U.S. Department of Health and Human Services

2015 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan

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EXECUTIVE SUMMARY

The *2015 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan (SIP)* describes the priorities that the U.S. Department of Health and Human Services (HHS), in collaboration with its interagency partners, will implement over the next five years. This plan updates the *2014 PHEMCE SIP* and is 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). The annual *PHEMCE SIP* provides the blueprint the PHEMCE will use to enhance national health security through the procurement and effective use of medical countermeasures (MCMs).

What is the PHEMCE?

The *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 high-consequence public health emergencies, whether naturally occurring or intentional.

The PHEMCE goals and objectives are examined annually for revision or update, as needed. Goals and objectives should remain constant over a more extended period; the current goals and objectives remain unchanged from the *2014 PHEMCE SIP* (see Table 1 below). The goals and objectives will be intensively re-examined in the *2018 PHEMCE SIP*.

The streamlined *2015 PHEMCE SIP* provides: 1) a summary of the major recent accomplishments; 2) updates to the activities from the *2014 PHEMCE SIP* only where significant changes have occurred; and 3) specific information required annually under PAHPRA reporting mandates. Over the past year the PHEMCE has made great progress in advancing national health security. The PHEMCE has assessed threats to our national health security, improved the MCM requirements and acquisition framework used to identify MCM needs posed by those threats, and conducted early and advanced research and development. PHEMCE agencies approved additional MCMs (including approvals under the regulatory mechanism known as the Animal Rule), manufactured and procured critical MCMs, addressed MCM needs of at-risk populations, developed and enhanced federal communication plans and MCM utilization guidance, and implemented policies for the international sharing of MCMs.

The priority activities identified in the *2014 PHEMCE SIP* for accomplishment through fiscal year (FY) 2019, and maintained or updated in the current document, span the PHEMCE mission areas. That includes 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. All activities are contingent on available appropriations. Work across the PHEMCE agencies against these priorities will continue to support the PHEMCE's strategic goals and objectives. The coordination of PHEMCE partner activities under the annual strategy and implementation plan continues to improve the national ability to effectively respond to a variety of high-consequence public health emergencies through the procurement and effective use of MCMs.

Table 1: Overview of PHEMCE Strategic Goals and Objectives[1]

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

Objective 1.1: Develop a strategic framework to prioritize PHEMCE resources and investments;

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;

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

Objective 1.4: Promote effective domestic and international partnerships with developers and manufacturers and support core services.

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 MCM development or use during public health emergencies and coordinate activities among PHEMCE partners to address those challenges;

Objective 2.2: Assist MCM developers in working interactively with FDA during product development and regulatory review.

[1] These goals and objectives are unchanged since the *2014 PHEMCE SIP*.

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;

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 and territorial (SLTT) and private sector response plans, and when possible international partners' and that ensure timely, safe, and effective MCM distribution and utilization;

Objective 3.3: Develop and provide MCM communications, training, and education information to inform all stakeholders; and,

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.

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;

Objective 4.2: Support MCM advanced development and procurement for at-risk individuals; and,

Objective 4.3: Develop and implement strategies, policies, and guidance to support the appropriate use of MCMs in all civilian populations during an emergency.

INTRODUCTION

The United States (U.S.) 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 nation must have the nimble, flexible capability to produce and effectively use MCMs[2] in the face of any attack or threat, whether known or unknown, novel or reemerging, natural or intentional. These capabilities must be communicated to the American public before and during an emergency. Accomplishing these goals requires coordination of MCM-related activities across federal departments. To provide this coordination, the U.S. Department of Health and Human Services (HHS) established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)[3] in July 2006, to coordinate federal efforts to enhance civilian preparedness 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 U.S. civilian population. The PHEMCE works to meet the public health emergency needs of the entire civilian population, including those of groups that require special medical considerations, such as children, pregnant women, and older adults, as well as first responders[4], health care personnel, and other critical infrastructure personnel, by taking a whole-of-community approach in planning, response, and recovery efforts.

[2] 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)).

[3] For more on the establishment of the PHEMCE, see http://www.gpo.gov/fdsys/pkg/FR-2006-07-06/pdf/06-6004.pdf. For more information regarding the structure and governance of the PHEMCE, refer to Appendix 2 of the *2014 PHEMCE SIP* available at http://www.phe.gov/Preparedness/mcm/phemce/Pages/strategy.aspx.

[4] This mandate includes consideration of the 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 needed support, including MCMs, is primarily described elsewhere. While particularly relevant activities may be called out in this document, broader efforts are not detailed here. They can be found at http://www.phe.gov/emergency/events/sandy/Pages/responder-safety.aspx and http://www.phe.gov/Preparedness/planning/cip/Pages/default.aspx.

Box 1: High-Priority Threats

The 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 unchanged from those listed in the *2014 PHEMCE SIP* and are (in alphabetical order):

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

Annual PHEMCE Strategy and Implementation Plan Process

Activities described in the *2014 PHEMCE SIP* are still priorities being pursued by PHEMCE partners unless specifically noted in the *2015 PHEMCE SIP*.

The *PHEMCE Strategy and Implementation Plan* (SIP) is released annually as required by Section 2811(d) of the Public Health Service (PHS) Act[5], as amended by section 102 of the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA). Many elements of the *PHEMCE SIP* (*i.e.*, goals, objectives, and priority activities) do not change significantly on an annual basis. Thus, the PHEMCE adopted the following process for the SIP (also summarized in Table 2 below):

- The *PHEMCE SIP* will be issued annually and will address all PHS Act requirements (listed in Appendix 6);
- Major updates to activities will occur on even-numbered years; this entails re-evaluation of all activities in the most recent *PHEMCE SIP* and considers necessary revisions and addition of relevant new activities. Adjustments will be made to activities annually (as needed) when significant changes have occurred or new activities have begun; and,
- Major re-evaluation of goals and objectives will occur in 2018 and every four years thereafter. Minor adjustments to goals and objectives (as needed) will be considered annually.

[5] 42 U.S.C. 300hh-10(d)

Table 2: Annual PHEMCE Strategy and Implementation Plan Process

SIP Elements	2012	2014	2015	2016	2017	2018
Major Re-Examination: Goals & Objectives	X	-	-	-	-	X
Minor Updates: Goals & Objectives	-	X	X	X	X	-
Major Re-Examination: Activities	X	X	-	X	-	X
Minor Updates: Activities	-	-	X	-	X	-
PAHPRA Reporting Requirements	N/A	X	X	X	X	X

Development of the 2015 PHEMCE Strategy and Implementation Plan

As in 2014, the Office of the Assistant Secretary for Preparedness and Response (ASPR) led the development of the *2015 PHEMCE SIP* through an interagency steering committee composed of representatives from across the PHEMCE agencies. The steering committee reviewed the PHEMCE-wide strategic goals and objectives contained in the *2014 PHEMCE SIP* and determined that they remained appropriate for 2015.

The PHEMCE developed a progress report of accomplishments toward completion of priorities set forward in the *2014 PHEMCE SIP* (summarized in Section 1: Accomplishments Since the *2014 PHEMCE SIP* with further details found in Appendix 5). New activities (not included in the *2014 PHEMCE SIP*) are described in Section 2: New Activities Since the *2014 PHEMCE SIP* and/or Appendix 5. Otherwise, activities described in the *2014 PHEMCE SIP* are still being pursued as PHEMCE priorities. Plans to pursue and accomplish the activities detailed depend on sufficient federal funding.

Consideration of Perspectives from National Advisory Committees

HHS has several national advisory committees the PHEMCE can leverage for guidance on scientific, technical, and other matters related to MCM preparedness and response. The *2015 PHEMCE SIP* was informed by previous recommendations provided to the HHS Secretary and the ASPR on PHEMCE-related issues by the National Biodefense Science Board (NBSB), now known as the National Preparedness and Response Science Board (NPRSB). Past NPRSB engagements of particular relevance included those conducted on the *2012 PHEMCE SIP*[6]; the long-term sustainability of the Strategic National Stockpile (SNS)[7]; and the PHEMCE development of MCM preparedness goals[8].

[6] NBSB Evaluation of the 2012 HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan (SIP), 2012. Available at http://www.phe.gov/Preparedness/legal/boards/nprsb/recommendations/Documents/NBSB-letter-to-Secretary-130131.pdf.

[7] 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

SECTION 1: ACCOMPLISHMENTS SINCE THE *2014 PHEMCE SIP*

Since the development of the *2014 PHEMCE SIP*, the PHEMCE has made significant progress in achieving the priorities described in the *2014 PHEMCE SIP's* activities, as highlighted below[9]. In general, the reporting period for the accomplishments in this section is from March 2014 to February 2015, except where noted. A more detailed description of progress can be found in Appendix 5.

Threat and Risk Assessments and MCM Requirements

The PHEMCE established an Emerging Infectious Diseases (EID) working group to evaluate the public health risk posed by EIDs and to inform PHEMCE resource decisions regarding investments to address such threats. The EID working group was chartered to evaluate the public health risk posed by EIDs and to provide recommendations to PHEMCE leadership regarding which pathogens, or pathogen classes, require PHEMCE response, and at what level.

The PHEMCE approved nine civilian MCM requirements that focus resources and priorities against viral hemorrhagic fevers; smallpox; chemical threats including nerve agents, cyanide, and pulmonary agents; pandemic influenza; botulism; and all-hazard recommendations. The requirements process has been streamlined to enhance support for MCM research, development, acquisition, and management plans, including consideration of at-risk population needs.

Research, Development and Procurement

The second half of 2014 and 2015's first quarter were dominated by the whole-of-government response to the Ebola epidemic in West Africa (as detailed in the *2014-15 Ebola Outbreak Response* sub-section below). PHEMCE members worked in close partnership to accelerate the development and initiate clinical trials of vaccines, therapeutics, and diagnostics. FY 2014 and FY 2015 also represented the first two fiscal years of implementing the Project BioShield Act, following the initial authorization of funding for FY 2004-13, and saw two Project BioShield Act procurements and other milestones in pandemic influenza and CBRN MCM development.

Four million additional doses, sufficient to immunize 2 million people, of modified vaccinia Ankara (MVA) smallpox vaccine were procured from Bavarian Nordic under Project BioShield in September 2014. This vaccine has the potential for use during an emergency under Emergency Use Authorization (EUA)[10] in individuals of all ages with HIV or atopic dermatitis,

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with Recommendations, 2013. Available at: http://www.phe.gov/Preparedness/legal/boards/nprsb/recommendations/Documents/nbsb-bsc-sns-2020-final.pdf.

[8] National Biodefense Science Board, Strategic Preparedness Goals Report, 2014. Available at: http://www.phe.gov/Preparedness/legal/boards/nprsb/meetings/Documents/phmce-stpreport.pdf.

[9] Accomplishments achieved before or after that period may also be referred to for context. While this reporting period was driven by the release of the *2014 PHEMCE SIP* and development timeline for the current document, accomplishments in future SIP iterations will be tied to fiscal year reporting cycles.

[10] The Emergency Use Authorization (EUA) authority allows FDA to help strengthen the nation's public health protections against CBRN threats by facilitating the availability and use of MCMs needed during public health emergencies. Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), if certain prerequisites (including a declaration by the Secretary of Health and Human Services) are met, the FDA Commissioner may in

including women who are pregnant or nursing. Bavarian Nordic completed a large Phase 3 safety study in 2014 and initiated their pivotal clinical trial to support licensure of MVA in 2015.

NIH's National Institute of Allergy and Infectious Diseases (NIAID) led a working group, which included FDA, ASPR's Biomedical Advanced Research and Development Authority (BARDA), CDC, and others to design dose-sparing studies with the anthrax vaccine to demonstrate the early onset of vaccine-induced protection in non-human primates (NHP). The final draft crosswalk report on the NIH's dose- and antigen-sparing study with BioThrax® vaccine showed that two full doses or three half doses generates sufficient immunity to justify the dose sparing strategy in an emergency when vaccine supply is limited. The use of less BioThrax® vaccine for each vaccination regimen, if necessary, could extend coverage when vaccine supply is limited.

Nearly 33,000 doses of raxibacumab, a monoclonal antibody anthrax antitoxin, were procured from GlaxoSmithKline under Project BioShield in September 2014 as replenishment for expiring doses. The FDA approved raxibacumab in December 2012 for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. The additional procurements will maintain current preparedness levels until 2019.

Four CBRN products achieved FDA licensure or approval during this time period or shortly afterward. Anthrasil™, a polyclonal anthrax antitoxin derived from human plasma and developed by Cangene/Emergent, was licensed by FDA in March 2015 for the treatment of inhalational anthrax disease. Under Project BioShield, Anthrasil™ has been included in the SNS since 2007. Neupogen® (filgrastim) received FDA approval in March 2015 for the treatment of patients with bone marrow suppression following exposure to high doses of radiation. The Amgen product is a granulocyte colony-stimulating factor and was previously approved for the reduction of neutropenic fever in patients receiving chemotherapy. Neupogen® was procured under Project BioShield for the SNS in 2013. Ciprofloxacin was approved in February 2015 under the Animal Rule for treatment of plague, including pneumonic and septicemic plague, due to *Yersinia pestis* and prophylaxis for plague in adult and pediatric patients from birth to 17 years of age. In addition, moxifloxacin was approved by FDA for plague under the Animal Rule in May 2015.

In October 2014, Emergent submitted a supplemental biologics license application (sBLA) for its anthrax vaccine, BioThrax®, for a post-exposure prophylaxis (PEP) indication. In March 2015, Elusys submitted its BLA in support of an anthrax treatment indication for their anthrax monoclonal, ETI-204.

Two influenza products (Flucelvax® and Rapivab®) received FDA licensure or approval and a third (FluBlØk®) received an expanded indication. Rapivab® (peramivir), a single-dose intravenously administered neuraminidase inhibitor for the treatment of uncomplicated influenza, got FDA approval in December 2014. FluBlØk®, a recombinant seasonal flu vaccine

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appropriate circumstances allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives. http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm

manufactured by Protein Sciences Corporation that was previously licensed for adults aged 18-49, received an expanded indication from FDA that licensed its use in all adults, including those over 50 years of age. BARDA's partnership with Novartis reached a milestone in June 2014 when the FDA licensed Novartis' manufacturing facility in Holly Springs, North Carolina, for the production of Flucelvax®. This facility can manufacture 200 million doses of pandemic influenza vaccine within six months.

BARDA and NIAID's Division of Microbiology and Infectious Diseases collaborated on clinical trials to test the antigen-sparing effect of oil-in-water adjuvants in combination with stockpiled H5N1 and H7N9 avian influenza vaccines. Results from these studies showed that both H5N1 and H7N9 inactivated vaccines had significantly improved immunogenicity using these adjuvants. BARDA and NIAID's Laboratory of Infectious Diseases (LID) collaborated to conduct prime/boost clinical studies using inactivated and live attenuated H7N9 influenza vaccines that showed effective priming. In April 2015, BARDA initiated a project with Sanofi Pasteur for development of a pandemic influenza vaccine using MF-59, another oil-in-water emulsion adjuvant.

NIAID supported the development and Investigational New Drug (IND)-enabling studies for an oral radionuclide decorporation agent that led to IND submission and FDA permission to proceed with the first-in-human, Phase 1 clinical safety studies. NIAID submitted data and a final report to an IND on the efficacy of Neulasta® (pegfilgrastim), to address potential neutropenia from a radiological or nuclear incident, in a NHP animal model of the hematopoietic acute radiation syndrome.

In March 2014, BARDA established a Clinical Studies Network (CSN) to assist MCM developers with clinical trial activities and to supplement existing clinical networks during public health emergencies. The CSN becomes the fourth element of BARDA's National Medical Countermeasures Response Infrastructure, along with the Centers for Innovation in Advanced Development and Manufacturing (CIADMs), the Nonclinical Development Network (NDN), and the Fill-Finish Manufacturing Network (FFMN). Two contract research organizations that belong to the CSN provide critical support to CDC with a clinical trial in Sierra Leone to evaluate the NewLink Genetics/Merck & Co. Ebola vaccine candidate.

In November 2014, ASPR launched a web-based portfolio tracking tool to enhance coordinated planning and management of MCM development across PHEMCE organizations. The tool is also in use by the defense and health establishments of three U.S. partner countries, Australia, Canada, and the United Kingdom.

In June 2014, FDA re-issued an EUA, with amendments, to authorize the emergency use by qualified laboratories of the CDC Novel Coronavirus 2012 Real-time RT-PCR Assay for the presumptive detection of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in patients with signs and symptoms of infection, in conjunction with clinical and epidemiological risk factors.[11]

[11] For additional information, see http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm

The PHEMCE coordinated a MERS-CoV Portfolio Review in March 2015 and held a Stakeholders' Workshop with academic and industrial partners in April 2015. These meetings summarized end-to-end efforts to better understand the virus and associated human disease, the maturity of animal models, the status of MCM development (*e.g.*, diagnostics, therapeutics, and vaccines), and issues relating to international communication and sample sharing.

Effective Utilization of MCMs

Robust relationships among federal planners, regional, SLTT, and practitioner stakeholders are necessary to ensure the nation can effectively use MCMs during an emergency. In FY 2014, CDC's Division of the Strategic National Stockpile (DSNS) staff trained 1,258 people at the federal, state, and local levels through 57 training opportunities covering preparedness and response topics, including the development of critical capabilities for the effective dispensing of stockpiled MCMs. DSNS also introduced a self-paced online training course that provided a detailed overview of SNS plans and capabilities for an additional 734 individuals. Similarly, DSNS exercise staff supported 28 exercises at the federal, state, and local level. That includes 16 state-level exercises utilizing SNS training materials, to exercise plans under realistic conditions, providing hands-on experience and evaluation of state and local capabilities and partnerships for MCM dispensing.

For chemical threats, which have limited specific MCMs, patient decontamination is a broad-spectrum MCM for exposed individuals and is prophylactic for responders and receivers, as it helps protect them from secondary exposure from dermal contact and to off-gassing of volatile chemicals from patients. Limited research has been conducted on decontaminating civilians; most current practices are adapted from military doctrine. In December 2014, ASPR and DHS published a guidance document, *Patient Decontamination in a Mass Chemical Exposure Incident: National Planning Guidance for Communities*.[12] The national planning guidance provides communities with evidence-based recommendations for planning and conducting mass patient decontamination following a chemical release.

In February 2014, CDC published "CDC Expert Panel Meetings on Prevention and Treatment of Anthrax in Adults" and "Special Considerations for Prophylaxis and Treatment of Anthrax in Pregnant and Postpartum Women" in *Emerging Infectious Diseases*. In May 2014, the CDC published the report "Pediatric Anthrax Clinical Management" in *Pediatrics*. In February 2015, CDC published "Clinical Guidance for Smallpox Vaccine Use in a Postevent Vaccination Program" in *Morbidity and Mortality Weekly Report*, which included recommendations for pregnant women, children, individuals with HIV infection, and individuals with eczema.

In May 2014, CDC published an infection prevention and control guidance[13] that recommended the highest level of respiratory precautions for the care of hospitalized patients with MERS-CoV given the considerations at that point that included: lack of a safe and effective vaccine and

[12] *Patient Decontamination in a Mass Chemical Exposure Incident* is available at, http://www.phe.gov/Preparedness/responders/Pages/patientdecon.aspx.

[13] MERS-CoV infection prevention and control guidance originally released in May 2014; updated June 2015 with more explicit information on training available at http://www.cdc.gov/coronavirus/mers/infection-prevention-control.html.

chemoprophylaxis; a suspected high rate of morbidity and mortality among infected patients; and incompletely defined modes of transmission of MERS-CoV. The infection prevention and control guidance issued by CDC includes recommendations on the use of personal protective equipment (PPE) for health care providers. These documents will be updated regularly as relevant information becomes available.

CDC has published a case definition for MERS-CoV[14] and *Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Patients Under Investigation (PUIs) for Middle East Respiratory Syndrome Coronavirus*[15]. CDC published guidance that requests health care providers to immediately report to their state or local health department any person being evaluated for MERS-CoV infection. Health departments have been asked to immediately report patients under investigation to CDC using the standard CDC MERS-CoV reporting form.

International Sharing of MCMs

ASPR's Office of Policy and Planning (OPP), in coordination with CDC and other HHS and U.S. government (USG) stakeholders, utilized the HHS Policy Framework for Responding to International Requests for Public Health Emergency Medical Countermeasures to respond to requests for MCMs from, and foster dialogues with, at least nine countries through the end of 2014. In one notable instance, the Framework was implemented to provide technical assistance and planning for MCM deployment and use in preparation for the 2014 World Cup soccer tournament.

Additionally, the Framework has served as a foundation for work that ASPR/OPP has led through the Global Heath Security Initiative (GHSI)[16] with Canada, France, Germany, Italy, Japan, Mexico, the United Kingdom, the European Commission, and the World Health Organization to develop a global framework to address legal, logistical, regulatory and funding challenges of deploying MCMs internationally. In January 2015, this global framework was adapted by GHSI to develop a checklist for the potential future deployment and distribution of Ebola vaccines.

DHS leads the U.S.-Canada Beyond the Border (BTB) Initiative for a shared approach to security[17]. ASPR/OPP leads public health engagement with Canada bilaterally under the BTB Initiative global health security chapter and collaboration with Canada and Mexico trilaterally under the North American Plan for Animal and Pandemic Influenza (NAPAPI)[18]. Specifically, ASPR/OPP leads efforts under both NAPAPI and BTB to identify and address barriers to deploying medical countermeasures internationally and to share information on utilization policies for MCMs during international public health emergencies. In 2014, ASPR/OPP led work with Canada through the BTB Initiative to identify the legal, regulatory, logistical, and funding issues, laws, regulations, and policies that may impact the international deployment of

[14] MERS-CoV case definition originally released in May 2014; updated June 2015 to account for South Korean outbreak available at http://www.cdc.gov/coronavirus/mers/case-def.html
[15] The interim guidelines (version 2.1) are available at http://www.cdc.gov/coronavirus/mers/guidelines-clinical-specimens.html
[16] More information is available at: http://www.phe.gov/Preparedness/international/ghsi/pages/default.aspx
[17] More information is available at: http://www.dhs.gov/beyond-border
[18] More information is available at: http://www.phe.gov/Preparedness/international/Documents/napapi.pdf

emergency MCMs across the U.S./Canada border to improve cross-border interoperability and to strengthen collective U.S./Canada health security.

In 2014, ASPR/OPP assumed the role of Chair of the North American Senior Coordinating Body and the North American Health Security Working Group (HSWG) to support the NAPAPI. In early 2015, ASPR/OPP convened a meeting of the HSWG that brought together subject matter and technical experts from the foreign affairs, security, agriculture, and health sectors of the U.S., Mexico, and Canada to exercise principles outlined in the NAPAPI. The exercise let NAPAPI partners discuss plans and challenges associated with the availability of, and access to, human and animal MCMs during an influenza pandemic, including access to manufacturing capacity, procurement, and international deployment, and served as a basis for identifying NAPAPI implementation action items on trilateral MCM collaborations moving forward in 2015 and beyond.

2014-15 Ebola Outbreak Response

The ongoing activities of the PHEMCE partners demonstrate an integrated approach to public health preparedness and response across a range of threats and capabilities. The PHEMCE-wide response to the 2014-15 Ebola epidemic in West Africa provides an excellent example of how the PHEMCE partners collaborated across missions areas during a real-time public health emergency. The Ebola epidemic tested the resources of the PHEMCE partners in ways that no prior outbreak or epidemic has. All components of the PHEMCE participated in and contributed to the response. The Department of Defense (DoD) and CDC deployed hundreds of people into the field. NIH and CDC organized critical clinical trials of needed MCMs, and BARDA called upon its core services to serve as a National Medical Countermeasure Response Infrastructure. The FDA worked closely with product developers and fellow agencies, rapidly reviewing IND applications to ensure MCMs could be initiated safely and quickly.

In September 2006, DHS determined that the Ebola virus and related viral hemorrhagic fever viruses presented a material threat to the U.S. population sufficient to affect national security, placing these pathogens on the PHEMCE's high-priority threat list. The DoD and NIAID have supported the preclinical development of vaccines and therapeutics against Ebola. As of summer 2014, none had reached a stage appropriate for transition to advanced research and development under BARDA. Due to these early efforts, there were numerous pre-clinical vaccine and therapeutic candidates in the pipeline when the West Africa Ebola outbreak began in 2014. The accelerated development of these candidate products was unprecedented due to the collaborations and skill sets within the PHEMCE.

BARDA, NIAID, DoD, and Mapp Biopharmaceutical collaborated on the development and manufacturing of ZMapp™, a monoclonal antibody cocktail directed against Ebola, in order to conduct clinical studies. Initial DoD NHP protection studies of ZMapp™, including dose optimization studies, were completed in 2014. The DoD also supported the initial manufacturing campaign to supply material for NHP protection studies. It will continue to support NHP protection studies in an aerosol infection model of Ebola, as well as studies to determine the therapeutic window for treatment. NIAID supported toxicology and other studies necessary for ZMapp™ development. BARDA transitioned ZMapp™ from early development at DoD into advanced development in September 2014 with a contract award to Mapp Biopharmaceutical,

the manufacturer of ZMapp™. The FFMN mobilized to fill and finish the ZMapp™ final product for clinical studies.

With participation from ASPR/BARDA, CDC, FDA, and DoD, representatives from Emory University and the University of Nebraska Medical Center, along with Liberian and Sierra Leonean counterparts, NIH led an effort to develop a common master protocol to evaluate experimental therapeutics developed for the Ebola outbreak. Counterparts from Sierra Leone, Guinea, and the Institut National de la Santé et de la Recherche Médicale later collaborated to expand the trial in West Africa. The common master protocol is an adaptive trial design created to test the optimal standard of care, including fluid and electrolyte management against candidate countermeasures in addition to optimal standard of care. Specific drug candidates were prioritized based on preclinical data and product characteristics (*e.g.*, availability, route of delivery), for inclusion in the protocol. ZMapp™ was selected as the first candidate for evaluation. A clinical trial for ZMapp™ using the common master protocol began in the U.S. and Liberia in February 2015, and expanded to Sierra Leone in April 2015 and Guinea in July 2015.

In parallel, working in partnership with Mapp Biopharmaceutical and other pharmaceutical companies (including Medicago, Fraunhofer, Regeneron, and Genentech), BARDA supported efforts to scale up manufacturing of ZMapp™ antibodies in tobacco plants and Chinese hamster ovary (CHO) cell production systems. The products will be evaluated for activity under BARDA's NDN. Regeneron's efforts include expression of "ZMapp™-like" antibodies in its specialized CHO cell line and development of novel antibodies using its proprietary platform. Both products, the "ZMapp™-like" and the novel antibody cocktail, have been evaluated in NHP Ebola challenge studies, which showed results similar to ZMapp™ in those studies. Genentech humanized the monoclonal antibodies comprising ZMapp™ and is expressing the antibodies in their specialized CHO cell line. The Genentech product faces evaluation in an NHP Ebola challenge study at the time of writing. Manufacturing of the Genentech candidate is slated for BARDA's CIADMs. NIAID supports BioCryst Pharmaceuticals to perform Phase 1 clinical trials for BCX4430, a small molecule, broad-spectrum therapeutic that has shown promise in treating Ebola in non-clinical models. The goal is to use BCX4430 in the randomized controlled trial protocol in Ebola patients in West Africa, if the Ebola epidemic continues. In addition, in March 2015, BARDA initiated a partnership with BioCryst Pharmaceuticals to advance the development of BCX4430 by supporting improvement of manufacturing processes and scaling up production capabilities while Phase 1 clinical trials were ongoing.

In October 2014, BARDA transitioned from NIAID a project with Profectus BioSciences to develop and manufacture clinical investigational lots of a monovalent vaccine against Ebola expressed in a recombinant Vesicular Stomatitis Virus (rVSV) vector for clinical studies to be conducted in 2015. In December 2014, BARDA formally initiated projects with BioProtection Systems (a NewLink Genetics subsidiary) and Merck & Co., and with GlaxoSmithKline to develop, optimize, and validate commercial-scale manufacturing processes for their respective Ebola vaccine candidates. The goal was to ensure millions of vaccine doses could be available in 2015 if the vaccines were shown to be safe and effective, and if mass vaccination campaigns were required to control the epidemic. BARDA supported efforts to develop more thermostable

vaccine formulations as a longer-term goal to simplify vaccine administration efforts and to cut storage and deployment costs.

Internally, NIAID and DoD supported Phase 1 safety and immunogenicity studies in the United States for two Ebola vaccine candidates (*i.e.*, cAd3-EBOZ and rVSV-ZEBOV). NIAID conducted a Phase 1 clinical trial of the cAd3 candidate at the NIH Clinical Center beginning in September 2014. Initial results were published in the *New England Journal of Medicine* in November 2014, revealing a promising safety profile and immune responses consistent with protection, as demonstrated in non-human primate trials. DoD, in partnership with NIAID, conducted two Phase 1 clinical trials of the VSV NewLink Genetics/Merck & Co. Ebola vaccine sponsored by the Defense Threat Reduction Agency – Joint Science and Technology Office (DTRA-JSTO). One was held at the Walter Reed Army Institute of Research and the other at the NIH Clinical Center. Results were published in the *New England Journal of Medicine* in April 2015. The DoD also conducted animal efficacy studies and immunological testing of nonclinical and Phase 1 samples at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), sponsored by Medical Countermeasure Systems – Joint Vaccine Acquisition Program (MCS-JVAP). These studies were instrumental because they enabled the product sponsor, NewLink Genetics/Merck & Co. to determine dose selection for expanded Phase 2 and 3 clinical trials in West Africa. DoD (*i.e.*, DTRA-JSTO in partnership with MCS-JVAP) contracted with NewLink Genetics/Merck & Co. to produce more than 100,000 doses of cGMP (current good manufacturing practices) VSV vaccine at Germany's IDT Biologika. Approximately 10,000 of these doses were returned to NewLink Genetics/Merck & Co. for use in the expanded Phase 2/3 clinical trials in Liberia (in partnership with NIAID), Sierra Leone (with CDC), and Guinea (with WHO/Norway), as well as for further process development and manufacturing improvement. MCS-JVAP will provide an additional approximately 10,000 doses for further trial work in West Africa from the DoD stockpile.

On February 2, 2015, the Liberia-U.S. Clinical Research Partnership, with NIH as the U.S. lead, launched a Phase 2/3 double-blind, randomized, placebo-controlled clinical trial, entitled PREVAIL I, comparing cAd3 and rVSV candidate vaccines, respectively, with placebo. Enrollment was brisk, but due to declining cases in Liberia, in March the trial there was converted to a Phase 2 safety and immunogenicity study enrolling 1,500 volunteers. Enrollment finished in April. Volunteers will be monitored for one year post-vaccination to determine the magnitude and durability of immune responses.

The Sierra Leone College of Medicine and Allied Health Sciences, the Sierra Leone Ministry of Health and Sanitation, and the CDC are working on an Ebola vaccine trial in Sierra Leone. The Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) protocol was reviewed and approved by the Sierra Leone Ethics and Scientific Review Committee, the Sierra Leone Pharmacy Board, and the CDC Institutional Review Board; and FDA approved the study to proceed. STRIVE is a non-blinded and individually randomized trial of the NewLink Genetics/Merck & Co. vaccine targeting health and other frontline workers in five districts in Sierra Leone. More than 350 Sierra Leone trial staff have been trained on good clinical practices and study protocol; critical cold chain needs for vaccine storage have been established so the clinical sites could receive vaccine shipments; vaccination and study site infrastructure has been renovated, and the contract research organization (CRO) is in place for

trial oversight. STRIVE launched in April 2015, and more than 7,150 participants have been enrolled in STRIVE and more than 3,450 (those randomized to the "early" arm) have been vaccinated as of June 2015. BARDA's CSN and BARDA clinical, laboratory, and logistics staff provided direct, in-country support for this trial. Depending on the outcomes of these clinical trials and other studies, BARDA will consider whether to support late-stage development and procurement of promising Ebola vaccine and therapeutic candidates under Project BioShield in FY 2016.

Beginning in late August 2014, BARDA convened a weekly meeting for information sharing and coordination of modeling results focused on the Ebola response. This "Modeling Coordination Group" included participants from USG agencies including ASPR, CDC, DHS, DoD, NIH, Department of State, and the United States Agency for International Development (USAID), as well as international partners and the academic modeling community. BARDA's modeling group produced weekly forecasts of Ebola cases starting in late October 2014, with the aim of supporting decision-making surrounding the clinical trials of therapeutics and vaccines. BARDA also worked closely with CDC modelers to develop estimates of the risk posed by case importation into the United States, as well as assessments of necessary domestic treatment capacity. BARDA also organized a meeting in December 2014, titled 'Public Health Issues for Ebola: Modeling for Policy', that aimed to translate pressing public health questions into actionable items for academic modelers to pursue.

Throughout the outbreak response, FDA engaged in intensified interactions with industry sponsors and federal partners that fund MCM development to provide early advice on product development and design of clinical trials to gather data to support the use of various therapeutics and vaccines. FDA's Ebola Task Force, composed of staff from across FDA, met regularly throughout this period. In addition, FDA convened regularly with international counterparts (European Medicines Agency[19], Health Canada, the Paul-Ehrlich-Institut, etc.) to achieve any possible regulatory convergence, speed product development and minimize redundancies. FDA also participated in multiple international meetings, most organized by the WHO, to further product development, share product-specific data, and evaluate clinical trial designs for studies to be conducted in Africa. FDA's coordination with these key stakeholders helped to expedite the development and availability of medical products – such as treatments, vaccines, diagnostic tests, and PPE – to help bring the epidemic under control as quickly as possible.

FDA used all regulatory mechanisms available, as well as intensified and enhanced regulatory interactions, to encourage the development of therapeutics, vaccines, and diagnostics for Ebola. As a result, multiple clinical trials for several vaccine and therapeutic candidates have been performed or initiated in Africa in record time. In addition to the critical importance of focusing on encouragement of interpretable clinical trials that can contribute both to access and to understanding of MCM benefits and risks, examples of other FDA regulatory mechanisms that

[19] The European Medicines Agency is a decentralized agency of the European Union, located in London. The agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. It began operating in 1995. (for more information, see http://www.ema.europa.eu/ema/)

can provide access to or encourage development of MCMs that meet the necessary criteria include:

- Emergency Use Authorization: If certain prerequisites, including a declaration by the Secretary of HHS, are met, FDA can enable the use of certain unapproved medical products, or the unapproved use of certain approved medical product during emergencies, when, among other circumstances, adequate preliminary data have been submitted to support such use according to the EUA criteria and there are no adequate, approved, and available alternatives. Between March 2014 and July 2015, FDA issued 10 EUAs for Ebola diagnostic devices.[20]
- Emergency Investigational New Drug (eIND) and other Expanded Access uses: Under certain circumstances, the FDA may enable access for individuals to investigational products through mechanisms outside of a clinical trial. In order for an investigational treatment to be administered in the United States, the product sponsor must agree, informed consent must be appropriately addressed, and a request must be submitted to and authorized by the FDA. The FDA stands ready to work with companies and investigators treating Ebola patients in dire need to enable access to an investigational product where appropriate.
- Orphan Designation: This designation, coupled with other FDA programs (*e.g.*, Fast Track, Priority Review) used to expedite product development, review, and approval, provides incentives to encourage companies to invest in and develop treatments for rare diseases like Ebola, with the goal of getting safe and effective products to U.S. patients as quickly as possible. Some sponsors of products proposed as potential Ebola countermeasures have applied for and received orphan designation.[21]

As part of hospital readiness guidance, the CDC helped to define the number of days of PPE supplies needed to manage the care of PUIs and Ebola cases based on a hospital's designated role (*e.g.*, Frontline Healthcare Facility, Ebola Assessment Hospital, or Ebola Treatment Center (ETC)) in the outbreak[22]. In addition, the CDC Rapid Ebola Preparedness teams conducted PPE assessments to identify gaps in hospital readiness and determine procurement goals based on CDC PPE guidance. The CDC also coordinated with ETCs and those hospitals caring for PUIs and informed commercial supply chain partners of those facilities in need of priority PPE delivery. Prior to state designation as an ETC, a CDC Rapid Ebola Preparedness team visited each designated hospital and conducted a PPE assessment to identify gaps in hospital readiness and determine procurement goals based on CDC PPE guidance. The CDC also fielded questions from, and provided critical updates to, state and local partners regarding the PPE supply chain and PPE readiness options. In addition, to support domestic PPE readiness for this response, the CDC/DSNS procured a 250-day supply of PPE for the SNS to assist any U.S. hospital health care team in caring for Ebola patients, if local supplies were exhausted.

[20] For more on the ten EUAs issued by FDA for Ebola diagnostic devices, see http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#ebola

[21] Details about Ebola-targeting products that have received FDA orphan designation can be found in FDA's database (available at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/)

[22] For a description of CDC's framework for a tiered approach, see http://www.cdc.gov/vhf/ebola/healthcare-us/preparing/hospitals.html

SECTION 2: NEW ACTIVITIES SINCE THE *2014 PHEMCE SIP*

This section describes activities not included in the *2014 PHEMCE SIP*. These are new, forward-looking activities; plans to pursue and accomplish the activities detailed hinge on federal funding levels. Time frames for these activities match the *2014 PHEMCE SIP*: near-term (FY 2015-16), mid-term (FY 2017-18), and long-term (FY 2019 and beyond). Activities described in the *2014 PHEMCE SIP* are still being pursued as PHEMCE priorities unless updated in this section or in Appendix 5.

Emerging Infectious Diseases

The threat of re-emerging and emerging infectious diseases (EID) poses a challenge to public health and national security that has been recognized by the PHEMCE since the release of the *2012 PHEMCE Strategy* and accompanying *Implementation Plan*. NIH maintains an active portfolio and will continue to support basic research, preclinical activities, and research into the development of novel vaccines and therapeutics for EIDs, such as Ebola and Marburg virus disease, MERS-CoV, chikungunya and dengue fever. The PHS Act, as amended by the Pandemic and All-Hazards Preparedness Act (2006), also directs BARDA to support advanced development of MCM for EIDs. While the *2014 PHEMCE SIP* noted some ongoing efforts, these will be amplified moving forward.

(T.EID.1) In the near-term, BARDA plans to establish an EID Program that will be managed by a new BARDA division, BARDA/EID that will have two overarching goals:

- To expand the MCM response capabilities of BARDA's National MCM Response Infrastructure with rapid new platform technologies for EIDs; and
- To ensure a MCM development pipeline exists to address high priority EID threats.

(T.EID.2) The PHEMCE will generate a list of high-priority EIDs to inform EID MCM development and utilization investments. The BARDA EID program will support MCM candidates for the top four or five high-priority threats that industry would not otherwise develop MCMs, absent government investment. BARDA also envisions augmenting the National MCM Response Infrastructure with "plug-and-play" vaccine manufacturing platforms and rapid response monoclonal antibody technologies.

Ebola Preparedness and Response[23]

(T.OV.27) The PHEMCE continues to support basic, preclinical, and clinical research that will lead to new approaches to prevent and treat Ebola. BARDA, NIH, and DoD support the development of multiple Ebola MCMs including the therapeutic candidates ZMapp™, BCX4430, AVI-7537 and favipiravir; and multiple vaccine candidates, including chimpanzee adenovirus vector type 3 (ChAd3), ChAd26/MVA vectors and rVSV vector. The FDA issued draft guidance to describe the Agency's premarket regulatory requirements and the performance testing

[23] This section describes planned activities as of summer 2015. Due to the evolving nature of the Ebola outbreak response at the time of this writing, priorities may shift in order to best meet newly identified preparedness and response needs.

needed to support liquid barrier claims for gowns intended for use in healthcare settings.[24] *(T.OV.28)* The CDC National Institute for Occupational Safety and Health (NIOSH) and DSNS are refining the NIOSH PPE-Info database[25] to provide a tool by summer 2015 for end-users to quickly identify gowns and coveralls on the market that meet CDC PPE guidance for handling Ebola patients or PUIs.

(T.OV.29) CDC and NIAID will continue to study the pathogenic properties of the new West African Ebola virus isolates compared with previous outbreak isolates and to support rapid assessment of promising antiviral therapeutics. CDC and NIAID will also work on *(T.OV.30)* development and validation of rapid (*i.e.*, point-of-care) Ebola diagnostic assays and multiplex assays for differential diagnosis and to guide patient care in Africa; *(T.OV.31)* deep sequencing analysis of Ebola virus isolates and clinical material for microvariant genotypes of virus isolates from the West African outbreak; *(T.OV.32)* and the development of experimental animal models (including ferrets, guinea pigs, and other rodent models) to analyze transmission, pathogenesis, and MCM effectiveness against West African Ebola viruses compared to previous outbreak isolates. CDC expects 200 Ebola genomes to be sequenced in FY 2015.

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

MERS-CoV emerged in Saudi Arabia in 2012, and HHS declared that MERS-CoV posed significant potential for a public health emergency in 2013[26]. As such, the PHEMCE has supported efforts to address MERS-CoV as a potential emerging threat. Human-to-human transmission of this virus is not fully understood, but a large majority of MERS-CoV cases to date at the time of writing appear to potentially have resulted from contact with infected animals (*e.g.*, camels and bats) or from nosocomial or healthcare setting-related transmission among close-contacts in hospitals in Saudi Arabia and the United Arab Emirates. In 2015, South Korea experienced the largest known travel-associated outbreak of MERS-CoV outside the Arabian Peninsula. As of this writing there have been only two imported cases in the U.S. (*i.e.*, in Indiana and Florida in 2014) with no transmission.

NIAID will continue to support activities to address MERS-CoV as a public health threat: *(T.MC.1)* maintenance of an active grant portfolio supporting basic research into MERS-CoV natural history, virology, and pathogenesis; *(T.MC.2)* and basic and preclinical research into the development of novel vaccines and therapeutics for MERS; *(T.MC.3)* development of transgenic mouse and other relevant animal models for MERS-CoV infection to perform exploratory activity studies on novel vaccines and therapeutics; and *(T.MC.4)* awarding contracts for screening MCMs against MERs-CoV *in vitro* and *in vivo*.

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[24] Premarket Notification Requirements Concerning Gowns Intended for Use in Health Care Settings - Draft Guidance for Industry and Food and Drug Administration Staff, FDA, 2015. Available at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm452804.pdf.

[25] A compendium of federal regulations and consensus standards for Personal Protective Equipment (PPE), is available at http://wwwn.cdc.gov/ppepros

[26] The HHS declaration of MERS-CoV as a public health threat available at http://www.phe.gov/emergency/news/healthactions/phe/Pages/MERS-CoV.aspx

(T.MC.5) CDC conducts domestic surveillance and will continue to be engaged in the Middle East, including deploying teams to assist in Saudi Arabia's MERS-CoV outbreak investigation and control.

(T.MC.6) In an effort to continue reinforcing awareness of the MERS-CoV potential threat, CDC will continue measures for border screening and travel notices including:

- Reinforcing guidance for CDC Quarantine Station staff to assess ill travelers for MERS-CoV, provide them with informational cards if case definitions are met, and coordinate with health departments if emergency medical transport is needed;
- Reminding airlines of the need for vigilance for recognizing ill travelers on flights from the Arabian Peninsula and to report to CDC under existing procedures;
- Ensuring MERS-CoV educational posters for outbound travelers are present and visible in departure areas of U.S. international airports;
- Displaying MERS-CoV messages for inbound travelers on CDC- and Customs and Border Protection-owned electronic message boards in arrival areas of international airports and supplementing with posters in airports where message boards are not available; and,
- Continuing the travel notice to practice enhanced precautions (*i.e.*, Level 2: Alert) currently on the CDC Travelers Health website.[27]

In an effort to continue reinforcing awareness of the MERS-CoV potential threat, DHS Customs and Border Protection, using just-in-time training (called "musters"), developed in coordination with CDC, should enhance vigilance for travelers with overt signs of illness at U.S. international airports.

National Strategy for Combating Antibiotic-Resistant Bacteria (CARB)

In September 2014, President Obama issued Executive Order (EO) 13676, *Combating Antibiotic-Resistant Bacteria*, which, among other activities, directed the PHEMCE to develop new and next-generation countermeasures that target antibiotic-resistant bacteria that present a serious or urgent threat to public health[28]. This EO resulted in the National Strategy for CARB[29] and the National Action Plan for CARB[30]. The PHEMCE agencies are heavily engaged in these activities.

NIAID's goals of advancing basic, translational and clinical research to develop better ways to prevent, diagnose, and treat antibiotic-resistant bacteria are furthered by the objectives and milestones within the National Action Plan for CARB. NIH's related activities will include *(C.AR.1)* development and maintenance of a National Sequence Database of Resistant

[27] More information on travel notice definitions is available at http://wwwnc.cdc.gov/travel/notices#travel-notice-definitions
[28] Combating Antibiotic Resistant Bacteria is available at https://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria
[29] The National Strategy for CARB is available at https://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf
[30] The National Action Plan for CARB is available at http://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

Pathogens; *(C.AR.2)* launching of a research program that uses systems biology to identify new drug targets that can be used to develop antibiotics with modes of action that make the development of resistance less likely; and *(C.AR.3)* establishment (in collaboration with BARDA) of a prize for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship. *(C.AR.4)* NIAID will fund new projects to support the discovery and development of new types of antibacterial products (***e.g.***, monoclonal antibodies, vaccines, or microbiota-based therapeutics), as well as adjunctive therapies to restore the activity of existing antibiotics.

BARDA will continue to stimulate the antibacterial pipeline by forming public-private partnerships with companies engaged in the research and development of novel antibacterials. Currently, BARDA has six partnerships through which it has funded development of eight candidate antibacterials; four are in Phase 3 clinical development. *(C.AR.5)* In FY 2015, BARDA will expand its antibacterial program by forming one antibacterial portfolio partnership, thus fulfilling the one-year goal set in the CARB National Plan requiring that ASPR/BARDA create at least one additional portfolio partnership with a pharmaceutical or biotechnology company by March 2016. In FY 2016, BARDA's antimicrobial program will hit a milestone for the first time since its 2010 inception. NDA filings for two BARDA-funded products (***i.e.***, eravacycline and solithromycin) are anticipated in 2016. *(C.AR.6)* In the near term, BARDA intends to diversify its portfolio by making initial investments in nontraditional antibacterial therapies (***e.g.,*** antibody or microbiome approaches) and products that can prevent infection upon entry into a hospital setting or reduce the length of a hospital stay.

DoD and USDA co-chair a CARB task force that is in the process of developing policy and implementation guidance to support all aspects of the National Strategy for CARB and the National Action Plan for CARB. *(C.AR.7)* Within 180 days of the release of the Action Plan and each year thereafter, the Task Force shall provide the President with an update.

The DoD also advanced a novel class of antibiotics to Phase 2 clinical testing in the second quarter of FY 2015. *(C.AR.8)* A novel topoisomerase small molecule broad-spectrum therapeutic against a panel of MDR clinical pathogens, including demonstrated efficacy against *Burkholderia pseudomallei* and MDR *Yersinia pestis*, will be advanced and submitted to FDA to review for IND by FY 2017. Ongoing preclinical evaluation in anthrax and tularemia should be completed by third quarter of 2015. Advanced pre-clinical testing, to include manufacturing, safety, and additional *in vivo* activity studies, is underway. Evaluation of potential for arrhythmias in humans should be completed in the fourth quarter of FY 2015.

To support the development of diagnostics to improve treatment of antibiotic-resistant bacteria, enhance infection control, and facilitate outbreak detection as described in the National Action Plan for CARB, the CDC will use its expertise and core strengths to *(C.AR.9)* support a new Resistant Bacteria Bank to provide a tool to aid development of antibiotics and diagnostics that was launched August 2015; *(C.AR.10)* contribute data to the National Sequence Database of Resistant Pathogens; and *(C.AR.11)* advance development and use of rapid and innovative diagnostic tests in collaboration with DoD.

CONCLUSION

This *2015 PHEMCE SIP* records progress made by the PHEMCE in the past year and updates the priorities included in the *2014 PHEMCE SIP* for federal MCM research, development, acquisition, stockpiling, distribution, dispensing, and monitoring programs. ASPR will continue to track execution of these priorities. Periodic updates will continue to be provided through the PHEMCE governance structure and included in future iterations of the *PHEMCE SIP*. Through this process the PHEMCE will facilitate accountability, foster coordination, and identify and address potential challenges in pursuit of these important goals and objectives.

APPENDIX 1: ACRONYMS

AABB	American Association of Blood Banks
ABA	American Burn Association
ARD	Advanced Research and Development
ARS	Acute Radiation Syndrome
ASPR	Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officials
AVA	Anthrax Vaccine Adsorbed
BAA	Broad Agency Announcements
BARDA	Biomedical Advanced Research and Development Authority
BAT	Botulism antitoxin
BLA	Biologics License Application
BTB	U.S.-Canada Beyond the Border Initiative
BWA	Biological Warfare Agent
CABP	Community Acquired Bacterial Pneumonia
CARB	Combating Antibiotic-Resistant Bacteria
CBRN	Chemical, Biological, Radiological, and Nuclear
CDC	Centers for Disease Control and Prevention
CERC	Crisis and Emergency Risk Communication
CEU	Continuing Education Units
cHA	Chimeric Hemagglutinin
ChAd3	Chimpanzee Adenovirus Vector Type 3
CHO	Chinese Hamster Ovary
CIADM	Centers for Innovation in Advanced Development and Manufacturing
cIAI	Complicated Intra-Abdominal Infection
CRE	Carbapenem-Resistant *Enterobacteriaceae*
CRI	Cities Readiness Initiative
CRO	Contract Research Organization
CSN	Clinical Studies Network
CVV	Candidate Vaccine Virus
CY	Calendar Year
DHS	U.S. Department of Homeland Security
DoD	U.S. Department of Defense
DSNS	Division of the Strategic National Stockpile (at CDC)
DTRA-JSTO	Defense Threat Reduction Agency–Joint Science & Technology Office (at DoD)
EID	Emerging Infectious Diseases
eIND	Emergency Investigational New Drug
EO	Executive Order
ETC	Ebola Treatment Center
EUA	Emergency Use Authorization
FAR	Federal Acquisition Regulation
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration

FEMA	Federal Emergency Management Agency
FFMN	Fill-Finish Manufacturing Network
FICOP-MCM	Federal Interagency Concept of Operations Plan—Medical Countermeasures Dispensing
FRMM	Influenza (Flu) Risk Management Meeting
FY	Fiscal Year
GHSI	Global Heath Security Initiative
GLP	Good Laboratory Practices
HCPWG	Pediatric Health Care Preparedness Working Group
HHS	U.S. Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HPP	Hospital Preparedness Program
HSWG	North American Health Security Working Group
IAA	Interagency Agreement
IDSA	Infectious Diseases Society of America
IM	Intramuscular
IND	Investigational New Drug
IOM	Institute of Medicine
IPT	Integrated Program Team
IRAT	Influenza Risk Assessment Tool
IVD	*In vitro* diagnostic
JBAIDS	Joint Biological Agent Identification and Diagnostic System
LID	Laboratory of Infectious Diseases (at NIH/NIAID)
LRN	Laboratory Response Network
MCM	Medical Countermeasures
MCS-JVAP	Medical Countermeasure Systems – Joint Vaccine Acquisition Program (at DoD)
MDR	Multi-Drug Resistant
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MSA	Metropolitan Statistical Areas
MTA	Material Threat Assessment
MVA	Modified Vaccinia Ankara (smallpox vaccine)
MYB	Multiyear Budget
NACCD	National Advisory Committee on Children and Disasters
NACCHO	National Association of County and City Health Officials
NAPAPI	North American Plan for Animal and Pandemic Influenza
NBSB	National Biodefense Science Board
NDA	New Drug Application
NDN	Non-Clinical Development Network
NGO	Non-Governmental Organizations
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health

NIOSH	National Institute for Occupational Safety and Health
NPRSB	National Preparedness and Response Science Board
OPP	Office of Policy and Planning (at HHS/ASPR)
OPT	Office of Pediatric Therapeutics (at FDA)
ORR	Operational Readiness Review
PAHPA	Pandemic and All-Hazards Preparedness Act
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act (Public Law 113-5)
PedsOB IPT	Pediatrics and Obstetrics Integrated Program Team
PEP	Post-Exposure Prophylaxis
PHAA	Public Health Actionable Assays
PHAC	Public Health Agency of Canada
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PHEP	Public Health Emergency Preparedness
PHP Summit	Public Health Preparedness Summit
PHS Act	Public Health Service Act
PK	Pharmacokinetic
POD	Point-of-Dispensing
PPE	Personal Protective Equipment
PUI	Patients Under Investigation
RCT	Randomized Controlled Trial
RDD	Radiological Dispersal Device
REC	Regional Emergency Coordinators (at HHS/ASPR)
RITN	Radiation Injury Treatment Network
rPA	Recombinant (anthrax) Protective Antigen
RPD	Respiratory Protective Devices
rVSV	Recombinant Vesicular Stomatitis Virus
sBLA	Supplemental Biologics License Application
SIP	Strategy and Implementation Plan
SLEP	Shelf-Life Extension Program
SLTT	State, Local, Tribal, and Territorial
SNS	Strategic National Stockpile (at CDC)
SRF	Special Reserve Fund
STRIVE	Sierra Leone Trial to Introduce a Vaccine against Ebola
TAR	Technical Assistance Review
TRA	Terrorism Risk Assessment
UASI	Urban Areas Security Initiative
USAID	United States Agency for International Development
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USDA	U.S. Department of Agriculture
USG	U.S. Government
VA	U.S. Department of Veterans Affairs
VAMPSS	Vaccine and Medications in Pregnancy Surveillance System
WHO	World Health Organization

APPENDIX 2: PHEMCE COORDINATION WITH NON-FEDERAL STAKEHOLDERS

The PHEMCE coordinates and collaborates with non-federal stakeholders through a variety of venues. This appendix highlights recent activities with SLTT, regional, international, industrial, and professional society stakeholders. These interactions shape federal MCM planning and identify 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 federal plans for ensuring MCM preparedness. NACCHO and ASPR hosted a webinar in March 2015 for SLTT partners to learn about the purpose and priorities of the PHEMCE. In addition, ASPR hosted a PHEMCE Town Hall session at the 2015 Public Health Preparedness Summit in April 2015 in Atlanta, Georgia. ASPR also hosted a learning session at the Summit focused on the requirements process and MCM medical utilization and response integration. This session stimulated valuable dialogue that identified gaps and potential solutions between federal and SLTT preparedness planning. These engagements highlighted the areas where federal plans may intersect with and impact state and local health department planning and encouraged increased connectivity at all levels of government.

ASPR also prioritizes the engagement of MCM developers and end-users to inform desired product characteristics. BARDA 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 have an opportunity to arrange individual meetings to discuss specific development and manufacturing technologies with federal officials. These events are well-attended. For example, the successful 2014 BARDA Industry Day included more than 600 participants from diverse backgrounds including industry, other federal agencies, local and state government, and academia. The 2015 BARDA Industry Day was held in October;
- BARDA collaborates with organizations such as the Biotechnology Industry Organization, the Alliance for Biosecurity, and the Center for a New American Security to inform stakeholders of BARDA and PHEMCE-wide priorities;
- The BARDA Broad Agency Announcements (BAA) were posted in October 2015 and a pre-proposal conference will be held within 30 days of posting;
- BARDA reaches out to end users in a variety of ways to gather information about needs, elicit feedback about existing products, and highlight recent advances in MCM development. BARDA staff periodically visit ASPR's Regional Emergency Coordinators (RECs), most recently in spring and early summer 2015, to provide briefings on BARDA initiatives. The RECs convey information about MCMs directly to state and local partners or facilitate interactions with BARDA staff as needed. BARDA also works with professional societies, such as the American Burn Association (ABA) and the Infectious Diseases Society of America (IDSA), and standard-setting organizations, such as the

American Association of Blood Banks (AABB), to identify end-user needs and priorities; and,

- BARDA has shared modeling and simulation tools directly with Los Angeles and New York City public health officials to facilitate local planning efforts. In 2015, BARDA staff began participating in local and national exercises sponsored by the Radiation Injury Treatment Network (RITN) and involving affiliated treatment centers.

Another key opportunity for industry and academic 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 to meet technical and regulatory challenges, and provide insight on how a product or technology may best address federal priorities. These meetings aim to provide the USG with the latest information about emerging technologies and tools that may guide 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 development of their MCM products and how they may work with the USG as part of this process. On average, BARDA hosts more than 100 TechWatch meetings annually. The TechWatch program has been an invaluable mechanism to gather information about potential medical products and technological solutions that may be of interest to BARDA or other PHEMCE partners, particularly during the Ebola response. With respect to Ebola, BARDA was contacted by 131 interested parties and conducted 85 TechWatch meetings as of April 2015.

One of the mandates of EO #13527, from December 2009, was the establishment of a timely federal response capability to dispense MCM following a biological attack.[31] In response to this EO, the DHS Federal Emergency Management Agency (FEMA), ASPR, and CDC championed the development of a Federal Concept of Operations describing how the USG would support states and local governments following a biological attack in rapidly providing MCMs. In January 2013, FEMA directed its regional staff to work with ASPR RECs and CDC/DSNS staff to develop a strategy for engaging state and local officials to employ an integrated multidisciplinary effort to operationalize the Federal Interagency Concept of Operations Plan—Medical Countermeasures Dispensing (FICOP-MCM) and implement EO #13527.

The efforts of ASPR RECs and CDC/DSNS staff include:

- Providing a collaborative federal, state and local interagency forum to organize, coordinate and execute MCM planning;
- Ensuring that federal planning efforts consider and respect the sovereignty of state and local governments by incorporating state and local entities in the workgroup from inception;

[31] Section III of EO 13527 states, "Sec. 3. Federal Rapid Response. (a) The Federal Government must develop the capacity to anticipate and immediately supplement the capabilities of affected jurisdictions to rapidly distribute medical countermeasures following a biological attack. Implementation of a Federal strategy to rapidly dispense medical countermeasures requires establishment of a Federal rapid response capability." The entire text is available at: http://www.gpo.gov/fdsys/pkg/FR-2010-01-06/pdf/2010-38.pdf

- Ensuring comprehensive creation, development, planning and execution of the initiatives in a collaborative effort with local, state and federal government entities, as well as with the private sector when appropriate; and,
- Leveraging information, ideas and best practices, subject-matter expertise and capabilities to strengthen MCM planning.

To this end, regional MCM planning efforts, co-led by FEMA and ASPR/Office of Emergency Management have been undertaken in the 10 largest Urban Areas Security Initiative (UASI) area jurisdictions based on the Cities Readiness Initiative (CRI)[32].

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, five territories, and three freely associated states[33]. 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 guidelines and/or recommendations. This planning is supported by guidance from ASPR and CDC (*e.g.*, the joint FY14 ASPR HPP - CDC Public Health Emergency Preparedness (PHEP) continuation grant guidance (CDC-RFA-TP12-120102CONT14)[34] provides opportunities and guidelines for HPP sub-awardee health care coalitions/hospitals to exercise the responder safety and health capability during joint exercises). This guidance also includes health care coordination with federal MCM programs, including the SNS.

As called for by the Global Health Security Agenda, ASPR continues to engage with international stakeholders to "improve global access to medical and non-medical countermeasures during health emergencies." 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. They include 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

[32] CRI is described in further detail below.
[33] Palau, Micronesia, and the Marshal Islands
[34] The HPP grant guidance available at http://www.phe.gov/Preparedness/planning/hpp/Documents/hpp-bp3-continuation-guidance.pdf

MCMs during a response. To strengthen MCM distribution and dispensing at the local level, designated PHEP funding is provided to 72 CRI jurisdictions to support MCM preparedness in the nation's largest cities and metropolitan statistical areas (MSAs) where a majority of the nation lives. 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 it shares resources and programmatic and scientific expertise. These stakeholders, as well as public health practitioners, clinicians, and clinicians' associations, get involved during the development of public health policies, clinical guidance, and recommendations for existing and new MCMs. CDC's Healthcare Preparedness Activity also 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 and after an emergency.

FDA works regularly with state and local public health authorities and responders, and public health NGOs to support MCM preparedness and response capabilities at the state and community levels. Activities in support of state and local readiness include responding to numerous MCM emergency use inquiries, including regulatory/legal questions about EUAs, expiration dating, and stockpiling. During the reporting period, FDA worked to ensure MCM availability, including by participating in the federal Shelf-Life Extension Program (SLEP). FDA also conducted scientific analyses on, and enabled new use dates for, certain auto-injector products while manufacturing issues were addressed. It also issued messaging to stakeholders, and responded to state/local, federal, and international stakeholder requests for information about these products. To further facilitate engagement with stakeholders, gain stakeholder perspectives, and communicate MCM-related updates, FDA participates in national-level workshops, meetings, and webinars. That includes organizing and participating in sessions at the 2015 Public Health Preparedness Summit and participating in the Institute of Medicine (IOM) Forum on Medical and Public Health Preparedness for Catastrophic Events (Preparedness Forum).

In support of the *Combating Antibiotic-Resistant Bacteria* (CARB) initiative, FDA and NIH hosted several workshops in 2014 to address antibiotic resistance:

- April 2014 – Public Workshop – Advancing Regulatory Science for High Throughput Sequencing Devices for Microbial Identification and Detection of Antimicrobial Resistance Markers[35] a workshop hosted by the FDA;

[35] Information on the advancing regulatory science workshop can be found at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm386967.htm

- July 2014 – The Development of New Antibacterial Products: Charting a Course for the Future[36] a workshop co-hosted by the NIH and FDA;
- September 2014 – Addressing Challenges in Antimicrobial Resistance: Overcoming Bottlenecks in Antibacterial Product Development and Coordinated Development of Diagnostics and Therapeutics[37] a workshop co-hosted by the NIH and FDA; and,
- September 2014 – Coordinated Development of Diagnostics & Therapeutics Workshop[38] a workshop co-hosted by the NIH and FDA.

[36] Information on the development of new antimicrobials workshop can be found at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm403009.htm

[37] Information on the addressing the challenges of antimicrobial resistance workshop can be found at https://respond.niaid.nih.gov/conferences/TherapeuticsWorkshops2014/Pages/default.aspx

[38] Information on developing diagnostics and therapeutics is available at https://respond.niaid.nih.gov/conferences/therapeuticsworkshops2014/pages/coordinated-agenda.aspx

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

Since the release of the *2014 PHEMCE SIP*, significant progress has been made in addressing the MCM needs of at-risk[39] populations. As required by section 2811(d) of the PHS Act[40] selected highlights of this progress are listed below. As in Section 1: Accomplishments Since the *2014 PHEMCE SIP*, the reporting period for progress in this appendix is from March 2014 to February 2015, except where otherwise noted.

Table 3: Progress in Addressing At-Risk MCM Needs

PHEMCE Mission Component[41]	Progress
Requirements Setting	• ASPR created new templates for PHEMCE requirements documents, which address at-risk population needs, ensuring that this analysis will be performed throughout the requirements process. • The Pediatrics and Obstetrics Integrated Program Team (PedsOB IPT) actively monitors requirements activities to ensure the needs of pediatric and obstetric populations are considered. • BARDA and PedsOB IPT leadership confirmed that the PedsOB IPT is the appropriate body to request inclusion of pediatric and obstetric populations in medical consequence analysis and with which to discuss future data and analysis that might be useful and available within the context of PHEMCE requirement setting and prioritization.
Advanced Development/ Manufacturing	• BARDA supports the development of a low-cost, portable ventilator that will be suitable for neonate, infant, and pediatric populations. • NICHD reviewed the SNS formulary and standard acute care supportive drugs for adequacy in dosing information for obese children and adults. The requisite pharmacokinetic (PK) data to enable proper dosing for obese populations exists for only 2 percent of obese children and 50 percent of obese adults. The Pediatric Trials Network will be performing opportunistic studies as well as conventional PK studies to fill gaps. • NICHD is developing a protocol with a study to follow noting which pediatric procedures can be done in an exposed environment wearing various levels of PPE, as well as which pediatric procedures can be done wearing Ebola PPE for EMS and the hospital. • Utilizing prior studies, NICHD is working on a manuscript that will provide midazolam IM injection dosing recommendations for the treatment of status epilepticus and (off-label) nerve agent induced seizures in children (both off-label uses).[42] • NIH, BARDA, and DoD funded clinical studies to support a seizure indication for midazolam, which would include pediatric use. In 2014, BARDA provided funding for the development of a

[39] At-risk individuals have needs in one or more of the following access or functional areas: communication, maintaining health, independence, services and support, and transportation. At-risk individuals may include children, older adults, and pregnant women as well those with 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. More information is available at: http://www.phe.gov/Preparedness/planning/abc/Pages/at-risk.aspx

[40] 42 U.S.C. 300hh-10(d)

[41] As listed in the *2012 PHEMCE Strategy*

[42] Midazolam is not FDA approved for seizures, including seizures due to nerve agents, and no EUA for midazolam has been issued. While utilization of midazolam for seizures is off-label, this manuscript will provide best-dosing guidelines pending completion of official approval processes for revised labeling.

PHEMCE Mission Component[41]	Progress
	juvenile rodent animal model to facilitate nonclinical testing of products intended for pediatric patients. 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 children and adults, as well as approval of midazolam for use in treating common prolonged seizures. • NIH CounterACT funds studies through an Interagency Agreement (IAA) with the DoD on the activity of existing and new therapeutics using juvenile and pediatric animal models. Studies conducted through this IAA include studies in animal models of geriatric populations. NIH CounterACT also funds some investigator-initiated grants using pediatric animal models. • NIH's NICHD conducted studies to obtain additional doxycycline PK data to support improved dosing recommendations for the treatment of *Bacillus anthracis* spore exposure in young children. The NICHD has also published a Task Force report on pediatric palatability.[43] • NIAID initiated activities to explore the development of rodent pediatric animal models through the product development support services contract and porcine pediatric animal models through an IAA. NIAID and BARDA will co-sponsor a symposium in summer 2015. • BARDA's Nonclinical Studies Network supported the development of Hematopoietic-acute radiation syndrome (ARS) irradiation minipig models. Results of these studies, which were presented at the 2014 Radiation Research Society Annual Meeting, suggested that the model could resemble many features of the human disease. • BARDA supported advanced development of Prussian blue for pediatric populations using nanotechnology. Formulation and *in-vitro* release tests for use in selecting a final granulated, spray-coated, and milled Prussian blue formulation with acceptable cyanide release and cesium binding efficacy occurred in 2014 and will continue in 2015. • BARDA continued support for the Vaccine and Medications in Pregnancy Surveillance System (VAMPSS). • BARDA supported GlaxoSmithKline to clinically evaluate H5N1 pre-pandemic influenza vaccine formulated with AS03 adjuvant in pediatric populations. GlaxoSmithKline will submit these data to FDA in a sBLA. • BARDA has supported the advanced development of candidate influenza antiviral drugs including peramivir and nitazoxanide, which may prove suitable for pediatric and other high-risk populations. • Based on NHP animal model efficacy studies supported by NIAID and human safety data provided by Amgen, FDA approved Neupogen® in March 2015 for adult and pediatric populations as the first radiation MCM to treat victims exposed to external radiation in a public health emergency.
Regulatory Science Management	• FDA established a Pediatric and Maternal Public Health and Security Action Team through its MCM Initiative. This Action Team completed an inventory of the SNS formulary to identify data gaps that could inhibit the effective use of stockpiled MCMs in children and pregnant and postpartum women. The analysis was presented to the PedsOB IPT, and the findings and recommended action items were approved and agreed upon by the IPT. The Action Team remains ready to address additional pediatric issues as warranted.

[43] The NICHD Task Force report on pediatric palatability is available at http://bpca.nichd.nih.gov/resources/publications/Documents/Report_Ped_Fmltions_Task_Force.pdf

PHEMCE Mission Component[41]	Progress
Procurement / Inventory Management / Stockpiling	• Subject matter experts on the PedsOB IPT determined and prioritized pediatric MCM gaps in the SNS as part of the 2014 SNS Annual Review. These recommendations will be considered as part of the annual HHS budget formulation process. The PedsOB IPT will engage in the SNS Annual Review process in 2015. • BARDA procured 4 million doses, sufficient to immunize 2 million individuals, of IMVAMUNE (smallpox MVA vaccine) as liquid-frozen product to maintain the current level of smallpox preparedness. This vaccine has the potential for use during an emergency under an EUA in individuals of all ages with HIV or atopic dermatitis, including women who are pregnant or nursing.
Deployment / Distribution / Dispensing / Administration	• During the development of the *Patient Decontamination in a Mass Chemical Exposure Incident: National Planning Guidance for Communities*, released in December 2014, stakeholders identified a need to develop pediatric-specific decontamination techniques. Preliminary work on this document began in January 2015 and is expected to be completed in the near-term. • In May 2014, the CDC published "Pediatric Anthrax Clinical Management" in *Pediatrics*. • In February 2014, CDC published "Special Considerations for Prophylaxis and Treatment of Anthrax in Pregnant and Postpartum Women" in *Emerging Infectious Diseases*. • In February 2015, CDC published "Clinical Guidance for Smallpox Vaccine Use in a Postevent Vaccination Program" in *Morbidity and Mortality Weekly Report*. This guidance provided specific recommendations for pregnant women, children, individuals with HIV infection, and individuals with eczema. • In June 2015, CDC published a systematic evidence review of the safety of smallpox vaccine use during pregnancy, which serves as the basis for recommendations about vaccine use among pregnant women, "Risks associated with smallpox vaccine use during pregnancy: A Systematic Review and meta-analysis" in *Obstetrics and Gynecology.* • CDC works to facilitate partnerships within the federal government, with state and local public health agencies, and with non-governmental organizations (*e.g.*, non-profits, healthcare, academia, and private industry) to ensure hard-to-reach and at-risk populations are included in planning and communicated with during an emergency. PHEP awardees are required to develop preparedness strategies that address the needs of at-risk individuals. One of the Public Health Preparedness Capabilities specifically addresses emergency communication with resources for communicating to at-risk populations. CDC activates a Children's Health Team and a Maternal Health Team within its Emergency Operations Center to integrate children's and maternal health needs in responses including communication for parents, educators, and pediatric health care professionals. • CDC continues to use multiple platforms including traditional and social media for the delivery of public health messages to the public. CDC developed STOPAnthrax™, an anthrax MCM text-messaging project as a stand-alone bidirectional text messaging program for patients who receive MCMs from PODs that provides text messages for users for up to 60 days. It provides a protocol specifically addressing pregnant women, relevant health education, encourages MCM adherence, and encourages reporting of adverse events.

Additionally, the PHEMCE has coordinated with the FDA's Office of Pediatric Therapeutics (OPT), through FDA's Pediatrics and Maternal Action Teams that includes members from OPT, to identify and address the needs of pediatric and maternal populations. OPT works closely with the FDA review divisions to facilitate the development and availability of MCMs for children. 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 enrolled only in clinical studies that are scientifically necessary and ethically appropriate. It also works to ensure that any pediatric studies conducted for MCMs are rigorously designed and conducted in accord with scientific understanding of issues such as exposure-response and extrapolation.

OPT also serves as a member of the National Advisory Committee on Children and Disasters (NACCD). The panel was established in 2014 under Section 2811A of the PHS Act, as amended by PAHPRA, to provide expert consultation to the Secretary of HHS and the ASPR on the medical and public health needs of children before, during, and after a disaster or public health emergency. In addition, the NACCD established several working groups and OPT chairs the Pediatric Health Care Preparedness Working Group (HCPWG). The HCPWG will address health care preparedness for public health threats, medical disasters, or mass trauma/casualty emergencies for the pediatric population. The working group plans to examine the state of facility preparedness, quality control programs, and MCMs (*i.e.*, drugs, devices, and PPE) in relation to the pediatric population, as well as to assess granting structures, develop mitigation strategies for identified gaps, and identify best practices and tools for increasing health care readiness involving children during health care emergencies.

APPENDIX 4: ADVANCED RESEARCH AND DEVELOPMENT AND PROCUREMENT

Project BioShield Authorities and Reporting Requirements

The Project BioShield Act of 2004 amended the PHS Act and the Federal Food, Drug, and Cosmetic Act (FD&C Act) to provide additional and more flexible authorities and funding to support the development and procurement of MCMs against CBRN threat agents. It was also designed to give the government the authority to quickly authorize such MCM use during emergencies. These authorities were further delineated, clarified, expanded, and extended by the Pandemic and All-Hazards Preparedness Act (PAHPA) and PAHPRA. Section 5 of the Project BioShield Act (42 U.S.C. 247d-6c) 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 Project BioShield Act, as enacted Section 319F-1 of the PHS Act (42 U.S.C. 247d-6a) and amended by PAHPA, authorizes 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 Project BioShield 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 FY 2004 through FY 2013 in a Special Reserve Fund for the procurement of security countermeasures that may be placed in the SNS. Furthermore, Section 3 of the Project BioShield Act as enacted Section 319F-2 of the PHS Act (42 U.S.C. 247d-6b), and amended by PAHPA and PAHPRA, authorizes the use and reporting of simplified acquisition procedures, the modified 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 Project BioShield Act, as enacted under Section 564 of the FD&C Act (21 U.S.C. 360bbb-3), and amended by PAHPRA, enables the FDA Commissioner[44] to issue an EUA to authorize the use of certain unapproved medical products, or to authorize certain unapproved uses of an approved medical products,[45] following a declaration by the Secretary of HHS that circumstances exist to justify the authorization based on one of four determinations by the Secretary of Defense, Secretary of Homeland Security, or Secretary of HHS. Before an EUA may be issued, FDA must conclude that certain criteria for issuance of the authorization (*e.g.*, the agent referred to in the HHS declaration can cause a serious or life-threatening disease or condition; the product may be effective in diagnosing, treating or preventing the disease or condition the known and potential benefits of the product outweigh its known and potential risks; and no adequate, approved, available alternatives) are met. Reporting is required on emergency uses of certain biologicals, drugs and devices, emergency declarations, and conditions of authorization.

[44] The HHS Secretary delegated the authority to issue an EUA to the FDA Commissioner.
[45] This authority is limited to products to respond to emergencies that involve biological, chemical, radiological, or nuclear agents.

In 2013, under PAHPRA, Congress repealed Section 5 of the Project BioShield 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 and is also described in the Project BioShield Annual Reports[46].

Authority Usage

In 2014, HHS used two of the authorities: one for the procurement of security countermeasures and the second, for the 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 acquisition activity in 2014.

HHS did not use authority for personal services contracts under PHS Section 319F-1(d) to hire experts or consultants for the purpose of performing, administering, or supporting qualified countermeasure research and development activities.

Advanced Research and Development (ARD) and Procurements

The annual appropriations amount provided in FY 2014 was $255 million for Project BioShield. Pursuant to the Joint Explanatory Statement accompanying the FY 2009 Omnibus Appropriation (P.L.111-8), BARDA will continue to provide monthly reports to the authorizing and appropriating committees detailing expenditures. These procurements are vetted through the PHEMCE leadership and are consistent with the annual *PHEMCE SIP* goals and objectives. While the Ebola response dominated the agenda for much of the reporting period, two Project BioShield procurements and other significant advances in CBRN MCM development are highlighted below. Highlights related to the Ebola response are described separately in the Section 1: 2014-15 Ebola Outbreak Response.

Key points include:

- An additional 4 million doses of modified vaccinia Ankara (MVA) smallpox vaccine were procured from Bavarian Nordic under Project BioShield in September 2014. That is sufficient to immunize 2 million people. This vaccine has the potential for use during an emergency under EUA in individuals of all ages with HIV or atopic dermatitis, including women who are pregnant or nursing;
- Nearly 33,000 doses of raxibacumab, a monoclonal antibody anthrax antitoxin, were procured from GlaxoSmithKline under Project BioShield in September 2014 as replenishment for expiring doses. The FDA approved raxibacumab[47] in December 2012 for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate;

[46] The Project BioShield Annual Reports are available at https://www.medicalcountermeasures.gov/barda/cbrn/project-bioshield-overview/project-bioshield-annual-report.aspx.

- Anthrasil®, a polyclonal anthrax antitoxin derived from human plasma and developed by Cangene/Emergent, was licensed by FDA in March 2015 for the treatment of symptomatic anthrax disease;
- Filgrastim, a granulocyte colony-stimulating factor manufactured by Amgen and previously approved for the reduction of neutropenic fever in patients receiving chemotherapy, received FDA approval in March 2015 for the treatment of patients with bone marrow suppression following exposure to high doses of radiation;
- In October 2014, Emergent submitted an sBLA for its licensed anthrax vaccine, Anthrax Vaccine Adsorbed (AVA, or also referred to as BioThrax®), for a post-exposure prophylaxis (PEP) indication;
- Solithromycin, a novel ketolide antibiotic manufactured by Cempra Pharmaceuticals achieved its primary milestone in a Phase 3 trial for community acquired bacterial pneumonia (CABP);
- Eravacycline, a next-generation tetracycline antibiotic that retains activity in the presence of some tetracycline resistance mechanisms, achieved its primary milestone in a Phase 3 trial for complicated intra-abdominal infection (cIAI); and,
- Carbavance™, a novel carbapenem/β-lactamase inhibitor combination being developed by Rempex Pharmaceuticals, entered a Phase 3 clinical trial for the treatment of complicated urinary tract infections and carbapenem-resistant *Enterobacteriaceae* (CRE) infections.

Table 4a: FY 2014 Advanced Research and Development Contracts

Threat Area	Time from Submission to Award	FY14 Award Amount ($M)	Benchmarks / Milestones
Broad-Spectrum Antimicrobials	Carbavance development (Rempex) – 7 months	$20	Data to support commercial application and potential use during an emergency
Diagnostics	Point of care rapid molecular-based diagnostic assay (Alere) – 12 months	$13	Development activities and data to support potential use during seasonal and pandemic influenza epidemics
	Development of a rapid flu A/B diagnostic test (InDevR) – 14 months	$8	Development activities and data to support potential use during seasonal and pandemic influenza epidemics
	Development of new biodiagnostic for anthrax disease (NanoMR) – 8 months	$6	Development activities and data to support potential use during an emergency and transition to procurement as product achieves this milestone
Innovation	Host-directed attenuator of cytokine storm (Atox Bio) – 12 months	$4	Data to support commercial application and potential use during an emergency
Influenza	High yield (high growth) reassortant seed influenza viruses (New York Medical College) – 8 months	$2	Development of improved candidate vaccine viruses for influenza vaccines
	Advanced development of antigen-sparing pandemic influenza vaccine (Sanofi Pasteur) – 10 months	$66	Data to support potential use during pandemic influenza epidemics
Ventilators	Development of next generation portable ventilator (Philips Healthcare) – 26 months	$14	Development activities and data to support potential use and transition to procurement as product achieves development milestones
Viral Hemorrhagic Fever	Development of ZMapp therapeutic for Ebola virus disease (Mapp) – 31 days	$25	Manufacturing process improvement and manufacturing of drug product for use in preclinical studies and clinical trials as part of the ongoing response to the West African Ebola epidemic
Total	—	$158	—

Table 4b: FY 2014 Project BioShield Procurement Contracts

Threat Area	Time from Submission to Award	FY14 Award Amount ($M)	Benchmarks / Milestones
Anthrax	Anthrax antitoxin replenishment (GSK)[48]	$105	Maintain antitoxin preparedness at current levels
Botulism	Botulism antitoxin therapeutic (Cangene)[49]	$4	Maintain antitoxin preparedness at current levels
Broad-Spectrum Antimicrobials	—	—	—
Chemical	—	—	—
Diagnostics	—	—	—
Plague	—	—	—
Radiological/Nuclear	—	—	—
Smallpox	Imvamune MVA acquisition option (Bavarian Nordic)[50]	$118	Dose delivery to SNS
Total	—	$227	—

[48] Time to award is not applicable here as this action entailed issuing a task order on an existing contract.
[49] Time to award is not applicable. These expenditures covered relabeling of vials and planning for a Phase 4 clinical trial as part of a post-marketing commitment to FDA.
[50] Time to award is not applicable here as this action entailed exercising an option on an existing contract.

Table 4c: FY 2014 Strategic National Stockpile (SNS) Procurement / Replenishment Contracts[51]

Threat Area	Actual FY14($M)
Anthrax	$221
Botulism	$0
Burkholderia	$0
Chemical	$17
Influenza	$10
Plague	$23
Radiological/Nuclear	$1
Smallpox	$37
Tularemia	$0
Federal Medical Station (FMS)	$1
Medical Supplies and Ancillary Items (MS&AI) and non-MS&AI[52]	$7
Total	$310

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 are captured in the PHEMCE Multiyear Budget (MYB) Report. Specifically, this document aggregates and analyzes the MCM-related spending estimates of NIH, ASPR, the

[51] SNS requirements for the stockpile are based on factors that vary from year to year. These include PHEMCE recommendations, expiring product, replenishment decisions, procurement costs and availability, shelf life extension, and funding considerations.
[52] 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.

CDC, and the 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 PHEMCE MYB Fiscal Years 2015-2019 report should go to Congress in early 2016.

Emergency Use Authorization

From March 2014 to July 2015, FDA used the EUA authority to issue fourteen EUAs to support critical preparedness and response activities for the following government- and industry-developed MCMs: two *in-vitro* diagnostics (IVD) to detect MERS-CoV, two IVDs to detect H7N9 influenza, and 10 IVDs (many of which were amended and reissued to reflect sponsors' requests) to detect Ebola virus in response to the 2014 West Africa outbreak.[53] In addition to issuing EUAs when necessary, FDA worked during the reporting period through its pre-EUA submission process to ensure that the U.S. government is as prepared as possible to deploy MCMs that may need to be used under an EUA. Through this process, FDA works with product sponsors or government agencies, including ASPR/BARDA, CDC, and DoD to facilitate the development of pre-EUA packages that will form the basis of an EUA request and issuance when circumstances justify.[54]

[53] Information on the FDA EUA is available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm.

[54] 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. The pre-EUA process allows FDA scientific and technical subject matter experts to begin a review of information and assist in the development of conditions of authorization, fact sheets, and other documentation needed for an EUA in advance of an emergency.

APPENDIX 5: PROGRESS AGAINST *2014 PHEMCE SIP* NEAR-TERM DELIVERABLES (AS OF FEBRUARY 2015)

Table 5: Progress Towards Near-Term *2014 PHEMCE SIP* Activities (as of February 2015)[55]

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
1.1.2	Submit the annual Multiyear Budget (MYB) report to Congress	ASPR	FY15-FY16	The 2014 PHEMCE MYB was transmitted to Congress in February 2015. Following a lessons-learned meeting with internal partners and a briefing to PHEMCE senior leaders, process improvements and scope of the report for 2015 will be identified.
1.1.3	Implement PHEMCE-wide portfolio tracking tools to further enable coordinated planning and management of CBRN MCM development	ASPR	FY15	COMPLETED - The web-based portfolio tracking tool for CBRN MCMs including analytics with drill-down capability was launched in November 2014. All agencies across the four CBRN MOU nations have been trained and provided access to the tool. The business process harmonization for the cost tool was completed in 2014 and prototype development has initiated. Business process harmonization is ongoing for a broad-based capabilities tool to capture non-product specific activities.
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	Metrics are being piloted with various MCMs.
1.2.1	Update initial anthrax Material Threat Assessment (MTA)	DHS	FY15	DHS has delivered illustrative scenarios for the anthrax MTA 2.0 to HHS partners and has completed modeling for those scenarios. DHS delivered an on-line tool enabling customer selection of modeling parameters and scenario details. Interactions with intelligence community and PHEMCE partners are ongoing, and the MTA Working Group is in process of down-selecting to the few scenarios to be written in detail for the final MTA 2.0 on anthrax.

[55] Unless otherwise noted. Note, any items that were marked "Complete" in the *2014 PHEMCE SIP* are not repeated in this table.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
1.2.3	Coordinate modeling efforts to ensure that the models and parameters are consistent to bring the Terrorism Risk Assessment (TRAs) and MTAs into alignment in support of MCM planning	BARDA / DHS	FY16	In execution of the *Bacillus anthracis* MTA, DHS and HHS modeling groups have met multiple times during 2014-2015 to deliberate modeling parameters and models. Continued interaction and dialogue expected for all agents.
1.2.4	Update the TRA development process in accordance with the *TRA Stakeholder Engagement Strategy*	DHS	FY15	TRA and MTA programs actively discussing how to integrate efforts better to ensure coordinated outputs and efforts.
1.2.5	Produce a TRA program implementation plan	DHS	FY16	A draft TRA Implementation Plan has been developed which intends to 1) establish a clear plan to guide engagement of strategic partners in the development of the TRAs; 2) identify policies and procedures for prioritizing future efforts to improve the TRAs, and 3) provide guidance and support to stakeholders in the use and interpretation of TRA results for USG preparedness efforts. Interagency discussions on finalizing the TRA Implementation Plan continue. Finally, DHS is reviewing a revised draft of the Integrated Terrorism Risk Assessments (ITRA) 3.0 report and will distribute to interagency stakeholders for final review prior to publication.
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	The EID Working Group reviewed the EID Architecture study conducted by DHS and is defining the critical parameters that will be included in the PHEMCE EID risk-assessment process.
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 of *2014 PHEMCE SIP*	ASPR	FY16	The PHEMCE approved nine civilian MCM requirements deliverables from March 2014 to February 2015 that help in focusing PHEMCE resources and priorities against viral hemorrhagic fevers; smallpox; chemical threats including nerve agents, cyanide, and pulmonary agents; pandemic influenza; botulism; and all-hazard recommendations.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
1.3.5	Make awards under a BAA entitled *Targeting Therapeutics Development to Relieve Bottlenecks in Translational Research*	NIH	FY15	COMPLETED - In FY15, NIH made awards to seven companies to develop new therapeutics representing four broad spectrum antibiotics and three antivirals.
1.3.6	In CY15 NIH plans to release a BAA entitled "Development of Therapeutic Products for Biodefense and Emerging Infectious Diseases" with awards to be made in FY16.	NIH	FY16	The BAA solicitation was released in July 2015 for FY16 awards.
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	COMPLETED - BARDA, in concert with other PHEMCE experts, convened meetings to re-evaluate the RDD threat scenarios and utility of existing radionuclide chelators in a response environment that informed development and procurement planning. BARDA and NIH are devising nonclinical studies to assess the efficacy of different formulations and modes of administration of MCMs in reducing acute injury and long-term health risk associated with radionuclide exposures.
1.3.10b	Acquire or maintain critical medical countermeasures as detailed in Table 4 of *2014 PHEMCE SIP*	BARDA / CDC	FY14	COMPLETED - BARDA: Procurement of Modified Vaccinia Ankara (MVA) smallpox vaccine, replenishment of raxibacumab, pandemic and pre-pandemic influenza vaccines, and ARS therapeutics were completed as planned by FY14 COMPLETED - DSNS: All MCMs programmed for procurement are underway, except for thermal burn (silver dressings), which is going to be procured by BARDA (and is underway).
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	FDA's internal policy work group is working on revisions to the 2007 guidance.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
3.1.1	Submit to Congress the SNS Annual Review report	HHS	FY14-16	The 2013 SNS Annual Review, which provided recommendations for FY16, was completed on time, and the 2014 SNS Annual Review (FY 2017 Plan) is on track for on-time completion.
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	ITRA Tailored Assessment of the SNS formulary completed Phase I (Radiological and Chemical MCMs) and Phase II (Biological and Improvised Nuclear Device MCMs). Initiated Phase III (operational and other constraints).
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	COMPLETED- CDC completed ORR evaluation with a set of early adopting sites in 2014 and is implementing the ORR on a biannual basis this year.
3.2.9	Develop national response strategies for anthrax (FY15), botulism, glanders and melioidosis, and smallpox	ASPR / CDC	FY16	ASPR works closely with PHEMCE partners on the following MCM response strategies: smallpox vaccine response strategy, anthrax MCMs (which will be informed by the anthrax MTA 2.0 under development), botulism MCMs, and filovirus vaccines.
3.2.10	Develop clinical practice guidelines for MCMs to address chemical agents, smallpox, anthrax, and botulism	ASPR / CDC	FY16	New botulism and ARS clinical guidance are underway at CDC and anticipated for completion within two years. Anthrax antitoxin guidance should be ready for clearance in early 2015. Smallpox guidance was published in Morbidity and Mortality Weekly Report in February 2015; Clinical Guidance for Smallpox Vaccine Use in a Postevent Vaccination.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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	FY15	In 2012 BARDA and ASPR's Office of Emergency Management (OEM) led two workshops (in Washington and New York City) to make a cursory determination as to how many myeloid cytokine doses could be delivered to a casualty population resulting from a nuclear detonation, in the locale (immediate vicinity and near/metropolitan-region) of the detonation. These workshops led to a range of estimated capability, and further work is needed to develop CONOPS and distribution planning to validate the administration strategy for myeloid cytokines. The results of these engagements are being prepared for presentation to PHEMCE leadership.
3.2.13	Develop planning guidance for patient decontamination in a mass exposure chemical incident	ASPR / CDC	FY15	COMPLETED - Guidance document *Patient Decontamination in a Mass Chemical Exposure Incident: National Planning Guidance for Communities* was released in December 2014 via Federal Register Notification, available for download at www.PHE.gov/patientdecon. A follow-on guidance document is being developed to focus on pediatric decontamination needs during a mass chemical exposure incident.
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	The PHEMCE has pursued activities to improve administrative preparedness in several areas, including immediate response funding needs, securing additional resources, department flow of funds, rapid funding execution, state and local capabilities, and reporting requirements. This will enhance funding templates, evaluation and monitoring parameters, awareness of how PHEP authority may be applied for guidance on response funding authority and programmatic flexibilities.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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 U.S.-Canada Beyond the Border Initiative, and as called for in the North American Plan for Animal and Pandemic Influenza	ASPR	FY16	ASPR/OPP led collaborations 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 U.S.-Canada Beyond the Border Initiative, and as called for in the North American Plan for Animal and Pandemic Influenza. Specifically, ASPR/OPP has led work with Canada under the Beyond the Border to identify the legal, regulatory, logistical and funding issues, laws, regulations, and policies that may impact the international deployment of emergency MCMs across the U.S./Canada border in order to improve cross-border interoperability and strengthen collective U.S./Canada health security. In 2015, ASPR/OPP will work with PHAC to implement these recommendations by exploring the development of memorandums of understanding and frameworks/toolkits to support the cross-border deployment of MCMs addressing these legal, regulatory, logistical, funding/cost-recovery and policy issues/challenges. Additionally, in 2014 ASPR/OPP assumed the Secretariat of North American Plan for Animal and Pandemic Influenza (NAPAPI) and held a meeting of the NAPAPI Health Security Working group in early 2015 that brought together policy makers and subject matter experts from the foreign affairs, security, agriculture, and health sectors of the U.S., Mexico, and Canada to exercise principles outlined in the NAPAPI. The exercise provided an opportunity for NAPAPI partners to discuss plans and challenges associated with the availability of and access to human and animal MCMs during an influenza pandemic (including access to manufacturing capacity, procurement, and international deployment) basis for identifying NAPAPI action items on trilateral MCM collaborations moving forward in 2015 and beyond.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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	The Division of Emergency Operations is responsible for the management of the CERC training program. During 2014: - CERC training was provided to 290 individuals via in-person training sessions through CDC University or other venues; - Approximately 10 presentations about CERC were given to Ebola deployees; Georgia Society for Public Health Education (GA SOPHE) chapter; Emory University; United Nations International Children's Emergency Fund; Public Health Webinar; Press Club; and FEMA; - More than 390 continuing education units (CEUs) were awarded to 597 individuals who completed CERC online training, with 737 completing the pandemic influenza online training module; - A total of 51,162 CERC website page views were generated during 2014.
4.2.1	Develop rodent and porcine juvenile models of ARS	NIH / BARDA / DoD	FY16	NIAID/Radiation and Nuclear Countermeasures Program has initiated activities to explore the development of rodent pediatric animal models through the product development support service contract and porcine pediatric animal models through an Inter-Agency Agreement. BARDA's Nonclinical Studies Network supported the development of Hematopoietic ARS irradiation minipig models. Results of these studies, which were presented at the 2014 Radiation Research Society Annual Meeting, showed the model supported the human disease. NIAID and BARDA co-sponsored a symposium on “Acute Radiation Syndrome in Pediatric Populations” held in June 2015.
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	BARDA continued under PBS to stockpile IMVAMUNE a smallpox vaccine for immunocompromised persons. Bavarian Nordic is performing a Phase 2 clinical trial to demonstrate comparability of the current liquid-frozen vaccine to a lyophilized formulation.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
4.3.9	The PedsOB IPT will work with ASPR on incorporating pediatric and maternal 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	COMPLETED - OEM and the PedsOB IPT jointly determined that a stand-alone pediatric annex to the All-Hazards Plan was not needed, but that pediatric-specific language about key options and actions may be useful for other annexes. The PedsOB IPT drafted a white paper on pediatric issues during emergencies and provided it to OEM for use in future annexes. The PedsOB IPT remains available to review and consult on annex documents in development.
T.A.1	Publish anthrax clinical guidance for use in the general population during a mass casualty event	CDC	FY16	Clinical guidance document for a mass casualty event is expected to be published in 2015.
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	NIH supported Phase 2 trial of AV7909, an adjuvanted Anthrax Vaccine Adsorbed (AVA). Trial started in January 2013 and fully enrolled in November 2013. The clinical study report was submitted to the FDA in September 2014 and an addendum to the report (showing no adverse events of special interest reported) is pending FDA submission.
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	NIAID led an interagency working group to design the dose-sparing studies. All relevant agencies participated in a meeting in 2014 to review study results and determine next steps forward. The final draft Crosswalk Report on the NIH's dose- and antigen-sparing study with AVA (BioThrax®) suggested that fewer vaccine doses or less antigen content per dose may afford some protective immunity. The use of less AVA vaccine for each vaccination regimen, if necessary, could extend coverage when supply is limited. Preliminary results were released in December 2014.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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	Anthrax Vaccine development contracts awarded in FY14: Emergent BioSolutions: Advanced development of a lyophilized formulation of AV7909 (adjuvanted AVA); PharmAthene: Advanced development of a lyophilized recombinant anthrax protective antigen (rPA) vaccine; Anthrax Vaccine development contracts awarded in FY12: Fraunhofer: Advanced development of the combination plant-based *Bacillus anthracis* PA (PA83) vaccine component with a saponin-based adjuvant, Matrix-M, to be administered intramuscularly: There have been some delays due to the change to a new adjuvant, as Matrix-M is no longer available; Pfenex: Advanced development of a subcutaneous pellet vaccine composed of rPA expressed from *Pseudomonas fluorescens* to be delivered via a Glide Solid Dose Injection (SDI) system with or without an adjuvant: Several stable formulations have been down-selected for further development; Public Health England (supported by NIAID): advanced development of an intranasal anthrax vaccine based on the Health Protection Agency's proprietary *Escherichia coli*-based rPA vaccine component combined with NanoBio's novel nanoemulsion adjuvant W805EC technology component, to be administered using the Pfeiffer Bidose nasal sprayer: Engineering lots of adjuvant and rPA BDS have been manufactured and pre-clinical studies are underway. Update on vaccine development contracts awarded in FY10: PaxVax: improved anthrax vaccine candidates based on replication competent, oral adenovirus serotype4 (Ad4) vaccine vectors expressing rPA: Different regimens of rPA-Ad4 vaccines, with or without the licensed AVA, were evaluated in a Phase 1 clinical trial. Data analysis is still underway.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
T.A.12	Submission for 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	FY15	Amoxicillin and amoxicillin/clavulanate have been tested in the cynomolgus macaque for PEP of inhalational anthrax and draft reports have been received. The studies will be audited in April and final reports will be issued by October 2015, for submission to FDA in 2016.
T.OB.2	Qualify animal models for anthrax, plague, and tularemia in support of PEP and treatment indications, through the FDA's Animal Model Qualification Program	NIH / BARDA	FY16	Qualification of anthrax models: Letter of intent submitted by BARDA and FDA requests received. Initial briefing package being prepared by NIAID with BARDA support. Qualification of plague model: Letter of intent submitted and FDA comments have been received, now in Consultation and Advice stage. Initial briefing package being drafted, to be submitted in FY 2015. Qualification of tularemia model: NIAID is working on the follow-up briefing package. It will include responses to the FDA comments, data from all natural history studies that were completed under NIAID and BARDA contracts, and cross-study data analyses for definition of model parameters for context of use and model endpoints.
T.OB.8	Initiate the testing of candidate products against *Burkholderia pseudomallei* and *Burkholderia mallei*	BARDA	FY16	BARDA evaluated two candidate products against *B. pseudomallei* and *B. mallei in vitro* and in small animal models of melioidosis and glanders diseases. Both candidates were active against *B. pseudomallei* strains that are resistant to meropenem alone.
T.S.2	Publish the National Smallpox Vaccine Response Strategy that 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	A National Smallpox Vaccine Response Strategy has been drafted and is being finalized.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
T.S.3	Develop contingency activities to ensure stockpile maintenance for ACAM2000 and VIGIV.	CDC / ASPR	FY16	Contingency activities ongoing to ensure stockpile maintenance for ACAM2000 and VIGIV through warm-base and manufacturing contracts.
T.S.6	Complete delivery to the SNS of the required treatment courses of the smallpox antivirals currently under contract	BARDA	CY14	Delivery of tecovirimat (ST-246) smallpox antiviral drug to the SNS under a BARDA-supported procurement began in March 2013 and continued in 2014. The delivery schedule has been extended due to regulatory guidance received from FDA in October 2014 indicating that the human dose for tecovirimat would be higher than originally expected. As a result of the dosing change, SIGA Technologies has had to undertake an additional manufacturing campaign to complete its firm fixed price commitment to deliver 1.9 million doses.
T.PI.3	Develop mechanisms to further integrate social media and other communication tools into preparedness activities	CDC	FY16	During a pandemic response, CDC will increase social media outreach to the public and other stakeholders via established social media platforms, including Twitter, Facebook, YouTube, and Pinterest. CDC will use these outlets to raise awareness regarding key messages, including actions that people should take to protect themselves. Social media outreach also will provide links to CDC's website and other communications products, including streaming video content. All social media outreach is designed to educate the public.
T.PI.5	Develop procedures to ensure that public information in future pandemics is provided in accessible and alternative formats	CDC	FY16	CDC continues to use multiple platforms for including traditional, web and social media for the delivery of public health messages to the public. The National Center for Immunization and Respiratory Diseases' Influenza Division and OPHPR's Emergency Risk Communications Branch develops strategies for communicating to the general public in advance of and during pandemics.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
T.PI.6	Refine and implement partnership strategies to improve communication with hard-to-reach and at-risk populations	CDC	FY16	Multiple teams within CDC's OPHPR are working to facilitate partnerships within the federal government, with state and local public health, and with non-governmental organizations (non-profits, healthcare, academia, private industry) to ensure hard-to-reach and at-risk populations are included in planning efforts and are communicated with during an emergency. PHEP awardees are required to develop preparedness strategies that address the needs of at-risk individuals. One of the Public Health Preparedness Capabilities specifically addresses emergency communication with resources for communicating to at-risk populations. CDC activates a Children's Health Team within its Emergency Operations Center to integrate children's needs in responses including communication for parents, educators, and pediatric health care professionals. CDC also activates a Maternal Health Team during responses (Ebola, Influenza, etc.)
T.PI.8	Develop an approach, definitions, tools, and models for a risk communication response plan	CDC	FY16	CDC is developing a communication strategy and implementation plan for outreach to external partners and internal stakeholders, especially as it relates to public health preparedness and response activities. CDC is reviewing and refining the database of Division of Emergency Operations' (DEO) and Emergency Risk Communication Branch's internal stakeholders and external partners. CDC is developing a needs assessment survey for external partners and internal stakeholders. CDC is updating the Joint Information Center (JIC) 101 training slides to reflect cooperative partnership between lead Chief Information Officer (CIO) communicators and Emergency Risk Communication Branch (ERCB) staff for communication activities during emergency responses.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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	The Influenza (Flu) Risk Management Meeting (FRMM) deliberated in 2014 on the composition, quantity, and usage of pre-pandemic influenza vaccine stockpiles including H5N1 and H7N9 bulk vaccine antigens, vaccine seed strains, and adjuvants during non-pandemic and pandemic periods and concluded that the size, composition, integrity, and Influenza Risk Assessment Tool (IRAT) process were suitable and that these vaccines should be made available for vaccination of persons working in high-risk settings with potential exposure to these viruses. There were no changes in the vaccine stockpiles due to new viruses or significant loss in potency of vaccines and adjuvants. CDC's Advisory Committee on Immunization Practices (ACIP) was slated at the February 2015 meeting to address usage of the stockpiled vaccine for high-risk workers.
T.PI.11	Maintain and update the existing stockpile of novel influenza viruses and pre-pandemic vaccines and adjuvants as needed	BARDA	FY16	BARDA with PHEMCE partners, including CDC, NIH, and FDA, deliberated on the pre-pandemic influenza vaccine stockpile composition using the IRAT leading to the decision that there were no changes needed in the stockpile composition at this time.
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	A comprehensive, integrated plan for manufacturing and timely delivery of influenza vaccines is under development. An HHS-wide collaborative project involving BARDA, CDC, NIAID, and FDA with industry and academic partners supported research and development to develop better potency and sterility assays as part of the Influenza Vaccine Manufacturing Improvement initiative. Assays were developed at FDA, CDC, industry, and academic labs, resulting in the first commercially available influenza vaccine potency assay called VAXrray. A new five-day microsterility assay was developed and entered beta-testing at manufacturers.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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	Multiple influenza vaccine potency assays were developed by FDA, CDC, and industry partners. Several of these potency assays are undergoing evaluation at influenza vaccine manufacturers in comparison studies with the standard single radial immune-diffusion (SRID) assay used currently.
T.PI.14	Develop a consensus working definition of a "universal influenza vaccine"	ASPR	FY16	CLOSED[56] - A formalized definition, while not specifically adopted, has been embraced in principle by the work progressing steadily toward an influenza vaccine that has expanded coverage of serotypes beyond those capabilities seen with current licensed approaches to seasonal vaccine.
T.PI.16	Move at least one universal influenza vaccine candidate into Phase 1 clinical trials	NIH / BARDA	FY16	NIAID collaborated with BARDA and CDC to support the first in man clinical trial to investigate the human immune response to stem-based chimeric HA influenza virus vaccines. CDC generated Good Laboratory Practices (GLP) seed virus constructs. BARDA contracted with bioCSL to produce and release clinical investigations lots of two cHA vaccine candidates. NIH supported ongoing toxicology studies to support the Phase 1 clinical trial. The trial is scheduled to begin in 2016.
T.PI.19	Initiate support of one or two promising influenza vaccines through the BAA funding mechanism	BARDA	FY16	BARDA supported a new project with Sanofi Pasteur for development of a pandemic influenza vaccine using MF-59, an oil-in-water emulsion adjuvant.

[56] "Closed" indicates activities that, due to a shift in approach, have been discontinued without completing the initially identified deliverable.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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	The HHS-wide collaborative project involving BARDA, CDC, NIAID, and FDA with industry and academic partners supported R&D for high-producing influenza vaccine seed strains and better potency and sterility assays as part of the Influenza Vaccine Manufacturing Improvement initiative. Five high-yield donors were identified for comparison with the traditional PR8 donor virus genes, improving CVV. The collaborative project has developed a half-dozen new laboratory assays at FDA, CDC, industry, and academic labs. Collaboration with International Federation of Pharmaceutical Manufacturers & Associations and global regulatory labs was established through a collaboration assessment survey.
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 U.S. in this time frame	BARDA	FY16	BARDA completed the advanced development of a large Phase 2b trial for nitazoxanide and continued support for an ongoing pivotal Phase 3 trial. BARDA has focused its efforts on identifying immunotherapeutics for the treatment of influenza and developed the market research to support release of an RFP in 2015.
T.PI.27	NDA filing for a small molecule, broad-spectrum anti-viral targeting pandemic and seasonal influenza	DoD	FY16	The EID treatment program concluded enrollment of 2,021 patients into their Phase 3 clinical trial for the use of favipiravir against influenza.
T.PI.28	Develop new plans for antiviral distribution and dispensing	CDC	FY16	Discussions with vendor regarding obstacles identified are underway. New date for completion pending.
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	BARDA initiated a project, with CDC collaboration, to develop a rapid assay for determining the sub-strain of influenza infection through sequencing techniques. This product is for use in diagnostics labs.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
T.OV.1	Move broad-spectrum antiviral candidates into clinical testing	NIH	FY16	Three BAA contractors were engaged in clinical trials with completion of a Phase 1 trial for an influenza therapeutic that will advance to Phase 2 testing in FY 2015 under NIAID support. There are ongoing Phase 1 programs for broad spectrum therapeutics to treat Ebola and dengue fever.
T.OV.5	Make additional awards for vaccine candidates based on supplemental funding.	BARDA	FY16	BARDA has received funding and anticipates awarding additional contracts to support the development of promising Ebola vaccines.
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	NIAID delivered the IND-enabling data to Mapp Biopharmaceutical to support Phase 1 use of ZMapp™. NIAID will conduct the Phase 1 trial to support ZMapp™ development.
T.OV.11	ZMapp™ is 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	Under NIH direction, ZMapp™ was shipped to Africa for use in the Ebola RCT protocol. HHS developed, with partners, a common master protocol to potentially evaluate multiple, experimental therapeutics against Ebola. NIAID'S IND for ZMapp™ clinical trials in the U.S. and Liberia using the common master protocol was allowed to proceed by the FDA in February 2015 and expanded to Sierra Leone in April 2015 and Guinea in July 2015.
T.OV.13	NIH is 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.	NIH / DoD	FY16	Multinational clinical trials on VSV vectored Ebola vaccine is ongoing and sponsored by Merck & Co. and NewLink Genetics with sponsorship by the DoD. The DoD/Walter Reed Army Institute of Research immunizations are complete; subject follow-up is through January 2016. In addition to the Phase 1 clinical trials, the DoD supports manufacturing efforts and the immunological testing from the multiple clinical trials.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
T.OV.14	Advance Ebola candidate vaccines to Phase 2/3 efficacy testing	NIH / DoD	FY16	The vaccine product has been manufactured to support the Phase 2/3 efficacy testing in West Africa. The Phase 2 trial is underway and started in February 2015. The DoD transferred 10,000 vials/50,000 doses for use in Phase 2 trials.
T.OV.21	Favipiravir, and another potential therapeutic, TKM-Ebola, may undergo Phase 2 trials in West Africa in early 2015	DoD	FY16	Clinical trials for Tekmira's TKM100802 siRNAs (TKM-Ebola) are suspended due to lack of demonstrated efficacy.
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	The serotype A botulism cocktail has completed Phase 1 testing. Phase 1 testing of the serotype B and E cocktails will be conducted FY 2015-16. Work is continuing for C&D serotypes to prepare for regulatory submission.
T.B.2	Evaluate botulism type "H"(Bot H) strain for sensitivity to the approved botulism antitoxin (BAT) as well as appropriate candidate monoclonal antibodies	NIH	FY16	NIAID is supporting manufacturing of the Bot H toxin to provide it for testing. NIAID has acquired the *Clostridium* strain that produces Bot H and has amplified it and placed it in the BEI Resources repository for distribution to qualified research laboratories. BARDA has taken the lead on this project, which involves collaboration with NIAID and CDC.
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	BARDA with PHEMCE partners reached out to industry partners and medical associations (IDSA and ABA) on products that they needed to inform our stockpiling investment decisions.
T.RN.5	Conduct exercises to pilot different cytokine distribution and dispensing models to address ARS-associated neutropenia	ASPR / VA	FY16	Funds are not available to perform this work.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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	A workshop was held in May 2013 with state and local stakeholders. The outcomes of this workshop informed a September 2013 BARDA acquisition of myeloid cytokines. The development of the subsequent manuscript has included interactions with clinical experts, reviews by state and local planners and professionals, and a professional society review is underway. Final review and publication is anticipated for 2015. ASPR and ASPR/BARDA staff participated in the Dana Farber Cancer Institute, Radiation Injury Treatment Network (RITN) Supported Full-Scale Radiological Exercise held in Boston in September 2014 to gain feedback on the use of federally-developed triage and other response operation guidance. BARDA is planning additional rad/nuc-focused end-user engagements for 2015, as well as participation in multiple stakeholder conferences. In addition to rad/nuc-focused engagements, ASPR plans webinar engagements with NACCHO and Association of State and Territorial Health Officials' (ASTHO) constituencies for spring 2015, and led a town hall session at the Public Health Preparedness Summit in April 2015 to engage state and local public health authorities in this area.
T.RN.10	Complete a re-evaluation of the 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	COMPLETED - BARDA's ADS Division performed medical consequence-modeling of radionuclide exposures and the effectiveness of decorporation agents and blocking agents and conveyed its findings to the Radiological and Nuclear Threats Integrated Program Team for consideration.
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	The Bioassay Lab Working Group has been working since September 2014 to build an economic risk assessment model to identify the risk the PHEMCE is assuming by not funding an additional bioassay lab. Non-economic risks are also being identified and developed. The work is projected to be completed by summer 2015.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
T.C.1	Develop an approach to prioritize chemical agents from the DHS Chemical TRA for MCM research, development, and procurement efforts	ASPR	FY16	COMPLETED - The PHEMCE Chemical IPT conducted an analysis, using an analytical hierarchy process decision tool, to identify priorities for developing requirements and funding R&D throughout the MCM pipeline. Initial prioritization has been completed and will be updated periodically. The prioritization project was briefed to the PHEMCE senior leaders in January 2014.
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	FY16	A draft document of methods to generate mock (spiked) samples for a bacteria, virus and parasite has been prepared. Awaiting completion of spiking experiments to validate methods and plan to submit the document for publication this summer. An overview of this project will be presented at the Biodetection Technologies conference (June 2015). The NIH CounterACT Program convened the "Neurological Effects after Chemical Nerve Agent Exposures" workshop in Feb 2014 to assess the availability of human and animal data on the nonlethal effects of nerve agent poisoning, and how these data can be used to develop animal models for testing promising therapeutics. A White Paper is being prepared of a Systematic Analysis of available data, and research gaps that could be filled by the generation of requisite datasets (FY 2015).

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
C.D.6	Develop highly sensitive, specific, and robust Public Health Actionable Assays (PHAA) for high-priority biological threat agents (i.e., bacterial, viral, and toxins) for deployment and employment through the CDC Laboratory Response Network (LRN)	DHS / CDC	FY16	DHS has completed the following PHAA assays to date (in collaboration with CDC): *Francisella tularensis*, *Yersinia pestis*, *Rickettsia prowazekii*, *Rickettsia rickettsii*, *Variola virus*, Ricin, and Abrin. DHS is currently working on developing assays for *Ebola virus*, *Marburg virus*, and *Clostridium botulinum*. Plans include: *Burkholderia mallei*, *Burkholderia pseudomallei*, *Bacillus anthracis*, *Brucella* spp., *Coxiella burnetti*, Venezuelan equine encephalitis, eastern equine encephalitis, Junin, Lassa, Crimean-Congo hemorrhagic fever, staphylococcal enterotoxin B, *as well as a multiplex assay for Bacillus anthracis; Yersinia pestis; Francisella tularensis; Burkholderia pseudomallei* and *Burkholderia mallei.* Numerous sources were used to determine which agents to include/exclude in the development and validation of PHAA assays. PHAA efforts leverage information from the Material Threat Assessments (MTAs) and Material Threat Determinations (MTDs) conducted by DHS S&T in addition to the HHS Federal Experts Security Advisory Panel (FESAP) derived National Select Agent List, Risk Assessments for mail screening, and NIH and CDC select agent lists. DHS also conducted a survey with participation from SMEs within DHS, CDC, ASPR/BARDA, FDA, and FBI to rank a list of biothreat agents to help determine prioritization for PHAA.
C.D.7	Develop additional pre-EUA assays for Joint Biological Agent Identification and Diagnostic System (JBAIDS) for Pan-Burkholderia and Ebola Bundibugyo	DoD	FY16	The JBAIDS EZ1 assay received an EUA from the FDA in August 2014 and has supported domestic and international responses to the Ebola outbreak. The DoD will continue to support Ebola response by seeking an EUA for an additional Ebola Zaire assay, as well as Ebola Bundibugyo pre-EUA test. The DoD continues to develop pre-EUA assays for Pan-Burkholderia.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
C.D.8	Develop FDA-approved IVD capabilities for anthrax and smallpox as part of the NGDS Increment 1 platform	DoD	FY16	Anthrax will be one of several biological warfare agent (BWA) IVD tests included in the anticipated 4QFY16 510(k) submission to the FDA. The other tests include *Yersinia pestis, Francisella tularensis*, Q-Fever, Marburg and additional targets for Ebola. A test for smallpox is anticipated for FDA submission in FY18.
C.D.9	Develop an environmental assay for smallpox as part of the NGDS Increment 1 platform	DoD	FY16	The BWA environmental panel includes several targets, to include smallpox which is anticipated to be DoD qualified in 2QFY17.
C.NP.4	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	CDC / ASPR	FY16	An initial assessment has been approved by the PHEMCE.
C.NP.7	Begin work with appropriate organizations to integrate the patient decontamination planning guidance into emergency response training curricula	HHS / DHS	FY16	DHS continues to discuss the implementation of the guidance with key stakeholders in various venues and a poster presentation was given at the 2015 Public Health Preparedness (PHP) summit.
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	BARDA's CIADMs reached several facility construction milestones and are on track for full operation in 2017. All three facilities will have full capabilities to develop and manufacture cell- and recombinant-based vaccines, monoclonal antibodies and other biologicals as needed. Two anthrax vaccine and five Ebola MCM development and manufacturing projects were in planning phases in 2014.

2014 Activity Number	Description	Lead Agency	2014 SIP Target Date	Progress
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	BARDA supported the construction, validation and licensure of the Novartis influenza vaccine manufacturing facility in Holly Springs, North Carolina. This facility was licensed in June 2014 to produce the first U.S-licensed cell-based influenza vaccine, Flucelvax® (licensed with BARDA support in 2013). The Texas A&M University System CIADM and GlaxoSmithKline worked through technology transfer of the company's cell-based influenza vaccine candidate and began manufacturing process optimization studies. Emergent CIADM and VaxInnate concluded their agreement and began technology transfer of VaxInnate's recombinant-based influenza vaccine candidates.
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	BARDA's Visualization Hub (VizHub) moved from the planning stage to architectural design phase in 2014. Separately, BARDA's ADS Division served as a coordinating body for modeling on Ebola among modeling groups from the Department of Energy (DoE), DoD, CDC, and NIH.
C.CC.3	Develop a matrix to determine high-priority programs for inclusion in the Regulatory Management Plan mandated under PAHPRA	FDA / BARDA	FY16	BARDA and FDA developed a draft version of an algorithm that is under review to determine which candidate products could potentially be considered for a Regulatory Management Plan under PAHPRA.
C.CC.7	Establish an MCM advanced development and manufacturing facility	DoD	FY16	The development of the facility at Nanotherapeutics in Alachua, Florida, is ongoing and will contain pilot and cGMP production suites. The groundbreaking ceremony was held in October 2013. Fit out, equipment installation, and Commissioning, Qualification, and Validation (CQV) will continue through FY 2015.

APPENDIX 6: PHS ACT REQUIREMENTS

Table 6: PHS Act Requirements

PHS Act Information Requirements	Location in *PHEMCE SIP*
Description of the CBRN agents that may present a threat to the U.S. and corresponding efforts to develop medical/security countermeasures and pandemic/epidemic products.	Introduction – Box 1 Section 2: Updates to the *2014 PHEMCE SIP* Maintained from *2014 PHEMCE SIP*, Section 1: Activities to Achieve Strategic Goals and Objectives, Goal 1
Progress evaluation of all activities related to countermeasures/products, including research, advanced research, development, procurement, stockpiling, deployment, distribution, and utilization	Section 1: Accomplishments Since the *2014 PHEMCE SIP* Appendix 3: Progress In Addressing At-Risk Population Medical Countermeasure Needs Appendix 5: Progress Against *2014 PHEMCE SIP* Near-Term Deliverables
Identify and prioritize near-, mid-, and long-term needs with respect to such countermeasures or products to address a CBRN threat(s)	Maintained from *2014 PHEMCE SIP*, Sections 1, 4, and 5 Updated in *2015 PHEMCE SIP* Section 2: Updates to the *2014 PHEMCE SIP* and Appendix 5: Progress Against *2014 PHEMCE SIP* Near-Term Deliverables
Summarize advanced development and procurement awards with respect to each category of CBRN threat: – Time elapsed since the issuance of the initial solicitation/request to adjudication – Projected timelines, anticipated funding allocations, benchmarks, and milestones for each MCM priority and evaluation of progress in meeting these timelines, allocations, benchmarks and milestones – Projected needs with regard to replenishment of the SNS	Appendix 4: Advanced Research and Development and Procurement
Be informed by recommendations from NBSB (now called the National Preparedness and Response Science Board (NPRSB))	Introduction – Considerations of Perspectives from National Advisory Committees
Report on the amount of funds available for procurement in the Project BioShield Special Reserve Fund and the impact this funding will have on meeting the requirements	Appendix 4: Advanced Research and Development and Procurement
Incorporate input from federal, state, local, and tribal stakeholders.	Appendix 2: PHEMCE Coordination with Non-Federal Stakeholders

PHS Act Information Requirements	Location in *PHEMCE SIP*
Identify progress made in meeting the MCM priorities for at-risk individuals: – Stockpiling and replenishment of the SNS – Addressing the needs of pediatric populations with respect to MCM and products in SNS: ▪ A list of MCMs needed for pediatric populations; ▪ Description of measures taken to coordinate with the Office of Pediatric Therapeutics (FDA) ▪ Description of existing gaps in the SNS and the development of such MCMs to address the needs of pediatric populations ▪ Evaluation of the progress made in addressing pediatric populations needs	Appendix 3: Progress In Addressing At-Risk Population Medical Countermeasure Needs Maintained from *2014 PHEMCE SIP*, Section 1: Activities to Achieve Strategic Goals and Objectives, Goal 4
Identify the use of certain authorities and activities added to the PHS Act by the Project BioShield Act: – The actions taken under the authority, including, the identification of the threat agent, emergency, MCM, etc. with respect to the use of such authority – The reasons underlying the decision to use such authority, including, the options that were considered and rejected with respect to the use authority – The number of, nature of, and other information concerning the persons and entities that received a grant, cooperative agreement, or contract pursuant to the use of such authorities, and the persons and entities that were considered and rejected for such a grant, cooperative agreement, or contract – Whether a contract was entered into within a year for procurements approved by the President (delegated to OMB) – The number of persons paid $50,000 and the number of persons paid $100,000 under personal services contracts.	Appendix 4: Advanced Research and Development and Procurement

PHS Act Information Requirements	Location in *PHEMCE SIP*
In the first *PHEMCE SIP* released following PAHPRA, description of the manner in which HHS is coordinating with DoD regarding countermeasure activities to address chemical, biological, radiological, and nuclear threats. Such report shall include information with respect to: – Research, advanced research, development, procurement, stockpiling, and distribution of countermeasures to meet identified needs – HHS-DoD coordination to address MCM needs for various segments of the population.	Fulfilled in the *2014 PHEMCE SIP,* Section 2: Interagency Partner Roles and Collaborations in Supporting Strategic Goals and Objectives; not required for subsequent *PHEMCE SIP* versions.