.8M.

Diagnostics	• Anthrax diagnostic (MRI Global) – 18 months[117] • Deepview thermal diagnostic for burns (Spectral MD) – 7 months	1.6 2.4	Data to support potential use during an emergency and transition to procurement as product achieves this milestone
Influenza	--	-	--
Plague	--	-	--
Radiological / Nuclear	• Stratagraft for burns (Stratatech) – 11 months • NOAH ointment for burns (Novan) – 6 months • YEL002 for GI injury (BCN BioSciences) – 12 months • Magellan definitive thermal burn care (Arteriocyte) – 8 months • Regenerative medicine (Cellphire) – 6 months • Orbeshield for GI injury (Soligenix) – 7 months	9.9 7.9 4.0 11.9 11.0 10.7	Data to support potential use during an emergency and transition to procurement as products achieve this milestone
Smallpox	--	-	--
Total	--	152.5	--

[117] Awards were on hold until PHEMCE requirements were approved.

Table 8b. SRF[118] Procurement Contracts

Threat Area	Time from Submission to Award	Current Award Amount[115] ($M)	Benchmarks / Milestones
Anthrax	• Anthrax antitoxin replenishment (Elusys) – 12 months	0	• Potential to increase preparedness and support approval of the product
	• Anthrax antitoxin replenishment (Emergent) – 12 months	0	• Cell bank establishment as risk mitigation
	• Anthrax antitoxin replenishment (PharmAthene) – 12 months	1	• Cell bank establishment
	• Anthrax antitoxin replenishment (GSK) – 12 months	197	• Maintain antitoxin preparedness at current levels and risk mitigation
	• Anthrax antitoxin replenishment (Cangene) – 12 months	63	• Maintain antitoxin preparedness at current levels
Botulism	--	0	--
Broad-Spectrum Antimicrobials	--	0	--
Chemical	• Midazolam anticonvulsant (Meridian) – 7 months	61	• Dose delivery to SNS
Diagnostics	--	0	--
Influenza	--	0	--
Plague	--	0	--
Radiological / Nuclear	• G-CSF cytokine for neutropenia associated with	158	• Dose delivery to SNS

[118] Special Reserve Fund authorized under the Project BioShield Act of 2004.

	radiation exposure (Amgen) – 11 months • G-CSF cytokine for neutropenia associated with radiation exposure (Sanofi-Aventis) – 11 months	37	• Dose delivery to SNS
Smallpox	• MVA acquisition option (Bavarian Nordic) [119] – 11 months	110	• Dose delivery to SNS
Total	--	627	--

Table 8c: SNS[120] Procurement / Replenishment Contracts

Threat Area	Actual FY13 ($M)[121]	Actual FY14 ($M) [122]
Anthrax	277.5	243.9
Botulism	0	0
Burkholderia	0	0
Chemical	1.3	16.5
Influenza	0	9.64
Plague	29.7	0
Radiological/Nuclear	12.3	1.1
Smallpox	1	37.02

[119] Time to award is not applicable here as this was exercising an option on an existing contract.
[120] Strategic National Stockpile
[121] FY13 product procurement data is from the HHS PHEMCE Multiyear Budget Report (FY2014 – FY2018). Additional detail regarding this projected spending can be found in that Report (anticipated for release by early 2015).
[122] FY14 product procurement data reflects FY14 funding executed in FY14 from the Integrated Resources Information System (IRIS), CDC's financial system of record

Tularemia	0	0
FMS	0.06	0.7
Medical Supplies and Ancillary Items (MS&AI) and non-MS&AI[123]	1.1	21.5

Projected PHEMCE Funding by Threat Area

Cost projections associated with the research, development, procurement and stockpiling of priority MCMs over the next five years for use against CBRN threats and emerging infectious diseases will be captured in the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) Multiyear Budget Report. Specifically, this document will aggregate and analyze the MCM-related spending estimates of the National Institutes of Health (NIH), the Office of the Assistant Secretary for Preparedness and Response (ASPR), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA), as needed to support the following activities: basic research; advanced research and development; approval, clearance, licensure, and authorized uses of products; procurement, stockpiling, and stockpile maintenance; and development and funding of critical infrastructure to achieve these outcomes. The 2014 PHEMCE Multiyear Budget Report is anticipated for release in early CY15.

Project BioShield Special Reserve Fund

The annual appropriations amount provided in FY 2014 was $255M for Project BioShield, under the authorized $2.8B by PAHPRA amendments to the PHS Act. Pursuant to the Joint Explanatory Statement accompanying the FY 2009 Omnibus Appropriation (P.L.111-8), BARDA will continue to provide monthly reports to both the authorizing and appropriating committees detailing the expenditures of funds. These procurements are fully vetted through the PHEMCE leadership and are consistent with the annual *PHEMCE Strategy and Implementation Plan* goals and objectives.

[123] Medical Supplies and Ancillary Items (e.g., sutures, catheters, gloves, syringes) and non-MS&AI (e.g., gelpacks, temperature monitoring devices, shipping containers) include a wide variety of items which support multiple threat categories.

APPENDIX 7:
PROGRESS AGAINST SELECTED *2012 PHEMCE IP* ACTIVITIES
(AS OF FEBRUARY 27, 2014)

Table 9. Progress Against Selected *2012 PHEMCE IP* Activities (as of February 27, 2014)[124]

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
1.1.1	Lead PHEMCE partner agencies to define strategic end-states for all PHEMCE capabilities based on a clear description of the preparedness goals across the PHEMCE.	ASPR	FY13	COMPLETE - In July 2013, PHEMCE leadership agreed that the strategic end states (or "preparedness goals") for all PHEMCE capabilities should be the full ability to successfully provide needed MCMs to the affected population under the current SBA of need. The PHEMCE is now engaged in assessing current and target levels of preparedness for each class of MCMs against five preparedness determinants: operational capacity; research and development; manufacturing; procurement and stockpiling; and planning and CONOPs. This analysis will be used by PHEMCE leadership to inform resource prioritization to achieve a target level of preparedness.
1.1.3	Continue to evolve the multi-year budgeting initiative to more tightly link investments across NIH, ASPR, CDC, and FDA.	ASPR	Ongoing	ONGOING - First multi-year budget annual report anticipated for completion and delivery to Congress in early 2015.
1.1.4	Implement PHEMCE-wide portfolio tracking tools to further enable coordinated planning and management of CBRN MCM development.	ASPR	FY13	The PHEMCE-wide portfolio tracking tool for CBRN MCMs is under final development and is anticipated for completion in late 2014.
1.1.5	Consider expansion of the portfolio tracking tools to include pandemic influenza or other EID portfolios as needed.	ASPR	FY18	Discussions have been initiated regarding expansion of the portfolio tracking tools to include pandemic influenza or other EID portfolios as needed.

[124] Unless otherwise noted

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
1.1.7	Further develop, implement, and evaluate the PHEMCE prioritization framework through the improvement of a suite of analytic decision support and visualization tools and models.	ASPR	FY17	A comprehensive survey of available decision support and visualization tools and models was conducted. Next steps are ongoing of working to enhance the decision-making process by which PHEMCE leadership prioritizes resource allocations.
1.1.9	Further develop, implement, and evaluate the PHEMCE prioritization framework by assessing strengths and limitations of the framework components.	ASPR	FY17	This evaluation will commence in FY14-15 following completion of the preparedness goal framework and implementation by the IPTs.
1.2.1	Formalize roles, responsibilities, policies, and procedures for conducting the next generation of MTAs and TRAs.	DHS / HHS	FY13	COMPLETE – Strategies and implementation plans for conducting future MTAs and TRAs have been signed by DHS and HHS leadership.
1.2.2	Develop updated disease assessments based on refinements to available data sources and modeling methodologies.	BARDA	FY14	BARDA and CDC continue to work closely together on this task through the BARDA Analytic Decision Support Division.
1.2.4	Develop or update MCM requirements for CBRN threats, as well as requirements that address multiple threats, as detailed in Objective 1.2.	ASPR	FY14	The ASPR has signed 14 deliverables that support the civilian MCM requirements process, following concurrence by the ESC. These recommendations increased the US civilian preparedness to prevent or mitigate potential adverse health impacts of CBRN agents and pandemic influenza, by informing MCM research, advanced development, stockpiling, and utilization.
1.2.5	Develop or update MCM requirements for CBRN threats, as detailed in Objective 1.2.	ASPR	FY17	In process or pending.
1.2.6	Develop capabilities-based requirements that capture MCM needs in broad areas, with a strong emphasis on end-user needs for biological diagnostics, CBRN therapeutics, prophylaxis for biological	ASPR	FY14	In process.

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
	threats, and non-pharmaceutical MCM needs, such as ventilators and respirators.			
1.3.1	Focus on basic and translational research, and the expansion of research infrastructure and research resources.	NIH	Ongoing	ONGOING - FY13 BAA contracts awarded for three anti-microbials, one anti-influenza antiviral drug, and one anti-viral.
1.3.5	Develop candidates for a next-generation anthrax vaccine, broad-spectrum antiviral, influenza antiviral, and a next-generation influenza vaccine to the stage where they can be considered for advanced development support.	NIH	FY17	In 2012, a broad-spectrum, host-targeted influenza therapeutic was transitioned to BARDA. In addition, a smallpox antiviral was transitioned to BARDA. Other contracts are being tracked and BARDA is being advised of their readiness for transition.
1.3.7b	Acquire or maintain critical MCMs as detailed in Table 4 of the *2012 PHEMCE Implementation Plan*.	BARDA / CDC	FY13	DSNS - The only MCM programmed for procurement through DSNS funds that is not under contract at this time is nuclear agents – thermal burn therapeutics. PHEMCE recommendation regarding this acquisition is pending.
				COMPLETE SRF – All MCMs programmed for procurement through the SRF were completed by September 30, 2013, exhausting the original SRF appropriation.
1.3.7c	Acquire or maintain critical MCMs such as detailed in Table 4 of the *2012 PHEMCE Implementation Plan*.	BARDA / CDC	FY17	DSNS - Currently there are no planned procurements for cyanide antidotes or respiratory protective devices. Other projected procurements continue to be procured or maintained, as funding allows and as prioritized by the PHEMCE.
				BARDA - No change in priorities. BARDA will continue to emphasize maintaining the established capabilities and capacities established under Project BioShield through 2013 and adding new products to the SNS as they become mature enough and have generated the data set for the potential use of the products during an emergency under EUA.

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
1.4.1	Increase domestic vaccine and biological therapeutics manufacturing capacity.	BARDA	Ongoing	ONGOING - BARDA achieved licensure of a renovated manufacturing facility in Swiftwater, PA, and awarded three CIADM contracts. Work is ongoing to approve a new cell-based manufacturing facility.
1.4.4	Establish a CRO Network.	BARDA	FY15	COMPLETE - A network of five CROs was established in early 2014, which will design and conduct clinical studies needed to develop MCMs – drugs, vaccines, and diagnostic tests that help protect health against bioterrorism, pandemic influenza, and other public health emergencies.
2.1.2a1	Develop guidance for industry on developing multiplexed diagnostic devices.	FDA	FY14	COMPLETE - FDA has published a Draft Guidance for Industry and FDA Staff entitled *Highly Multiplexed Microbiological/Medical Countermeasure* in Vitro *Nucleic Acid Based Diagnostic Devices*. FDA also continues a collaboration with the DTRA and the NCBI to establish a publicly available, well-curated reference database that will be critical to developers seeking to validate their candidate multiplex *in vitro* diagnostic tests.
2.1.2b2	Develop guidance on establishing the performance of radiation biodosimetry devices.	FDA	FY14	FDA is working to facilitate the development and regulatory assessment of biodosimetry devices through holding workshops on regulatory science considerations for MCM radiation biodosimetry devices.
2.1.5	Develop a partners program to link FDA scientists with extramural partners to pursue cutting-edge regulatory science projects.	FDA	FY14	ONGOING - FDA works on an ongoing basis to link its scientists with extramural partners to facilitate MCM regulatory science. For example, FDA has established scientific partnerships with federal partners including the NIH, Defense Advanced Research Projects Agency (DARPA), DTRA, and NICBR. In addition, FDA links FDA scientists with extramural partners on an ad-hoc basis to inform external MCM science programs. FDA will continue to link its scientists with external partners and to establish collaborations as necessary to support MCM regulatory science.

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
2.2.1	FDA will assist in the clarification of regulatory pathways and reduction of regulatory challenges.	FDA	Ongoing	ONGOING - FDA holds formal meetings, as needed, at the request of product sponsors or applicants and requests for meetings are granted unless there is a substantive reason for denying the request. For example, in FY 2013, FDA held 94 formal meetings with MCM product sponsors or applicants. FDA continues to provide technical assistance to minimize risk during MCM manufacturing, including pre-approval inspections or site visits to ensure that manufacturing establishments are capable of adequately manufacturing products, and that submitted application data are accurate as well as conducting post-marketing current good manufacturing practices (cGMP) inspections for facilities that produce MCMs to ensure that these products were produced under cGMP and to help identify and resolve any issues that could potentially lead to a shortage due to manufacturing issues. In FY 2012 – FY 2013, FDA issued four draft guidance documents and three final rules directly related to, or applicable to, MCM policies or regulatory issues. In FY 2012 – FY 2013, FDA held 12 workshops and 11 Advisory Committee meetings on issues directly related to, or applicable to, MCMs.
2.2.2	BARDA and NIH will develop and qualify animal models through the new Animal Model Development Program, and perform efficacy evaluations in compliance with GLP requirements and testing of CBRN countermeasures in qualified animal models.	BARDA, NIH	Ongoing	ONGOING - NIH/NIAID is leading or collaborating on five infectious disease animal model qualification programs with FDA (i.e., three for anthrax, one for plague, and one for tularemia). NIH/NIAID also continues to develop additional animal models to support infectious disease MCM product development under the Animal Rule. NIH/NIAID has also expanded animal model testing facilities for the evaluation of products for hematopoietic and gastrointestinal ARS, including continued support for GLP facilities. BARDA continues to work with PHEMCE partners to submit the data for qualification of the added benefit model for anthrax antitoxins. BARDA also continues to support development of multiple animal models to evaluate products for ARS, smallpox, and *Burkholderia spp*.

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
2.2.3	BARDA subject matter experts will assist private-sector partners in the development of regulatory strategies, including the design and execution of pivotal animal studies and clinical studies, preparation of regulatory documentation, and strategic communication on regulatory issues.	BARDA	Ongoing	ONGOING - BARDA subject matter experts in regulatory submissions, clinical study design and execution, non-clinical study design and execution, and manufacturing continue to work with all manufacturers/sponsors under contract with BARDA. BARDA works with its partners to review documents prior to submission to the FDA to ensure the appropriate data is clearly presented. In addition, BARDA performs "audits" of subcontracted manufacturing facilities and contract research organizations. These audits are unofficial, but are intended to support better outcomes for any future official FDA audits.
3.1.1	Perform an annual review of the contents of the SNS to identify and prioritize formulary gaps and recommend additions or modifications.	ASPR	Annual	COMPLETED ANNUALLY – Both the 2012 SNS Annual Review (which provided recommendations for FY 2015) and 2013 SNS Annual Review (FY16 Plan) were completed on time
3.1.2	Develop a risk-based analysis of investment needs by using perspectives from the intelligence community and DHS risk assessment processes.	CDC / DHS	FY14	COMPLETE
3.1.7	Charge the NBSB and the BSC to: • Identify the anticipated responsibilities of the SNS in the year 2020 • Recommend approaches for meeting those responsibilities as efficiently as possible • Propose metrics for reporting program capability and informing improvement.	ASPR / CDC	FY13	COMPLETE - The NBSB and CDC/OPHPR/BSC developed a joint report addressing these questions, which was made available on the ASPR website in Fall 2013. CDC is currently developing a response to and plan for implementation of these recommendations, which will be presented at the next BSC meeting.
3.2.2	Use the lessons learned at all levels from previous incident responses to develop and share MCM response strategies, utilization	ASPR, CDC	FY17	• CDC has hosted various meetings and workshops in order to develop updated clinical guidance for anthrax MCMs for pediatrics, pregnant women, the general population, and under

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
	guidances, CONOPs, and clinical practice guidelines with end-users as appropriate.			mass casualty conditions. • CDC has also developed an anthrax vaccine prioritization strategy and collaboratively developed a smallpox vaccine utilization strategy. • Through the Training, Exercises and Lessons Learned (TELL) system, ASPR continues to apply lessons learned at all levels from previous responses for inclusion in the development of MCM response strategies and CONOPs plans. • ASPR, in collaboration with FEMA, is also leading regional Urban Areas Security Initiative (UASI) MCM planning efforts in all 10 regions and the National Capital Region with anticipated completion in 2015. This planning initiative develops operational plans from which the federal government will rapidly augment the capabilities of the affected area in response to a widespread aerosolized attack. Partners involved in this effort include, but are not limited to, state, local, and regional health departments, emergency management offices, public information offices and federal regional partners. • ASPR conducted clinical utilization guidance workshops to develop recommendations for health care professionals to utilize MCMs provided by the SNS for botulism and hematopoietic-acute radiation syndrome. These workshops gathered together subject matter experts from clinical and technical backgrounds to provide individual recommendations to the federal government that were considered in the development of clinical guidance documents. These guidances are expected to be released in 2015.
3.2.4	Establish a process to validate laboratory methods and enhance national capacity to rapidly test clinical specimens and determine who has been exposed to	CDC	FY17	COMPLETE - CDC validates laboratory methods according to guidelines developed by the LRN Technical Review Committee and FDA.

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
	biological agents.			
3.2.5	Develop rapid antimicrobial resistance testing to quickly identify agents that may be resistant to first-line MCMs in the SNS.	CDC / DHS / DoD	FY17	Rapid anthrax susceptibility tests against the first-line MCMs are anticipated for submission to the FDA in 2014. Additional susceptibility tests are in development for anthrax and the agents causing plague and melioidosis and are anticipated for submission to the FDA by 2016.
3.2.6a	Develop national smallpox vaccine and anthrax response strategies.	ASPR / CDC	FY13	An anthrax vaccine prioritization strategy was developed by CDC and approved by the PHEMCE in FY13. A national smallpox vaccine response strategy has been developed and should be final in FY15. The anthrax response strategy is now anticipated for finalization in FY15, to allow consideration of updated threat assessment and MCM requirements information.
3.2.6b	Develop clinical practice guidelines.	ASPR/CDC	FY14-17	Clinical practice guidelines for glanders and melioidosis were completed in FY12. Clinical guidance for anthrax MCMs for pediatrics, pregnant women, the general population, and under mass casualty conditions were completed by CDC in FY13-14. Smallpox, anthrax antitoxin, botulism, and ARS-associated neutropenia clinical practice guidelines are anticipated for FY14-15.
3.2.6c	Develop an assessment of state and local capacity to utilize cytokines for ARS-associated neutropenia following use of an improvised nuclear device.	ASPR / CDC	FY13	A workshop was held in May 2013 with appropriate state and local stakeholders. Final assessment under development with completion now anticipated in FY15.
3.2.6d	Develop a decision-making and planning guidance for dispensing models to meet the diverse needs of communities.	ASPR / CDC	FY14	CLOSED - CDC updated such guidance (entitled *Receiving, Distributing, and Dispensing Strategic National Stockpile Assets: A Guide for Preparedness*) and released this on their website in FY14
3.2.6e	Develop end-user handbook(s) for various stakeholders that will include: response strategies, MCM CONOPs, utilization	ASPR / CDC	Mid- to long-term	CLOSED - While the individual pieces of information listed here are being worked on, and tracked separately, there is no current effort underway to assemble this information in to a "handbook" due to the challenges involved in ensuring such a compilation would remain up-

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
	guidance, and clinical practice information.			to-date as the individual pieces were updated.
3.2.6f	Develop planning guidance for patient decontamination in a mass exposure chemical incident.	ASPR / CDC	FY13	Guidance has been drafted and posted in the Federal Register for public comment.
3.2.12	Develop and implement a strategic policy framework to respond to international requests for HHS public health emergency MCMs, and to accept assistance from foreign countries.	ASPR	FY14	COMPLETE - The *Policy Framework for Responding to International Requests for Public Health Emergency Countermeasures from the U.S. Department of Health and Human Services* has been cleared through all HHS stakeholders and established as the official policy by which the USG, through an interagency process, will receive, consider, decide, communicate, and respond to international requests for the sharing of public health emergency MCMs. This Framework establishes the International Sharing of Medical Countermeasures Policy Group, which will continue to develop recommendations for HHS and USG leadership on response to international requests for HHS MCMs as well as address ongoing barriers to the international deployment of MCMs.
3.2.14	Work with Canada and Mexico to address barriers to providing mutual assistance and harmonizing utilization policies for MCMs during international public health emergencies under the framework of the US-Canada Beyond the Border Initiative, and as called for in the NAPAPI.	ASPR	FY15	Under the Beyond the Border Initiative, the Office of Policy and Planning (OPP) within ASPR has been working to improve cross-border interoperability and strengthen collective US/Canada health security by strengthening capacities to share MCMs rapidly across the US-Canada border during public health and medical emergencies. ASPR/OPP has led the development and analysis of a joint US/Canada survey on MCM capabilities and barriers to the sharing of MCMs internationally. Additionally, ASPR/OPP is working in collaboration with the Public Health Agency of Canada to identify the current legal, regulatory, and logistical challenges surrounding the international deployment of MCMs, and to propose recommendations to address these challenges. Additionally, under NAPAPI, ASPR/OPP has been working to improve North American health security by strengthening capacities

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
				to rapidly share influenza human and animal MCMs with Canada and Mexico. ASPR/OPP developed a trilateral survey on influenza MCM capabilities and barriers to the international sharing of MCMs, which has been circulated to the three countries for completion. Additionally, ASPR/OPP has drafted, with agriculture sector colleagues, a survey on the barriers to the sharing of animal MCMs internationally, which will be finalized and circulated for completion in FY15.
3.3.1	Develop a comprehensive MCM messaging program and multi-year implementation plan.	ASPR / CDC	FY15	The *Emergency Support Function 15 Standard Operating Procedures* (2013 edition; available at http://www.fema.gov/media-library/assets/documents/34369) is the primary federal guiding document to coordinate outreach and ensure consistent public information through an integrated federal incident communications system. ASPR is convening a working group to specifically address the emergency communication needs for at-risk populations. For those for whom English is a second language, CDC provides public service announcements in various formats (http://emergency.cdc.gov/disasters/psa/index.asp), fact sheets in multiple languages, and much of its website content is also provided in Spanish.
3.3.4	In addition, ASPR will develop and implement a plan to disseminate best practices for establishing and maintaining regional coordination for public health emergencies. Specifically, the PHEMCE will promote partnerships over the next two years among emergency management, healthcare, behavioral healthcare, and human services stakeholders by providing technical assistance and education to SLTT and non-governmental partners in a	ASPR	FY14	ONGOING - The HHS RECs, as the ASPR's regional focal points for regional, state, and local planning and coordination efforts, work in collaboration with departmental, federal interagency (e.g., FEMA, DoD, VA), state, local, and tribal counterparts to continually build partnerships and close working relationships. They work with regional partners to conduct risk assessments and analyses, identify current capabilities, gaps, capacity, and community resiliency building efforts. They are the HHS lead for federal public health and medical planning activities in the regions. To assist this collaboration, the RECs co-chair a Regional Area Council (RAC) in each region, a group that brings all of the HHS and interagency federal partners

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
	sustainable, scheduled forum.			together to discuss preparedness, mitigation, response, and recovery activities. The RACs typically meet monthly. The RAC also uses the group's structure during emergencies and disasters to facilitate rapid communication and coordination. The RECs also have routine meetings with their state public health or department of health representatives. They typically meet quarterly to update the states on regional work and invite the states to bring issues, concerns, and developments forward for the group's consumption. ASPR has also developed "Regional Readiness Indicators" and is in the process of piloting them with the regions. These will allow HHS to measure a region's ability to respond to an all-hazards event/incident.
3.4.1	Develop a comprehensive Action Plan for monitoring the safety and clinical benefit of MCMs during public health emergencies.	FDA / CDC	FY14	COMPLETE - This Action Plan was completed and approved by the PHEMCE in 2013.
4.3.1	Provide clinicians with dosing and use guidance for applying stockpiled MCMs to pediatric populations, with the caveat that this guidance could only be used in an emergency (e.g., under an EUA)	ASPR / CDC	FY17	CDC and the American Academy of Pediatrics co-hosted a meeting in November 2012 to develop pediatric clinical guidelines for the use of MCMs for PEP and treatment of children for anthrax. The final report was published in *Pediatrics* in April 2014. Experts from the CDC, the AAP, and other collaborating organizations are currently working on any adaptations to the recommendations in this report that may be needed during a mass casualty event. The PedsOB IPT is also addressing the need for pediatric dosing and use guidance in support of PHEMCE partners.
4.3.2	Ensure that public health and medical information distributed during public health emergencies is delivered in a manner that takes into account the range of communication and other functional needs of the intended recipients, including at-risk individuals.	ASPR / CDC	FY14	CDC is working with FDA and other PHEMCE partners, including the PedsOB IPT, to develop video instructions on the home preparation of crushing doxycycline tablets and mixing them with food for children and adults who cannot swallow pills, in anticipation of a potential shortage of pediatric/liquid formulations of doxycycline during public health emergencies. The video instructions incorporate feedback received from various internal and external groups, including the

2012 IP Activity Number	Description	Lead Agency	2012 IP Target Date	Progress
				PedsOB IPT. It will have captioning for persons who are deaf or hard of hearing. This video will serve as a companion piece to the revised CDC and FDA crushing and mixing instructions pamphlet (forthcoming), which will replace the 2008 FDA pamphlet. This video is anticipated for completion in FY15. CDC translated doxycycline patient information into 56 languages. Additionally, ASPR will work with CDC to increase coordination around messaging for at-risk populations. This will support PHS Act requirements, including new requirements added to the PHS Act by PAHPRA and the department's renewed commitment, as outlined in the recent ASPR Language Access Plan, to ensuring meaningful access to programs and services (including emergency communications) to people with limited-English proficiency.
4.3.4	Implementation of the CHILD Working Group 2011 report recommendations.	ASPR, CDC	Ongoing	ONGOING - PHEMCE partner agencies have been working collaboratively to implement the 2011 Report recommendations. CDC progress includes incorporating pediatric scenarios in the national capstone exercise (April 2014); ensuring pediatric subject matter expertise in the development of anthrax clinical utilization guidelines for a mass casualty event; development and readiness of pediatric push packages in the SNS to ensure pediatric MCMs are rapidly available to communities; and continued engagement with the American Academy of Pediatrics Disaster Preparedness Advisory Council.
4.3.7	Support the development of pediatric-specific training curriculum guidance for managing children's needs in times of disasters.	ASPR	Ongoing	ONGOING - In February 2012, the federal panel of the NCDMPH met and determined that the three prioritized topics for initial development of a pediatric disaster training curriculum are: Tracking & Reunification of Pediatric Disaster Victims, Overview of Radiation Exposure in Children, and Psychosocial Impacts on Children. Following that determination, a number of online-based learning modules, webinars, and other materials have been developed and

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				promulgated in these three areas.
4.3.8	Integrate operational requirements, considerations, resources and action items for pediatric and other at-risk populations into ASPR Playbooks.	ASPR	FY14	The PedsOB IPT developed a white paper on addressing pediatric needs in a public health emergency and is continuing to work with ASPR on incorporating at-risk individual needs into the new *HHS All-Hazards Plan* and threat-specific annexes that will be replacing the ASPR Playbooks.
T.A.1	Complete several stakeholder engagements and subject matter expert meetings to update anthrax clinical guidelines for all populations.	CDC	FY14	COMPLETE – CDC successfully held these meetings and used the resulting inputs to inform a series of updated anthrax clinical guidances, many of which have already been published (see item T.A.2 below).
T.A.2	Publish an updated anthrax clinical guidance.	CDC	FY14	Anthrax clinical guidance documents for the general population, pregnant women, and children have been published. Anthrax clinical guidance for a mass casualty event is under development.
T.A.6	Work with the anthrax vaccine manufacturer to support research into dose-sparing strategies for PEP vaccine use.	NIH / CDC / FDA	FY13	Research support and analysis is ongoing.
T.A.9	Complete anthrax vaccine prioritization guidance.	CDC	FY14	COMPLETE – This guidance was finalized in April 2013.
T.A.10	BARDA will support the pursuit of FDA approval for the most advanced-stage anthrax antitoxins, including late-stage development and deliveries to the SNS.	BARDA	FY14	COMPLETE - FDA approval achieved for Human Genome Sciences/GlaxoSmithKline Raxibacumab anthrax monoclonal antibody in December 2012.
T.A.13	BARDA, in coordination with CDC, will hold antitoxin-related outreach, communication, and education programs with RECs and ASPR recovery planners.	BARDA, CDC	FY14	COMPLETE - BARDA and CDC held an end-user engagement in Seattle for the use of anthrax antitoxins. Additional engagements have also been held on use of various MCMs against a number of threats.
T.A.15	Support expansion of domestic manufacturing capacity for the currently	BARDA	FY17	Support is ongoing.

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	approved anthrax vaccine, to include: validating new manufacturing processes; conducting additional non-clinical and clinical studies; and pursuing licensure of a new facility.			
T.OB.2	Qualify animal efficacy models for anthrax, plague, and tularemia in support of PEP and treatment indications, through the FDA's animal model qualification process for use under the Animal Rule.	NIH	FY14	Research is ongoing with qualification of these animal models for use under the Animal Rule now anticipated for FY15.
T.OB.6	Develop animal models for testing MCMs against *Burkholderia pseudomallei* and *Burkholderia mallei.*	BARDA	FY14	Development is ongoing.
T.S.1	Maintain sufficient quantities of smallpox vaccines in the SNS to provide a vaccination response capability for every American during a smallpox emergency, if appropriate.	CDC / BARDA	FY14	ONGOING - The SNS holds more than enough smallpox vaccines for the entire US population, including millions of regimens of the unlicensed MVA vaccine that has the potential to be used in an emergency under an EUA in individuals of all ages with HIV or atopic dermatitis, including nursing and pregnant women.
T.S.4	Deliver to the SNS a subset of the required treatment courses of the smallpox antivirals currently under contract, with full delivery being completed in the mid-term.	BARDA	FY14 / FY17	Delivery to the SNS began in March 2013 and is continuing.
T.S.5	Develop IND protocols and/or pre-EUA packages for smallpox antivirals for regulatory review by FDA to allow for the stockpiling, distribution, dispensing, and utilization of these products in the event of an emergency.	CDC	FY14	COMPLETE – An IND for tecovirimat to treat orthopox infections was submitted in December 2012 and is in effect with FDA. A pre-EUA package for treatment of smallpox and for treatment of vaccinia-related complications was submitted to FDA in August 2013.

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T.S.9	BARDA, working with CDC, will support activities to achieve FDA approval for the MVA smallpox vaccine (intended for use in at-risk populations).	BARDA, CDC	FY17	MVA is in the SNS and has the potential to be used during an emergency under EUA in at-risk individuals. BARDA continues to support approval of this product.
T.PI.2	Ensure that all operational plans for pandemic influenza communication are updated, exercised, evaluated, and improved to facilitate effective communication strategies; and develop an approach, definitions, tools, and models for a risk communication response plan.	CDC	FY17	CDC has established and maintained relationships with key partners and networks (e.g., DHS, HHS Assistant Secretary for Public Affairs, WebMD) to improve communication materials and operational response plans for pandemic influenza. CDC developed the Clear Communication Index to help ensure communications were in plain language. They have updated their operations plans for pandemic influenza communications and developed communications and plans for broad audiences in the appropriate languages, plans for partnership engagements within hard-to-reach and at-risk populations, and a variety of public service announcements. They have increased their presence and interactions on social media sites and developed applications such as Solve the Outbreak, FluView, and Flu app for clinicians.
T.PI.3	Maintain and update the existing stockpile of novel influenza virus and pre-pandemic vaccines and adjuvants, as needed.	BARDA	FY14	ONGOING - BARDA collaborates closely with PHEMCE partners, including CDC, NIH, and FDA, to make decisions regarding influenza vaccines suitable for the pre-pandemic vaccine stockpile. Decisions regarding the composition of the pre-pandemic stockpile are informed by the use of the CDC Influenza Risk Assessment Tool that measures the potential pandemic risk posed by influenza A viruses. BARDA awarded three-year contracts to all five US-approved influenza vaccine manufacturers to produce master vaccine seed stocks for viruses with pandemic potential before a pandemic occurs. The contracts also allow HHS to purchase in a pandemic cell-based vaccine in addition to conventional egg-based vaccine.
T.PI.4	Develop rapid methods to produce candidate vaccine viruses that allow	CDC / BARDA /	FY14	A comprehensive, integrated plan for manufacturing and timely delivery of influenza vaccines is under development.

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	accelerated production of vaccine lots for eventual fill and finish by manufacturers. Complete work on development of rapid laboratory methods to expedite testing to determine the antigen content of influenza vaccine bulks and enable vaccine formulation prior to product fill and finish.	FDA		
T.PI.8	BARDA is supporting the advanced development and pursuit of FDA approval for cell-based influenza vaccines.	BARDA	FY14	In November 2012, Novartis's Flucelvax was approved by FDA; the first cell-based vaccine approved in the US. BARDA partnered with Novartis for the development of this cell-culture manufacturing technology and for construction of the state-of-the-art, cell-based vaccine and adjuvant manufacturing facility in Holly Springs, NC.
T.PI.9	Support the development of novel recombinant vaccine candidates for both pandemic and seasonal influenza through Phase 2 clinical trials.	BARDA	FY14	The first recombinant influenza vaccine (i.e., FluBlØk) was approved in the US in January 2013. BARDA continues to support the advanced development of three recombinant influenza vaccine candidates.
T.PI.13	Award contracts for the advanced development of new influenza antiviral drugs.	BARDA	FY14	BARDA is supporting the development of two neuraminidase inhibitor and two host-targeted drug candidates. The BARDA Influenza BAA continues to seek additional opportunities to develop new antiviral treatments, with a focus on products with novel mechanisms of actions, and those effective in severely ill, hospitalized patients and suitable for at-risk populations, including pediatrics.
T.PI.14	Expand surveillance for antiviral susceptibility.	CDC	FY14	COMPLETE - Eleven public health laboratories have been trained to monitor for influenza virus resistance to antiviral agents using genotypic testing. This exceeds the original target number of laboratories. Data from these laboratories is now included in CDC's national surveillance report (i.e., FluView).
T.PI.15	Review and evaluate potential benefits and disadvantages of different antiviral use	CDC / NIH / BARDA /	FY14	Anticipated for completion in FY15.

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	strategies, and reassess the quantity and composition of antiviral stockpiles by various levels of government and other partners, taking fiscal constraints and manufacturing capacity into account.	FDA		
T.PI.16	Develop new plans for antiviral distribution and dispensing.	CDC	FY14	Under development.
T.PI.17	NIH will sequence genomic data for influenza viral isolates to support current and future diagnostics efforts. In addition, NIH will continue to add representative influenza viral isolates to NIH's NIAID BEI Research Resources Repository in order to make strains available for developing next-generation diagnostic tests.	NIH	Ongoing	In 2013, the Influenza Genome Sequencing Project (IGSP) at the NIH/NIAID-funded Genome Sequencing Center at the J. Craig Venter Institute sequenced and released into the public domain GenBank, almost 14,000 complete genomes of influenza. The IGSP continues to provide the scientific community with complete genome sequence data for human and animal influenza viruses. The IGSP has submitted nearly 1000 viruses to BEI.
T.PI.21	Commence development of new sequencing-based diagnostic assays and prototype device development for detection of influenza viruses and other respiratory pathogens.	CDC / BARDA	FY14	In March 2013, BARDA awarded a contract for the advanced development of a rapid assay to detect influenza as well as other drug-resistant viruses. The BARDA Influenza BAA language has been modified to focus specifically in this targeted area for improved and next-generation diagnostics. Additional contracts will be awarded contingent upon the availability of funds.
T.PI.24	CDC will seek to increase the percentage of persons receiving annual influenza vaccinations.	CDC	Ongoing	Increased demand for seasonal influenza vaccination is a core element of CDC work and a focus of the National Adult and Influenza Immunization Summit. Vaccination coverage for the US population has steadily increased from 43% in 2010-11 to 45% of the total population as of the 2012-13 influenza season (FluVaxView). CDC is also working closely with ASTHO to expand the role of pharmacies/ pharmacists as vaccinators in state pandemic preparedness and response.

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T.PI.25	Work with federal and SLTT partners to implement guidance developed by the USG for situations in which limited vaccine availability requires targeted vaccination of persons with high-risk conditions.	CDC	FY17	The CDC's Advisory Committee on Immunization Practices (ACIP) has existing guidance on the use of vaccine during periods of shortages. CDC is also working with HHS and DHS to update the *2008 HHS Guidance on Allocation and Prioritization of Pandemic Vaccine*.
T.PI.27	Move several universal influenza vaccine candidates into early-phase human clinical testing.	NIH	FY17	NIH and BARDA continue to work together with the goal of moving a universal influenza vaccine candidate into a Phase 1 clinical trial by FY15-FY16.
T.PI.28	Support at least one novel viral antigen or universal vaccine candidate expected to be evaluated in Phase 2 clinical studies in the mid-term.	BARDA	FY17	BARDA plans to initiate support in the near-term of one or two promising influenza vaccine candidates with improved effectiveness through the BAA funding mechanism.
T.PI.30	Support advanced development of at least two drugs with novel mechanism(s) of action through Phase 3 clinical studies.	BARDA	FY17	BARDA has supported the advanced development of two antiviral drugs with novel mechanisms of action, including a large Phase 2b trial for one novel product and an ongoing Phase 3 trial for another novel product. BARDA continues to solicit, through its BAA and other mechanisms, opportunities to support antiviral drugs and other therapeutics for the treatment and prevention of influenza disease, including those effective in hospitalized, severely ill patients, those suitable for use in pediatric populations, and products with greater impact in reducing influenza illness and with reduced risk of resistance.
T.OV.1	Support research into therapeutic candidates for broad-spectrum antiviral treatments.	NIH	Ongoing	NIH has awarded BAA contracts for development of broad-spectrum antiviral compounds that have activity against biological threats, such as smallpox and filovirus. One of those products has reached the IND stage with Phase 1 to be completed in the near-term. Several novel therapeutics are being supported through preclinical services support.
T.B.1	BARDA will support pursuit of FDA approval	BARDA	FY14	COMPLETE – FDA licensure was achieved in March 2013.

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	of the equine-derived, heptavalent botulism antitoxin product.			
T.RN.4	Assess results from the current proof-of-concept studies for promising candidates for thermal burn injuries and continue to support the development of thermal burn definitive care products.	BARDA	FY14	BARDA awarded three contracts in FY 2013 to address thermal burns. In addition, an award was made under the diagnostic program for a device that can assist with the debridement of burns. BARDA will continue to support these efforts and add new candidates based on availability of funds.
T.RN.7	Qualify rodent and non-human primate animal models for pivotal animal efficacy studies.	NIH	FY17	NIH has expanded rodent radiation testing facilities for hematopoietic and gastrointestinal ARS, and continues to support GLP facilities for testing of MCMs for both rodent and non-human primate models.
T.RN.8	Finalize clinical guidance for MCMs to address radiation-induced neutropenia.	CDC / ASPR	FY17	This is under development and anticipated for finalization in FY15.
T.C.2	Support the advanced research and development of novel compounds for treatment or PEP following exposure to chemical agents.	BARDA	Ongoing	BARDA is currently funding three advanced research and development programs in this area. A contract was also awarded under Project BioShield in FY13 for late-stage development and procurement of midazolam.
C.D.1	Initiate funding for the development of biological agent diagnostic systems, chemical agent diagnostic systems, and systems to identify and characterize unknown threats, including development of assays and instrumentation to address PHEMCE requirements for high-throughput and POC usage.	NIH	FY14	A Request for Applications (RFA) for the development of multiplex diagnostic platforms was issued in April 2013, and awards were anticipated in FY14. An additional RFA in this area is scheduled for release in March 2014, with awards anticipated in FY15.
C.D.5	Develop reference profile panels of threat agents that will support generation of requisite datasets required for approval of a next-generation diagnostic platform.	NIH	FY17	Multiple strains of biothreat pathogens and their near neighbors (i.e., Bacteria: *B. anthracis*, *Francisella tularensis*, *Yersinia pestis*, *Brucella*, *Burkholderia*, *Clostridium*, *Coxiella*; Viruses: Ebola, Lassa, Rift Valley, Eastern equine encephalitis, Japanese equine encephalitis, Venezuelan equine encephalitis) are available from the

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				BEI Resources repository, as well as related reagents including genomic material, proteins, antibodies/antisera, inactivated antigens, primers/probes, and more. In addition, BEI Resources offers nucleic acids, antibodies/antisera, and inactivated antigens developed by the DoD Critical Reagents Program. All of these materials are available to facilitate early stage development.
C.D.7	Develop and validate additional radionuclide bioassay diagnostic tests to allow rapid detection and measurement of radionuclides in clinical specimens.	CDC	FY17	Bioassay methods have been developed to measure 14/22 priority radionuclides rapidly and quantitatively; methods for three additional radionuclides are underway.
C.NP.2	Encourage RPD manufacturers to pursue both NIOSH certification and FDA approval to ensure an ample supply of FDA-approved N95 respirators.	CDC	FY12-14	Project BREATHE (Better Respiratory Equipment using Advanced Technologies for Healthcare Employees) is an interagency effort of the USG chaired by the VA. This project seeks to shepherd new respirators to the US marketplace that can meet the standards of both NIOSH and FDA. CDC is currently testing prototypes from two manufacturers.
C.NP.4	Reassess the quantity and composition of respirator stockpiles for pandemic influenza and other threats, taking fiscal constraints into account, to determine whether the stockpiling of respirators in the SNS should be continued.	CDC	FY14	This assessment is under development and anticipated for completion in FY15.
C.NP.6	Develop an all-hazards ventilator assessment that will define both the quantities of ventilators for stockpiling and the desired device attributes for effectively responding to a range of lung injuries associated with different threat agents.	ASPR	FY14	COMPLETE - This assessment was completed and approved by the PHEMCE in May 2013. The results are being incorporated into the stockpiling recommendations and acquisition strategies under development.
C.NP.7	Publish national planning guidance for	ASPR / DHS	FY14	This draft guidance was released in the Federal Register for public

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	conducting mass patient decontamination in a chemical incident.			comment in Spring 2014.
C.NP.9	Initiate a research program to address critical knowledge gaps in the subject of patient decontamination.	BARDA	FY14	COMPLETE - BARDA awarded a contract to the University of Hertfordshire at the end of FY12 to pursue this research. In FY13, BARDA, in collaboration with the Office of Emergency Management (OEM), held two exercises in Los Angeles and Boston for decontamination of individuals exposed to chemical agents. Results from these exercises will be incorporated into the ongoing research program.
C.CIADM .2	Establish the CIADM governance structure.	BARDA	FY14	COMPLETE – An MOU has been established between DoD and HHS on shared roles, responsibilities, and cost for the Centers and the ADMC and a governance structure has been approved.
C.CIADM .3	Construct and qualify CIADM infrastructure.	BARDA	FY17	The CIADM contractors are proceeding on schedule, and within their established budgets, to ready the necessary infrastructure, equipment, and personnel to provide their full complement of advanced development and manufacturing core services.
C.CC.1	Establish a Fill-Finish Network.	BARDA	FY14	COMPLETE – Contracts awarded in September 2013.
C.CC.3	Establish the medical countermeasure strategic investor (MCMSI) and MCMSI Interface Office.	BARDA	FY14	CLOSED – This was not authorized by Congress.
C.CC.4	Establish a Visualization Hub to provide analytic decision support and access to real-time modeling capabilities to senior decision-makers within ASPR and the PHEMCE.	BARDA	FY14	This is under development.
C.CC.10	Manage the LRN, a group of local, state, federal, and international laboratories with unique testing capabilities for detecting high-	CDC	Ongoing	One hundred thirty-six domestic laboratories participate in the LRN and are provided training in real-time PCR and conventional microbiology methods, as well as proficiency test challenges to

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	priority biological and chemical threat agents.			maintain their readiness. In FY13, approximately 300 white powders or threat letters were processed by 54 public health LRN laboratories.
C.CC.13	Establish an MCM advanced development and manufacturing facility.	DoD	FY14	The groundbreaking ceremony for this facility was held in October 2013. Completion is now anticipated in FY15.
C.CC.14	Establish a dedicated BSL-4 laboratory capable of conducting GLP testing and evaluation of MCMs.	DoD	FY17	BSL-4 GLP laboratory capability will be included in the newly constructed biological research laboratory that will be a part of the National Interagency Confederation for Biological Research at Fort Detrick.