U.S. Department of Health and Human Services

2017-2018 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan

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EXECUTIVE SUMMARY

The *2017-2018 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 strategy updates the *2016 PHEMCE SIP* and fulfills the annual requirement established 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 Enterprise will use to enhance national health security through the procurement and effective use of medical countermeasures (MCM).

Starting with this iteration of the SIP, the PHEMCE is retitling its SIP to reflect a more forward-focused strategic document by referring to the year the PHEMCE developed it as well as the following year. For example, the PHEMCE developed this SIP in 2017; therefore, it is the *2017-2018 PHEMCE SIP*.

What is the PHEMCE?

The *PHEMCE* is an interagency coordinating body led by the HHS Assistant Secretary for Preparedness and Response, comprising the Centers for Disease Control and Prevention, the National Institutes of Health, the Food and Drug Administration, and interagency partners at the Departments of Defense, Veterans Affairs, Homeland Security, and Agriculture. It coordinates the development, acquisition, stockpiling, and recommendations for use of medical products that we need to effectively respond to a variety of high-consequence public health emergencies, whether naturally occurring or intentional.

The PHEMCE examines the SIP goals and objectives annually by taking into consideration the progress achieved and the remaining strategic gaps in MCM preparedness. During the development of the *2017-2018 PHEMCE SIP*, the PHEMCE examined the goals and objectives articulated in the *2016 PHEMCE SIP* and determined that no changes were necessary at this time.

The streamlined *2017-2018 PHEMCE SIP* provides: 1) a summary of the major recent accomplishments; 2) new activities; 3) updates to the activities from the *2016 PHEMCE SIP*; and 4) specific information required annually under PAHPRA reporting mandates.

The *2016 PHEMCE SIP* identified priority activities in the near-term (fiscal year (FY) 2017-2018), mid-term (FY 2019-2020), and long-term (FY 2021 and beyond) timeframes. The PHEMCE maintained these timeframes in the *2017-2018 PHEMCE SIP*. The PHEMCE is still pursuing activities detailed in the *2016 PHEMCE SIP* unless otherwise noted in this document. All activities described are contingent on available appropriations.

PHEMCE Strategic Goals and Objectives

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

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 production, inventory management, deployment, dispensing, 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 MCMs), and includes consideration of viable commercial markets and/or routine public health applicability; and

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

Goal 2: Establish and communicate clear regulatory pathways to facilitate MCM 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; and

Objective 2.3: Establish and implement strategies to expedite the development and evaluation of MCMs during a public health emergency.

Goal 3: Develop logistics and operational plans for optimized use of MCMs 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 MCM utilization policy, guidance, and response strategies, which take into account FDA regulatory frameworks and are responsive to end-user needs;

Objective 3.3: Develop logistics and operational plans that promote innovative approaches to distribution, dispensing, and administration to ensure timely and efficient access to MCMs;

Objective 3.4: Develop and provide MCM communications, training, and education to inform all stakeholders; and

Objective 3.5: Develop and implement strategies to assess, evaluate, monitor, and communicate MCM safety, performance, and patient adherence during and after a public health emergency response.

Goal 4: Address MCM 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 U.S. continues to face a range of serious threats to its health security from the unintentional release or deliberate use of chemical, biological, radiological, and nuclear (CBRN) agents, as well as naturally occurring emerging infectious diseases (EID), including pandemic influenza (see Box 1 below). A failure to anticipate these threats – or the lack of a capacity to respond effectively to them – could result in substantial illness and death among the U.S. population. The nation must have the nimble, flexible capability to produce, and effectively use MCM[1] in the face of any attack or threat, whether known or unknown, novel or reemerging, natural or intentional. The U.S. government must communicate these capabilities to the American public before and during an emergency. Accomplishing these goals requires coordination of MCM-related activities across federal departments. To this end, HHS established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) [2] in July 2006, to coordinate federal efforts to enhance civilian MCM preparedness. The PHEMCE is responsible for coordinating 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,[3] health care personnel, and other critical infrastructure personnel, by taking a whole-of-community approach in planning, response, and recovery efforts. It also seeks to leverage and coordinate with, as appropriate, efforts to address the needs of military populations, especially where product development efforts are parallel.

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1 MCMs 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 are used to prevent, mitigate, or treat the adverse health effects of a deliberate, an unintentional, 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)).

[2] HHS Office of Public Health Emergency Preparedness; Statement of Organization, Functions, and Delegations of Authority, 71 C.F.R. § 129 (2006). https://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 PHEMCE Governance at Public Health Emergency. (2017). *PHEMCE Governance*. https://www.phe.gov/Preparedness/mcm/phemce/Pages/governance.aspx.

[3] This mandate includes consideration of the needs of first-responder populations who face particular risk in the course of their duties and critical infrastructure workers. The role of HHS in working with interagency partners is to ensure these populations have access to support, including MCMs. While the PHEMCE may call out particularly relevant activities in this document; broader efforts are not detailed here. These efforts are found at Public Health Emergency (2012). *Health and Safety Resources for First Responders*. https://www.phe.gov/emergency/events/sandy/Pages/responder-safety.aspx and Public Health Emergency (2017). *Critical Infrastructure Protection for the Healthcare and Public Health Sectors*. https://www.phe.gov/Preparedness/planning/cip/Pages/default.aspx.

Box 1: PHEMCE High-Priority Threats

The PHEMCE will continue to address MCM needs to protect against high-priority threats for which the Secretary of Homeland Security made a determination pose a material threat sufficient to affect national security or PHEMCE leadership determines to have the potential to threaten national health security. This year, the PHEMCE added three chemical agents (chlorine, phosgene, and vesicants); otherwise, the high-priority threats are unchanged from those listed in the *2016 PHEMCE SIP*. The PHEMCE high-priority threats are (in alphabetical order by threat area):

Biological Threats
- *Bacillus anthracis* (anthrax)* and Multi-drug resistant *B. anthracis* (MDR anthrax)*
- *Burkholderia mallei* (glanders)* and *Burkholderia pseudomallei* (melioidosis)*
- *Clostridium botulinum* toxin (botulism)*
- Ebola virus (Ebola hemorrhagic fever)*
- Emerging infectious diseases[4]
- *Francisella tularensis* (tularemia)*
- Marburg virus (Marburg hemorrhagic fever)*
- Pandemic influenza
- *Rickettsia prowazekii* (typhus)*
- *Variola* virus (smallpox)*
- *Yersinia pestis* (plague)*

Chemical Threats
- Acetylcholinesterase inhibitor nerve agents*
- Chlorine[5]
- Cyanide salts (potassium and sodium cyanide)*
- Hydrogen cyanide*
- Phosgene[5]
- Vesicants*

Radiological* and Nuclear* Threats

(*) indicates threats identified under the following authorities related to MCMs: (1) emergency use authorities that rely on section 564(b)(1)(D) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); (2) priority review vouchers PRVs) under section 565A of the FD&C Act;[6] and, (3) procurements of security countermeasures under section 319F-2 of the PHS Act.

4 EIDs continue to remain a high-priority threat for the PHEMCE. The PHEMCE developed a risk assessment framework to assess whether specific emerging pathogens should be included explicitly as a high-priority threat. These pathogens may be included if PHEMCE leadership determines they have the potential to affect national health security.

5 The PHEMCE added additional chemical threat agents to the high-priority threat list after considering multiple factors, including recent reported intentional use of agents as weapons, accidental releases, availability of agents in industry, and health impacts of exposure.

6 It is possible that a drug product meeting the requirements of section 565A (material threat MCM priority review vouchers (PRVs)) also may meet the requirements of section 524 of the FD&C Act (which enables sponsors of certain tropical disease applications to receive PRVs). However, under section 565A(e), the same application is not permitted to receive more than one voucher. U.S. Food & Drug Administration (2017). *Tropical Disease Priority Review Voucher Program*. https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm534162.htm and U.S. Food & Drug Administration (2017). *21st Century Cures Act: MCM-Related Cures Provisions*. https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm566498.htm#prv.

The Assistant Secretary for Preparedness and Response (ASPR) leads the PHEMCE.[7] Core HHS members are the Director of the Centers for Disease Control and Prevention (CDC), the Director of the National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH), and the Commissioner of the Food and Drug Administration (FDA). Key PHEMCE interagency partners include senior leadership from the Department of Defense (DoD), Department of Veterans Affairs (VA), the Department of Homeland Security (DHS), and the Department of Agriculture. Additionally, the PHEMCE works with HHS and U.S. government partners, when appropriate, to consider international aspects of its mission. The PHEMCE also works closely with non-federal partners including state, tribal, local, and territorial (STLT) governments, health systems, academia, private industry, non-governmental organizations (NGO) and ultimately the American people.

DEVELOPMENT OF THE 2017-18 PHEMCE SIP

Annual PHEMCE Strategy and Implementation Plan Process

The PHEMCE releases the SIP annually as required by Section 2811(d) of the PHS Act,[8] as amended by section 102 of PAHPRA. The PHEMCE adopted the following process for the SIP (also summarized in Table 2 below):

- The PHEMCE issues the SIP annually and addresses all PHS Act reporting requirements (listed in Appendix 6).
- Starting with this iteration of the SIP, the PHEMCE is retitling its SIP to reflect a more forward-focused strategic document by referring to the year the PHEMCE developed it as well as the following year. For example, the PHEMCE developed this SIP in 2017; therefore, it is the *2017-2018 PHEMCE SIP*.
- Major re-evaluation of goals and objectives will occur in 2018-19 and every four years thereafter. The PHEMCE will consider minor adjustments to goals and objectives (as needed) annually.
- 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. The PHEMCE will make adjustments to activities annually (as needed) when significant changes have occurred or new activities have begun.

[7] The Office of the ASPR includes component offices with key PHEMCE roles such as the Immediate Office; Biomedical Advanced Research and Development Authority; Office of Policy and Planning; Office of Acquisitions Management, Contracts, and Grants; Office of Emergency Management; and, Office of Financial Planning and Analysis.

[8] 42 U.S.C. 300hh-10(d)

Table 1: Annual PHEMCE Strategy and Implementation Plan Process

SIP Elements	2012	2014	2015	2016	2017-2018	2018-2019
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

2017-2018 PHEMCE SIP Steering Committee

ASPR led the development of the *2017-2018 PHEMCE SIP* through an interagency steering committee comprised of representatives from across the PHEMCE agencies. The steering committee reviewed the PHEMCE-wide strategic goals and objectives contained in the *2016 PHEMCE SIP* and determined that the goals and updated objectives continued to appropriately align with agency-level strategies and priorities.

The PHEMCE developed a progress report of accomplishments toward completion of priorities set forward in the *2016 PHEMCE SIP* (summarized in Section 1: Accomplishments in FY 2016 with further details in Appendix 5, which includes minor changes to activities as appropriate). The PHEMCE also included new activities (not included in the *2016 PHEMCE SIP*) described in Section 2: New Activities Since the *2016 PHEMCE SIP*. Otherwise, PHEMCE partners are still pursuing all activities described in the *2016 PHEMCE SIP* as PHEMCE priorities. Plans to pursue and accomplish the activities detailed depend on availability of appropriations. Following review and input from across the PHEMCE, the interagency approved the *2017-2018 PHEMCE SIP* prior to public release. As in previous iterations of the PHEMCE SIP, activities are assigned a code, which appears in gray font in front of the activity text to which it is assigned. The PHEMCE uses these codes to facilitate progress tracking.

Consideration of Perspectives from National Advisory Committees

HHS has several national advisory committees that the PHEMCE can leverage for guidance on scientific, technical, and other matters related to MCM preparedness and response. The *2017-2018 PHEMCE SIP* was informed by previous recommendations provided to the HHS Secretary and the ASPR on PHEMCE-related issues by the National Preparedness and Response

Science Board (NPRSB).[9] Past NPRSB engagements of particular relevance included those conducted on the 2012 PHEMCE SIP;[10] the long-term sustainability of the Strategic National Stockpile (SNS);[11] the PHEMCE development of MCM preparedness goals,[12] and a review of the PHEMCE MCM preparedness assessment process and pilot studies.[13]

[9] Previously called the National Biodefense Science Board (NBSB).

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

[11] National Biodefense Science Board and the Office of Public Health Preparedness and Response Board of Scientific Counselors, (2013). *Anticipated Responsibilities of the Strategic National Stockpile (SNS) in the Year 2020: An Examination with Recommendations,* from https://www.phe.gov/Preparedness/legal/boards/nprsb/recommendations/Documents/nbsb-bsc-sns-2020-final.pdf.

[12] National Biodefense Science Board, (2014). *Strategic Preparedness Goals Report*, from https://www.phe.gov/Preparedness/legal/boards/nprsb/meetings/Documents/phmce-stpreport.pdf.

[13] National Biodefense Science Board, (2016). MCM Preparedness Assessment Report, from https://www.phe.gov/Preparedness/legal/boards/nprsb/meetings/Documents/nprsb-phemce-pilot-wg-assessmt.pdf

SECTION 1: ACCOMPLISHMENTS IN FY 2016

Since the publication of the *2016 PHEMCE SIP*, the PHEMCE made significant progress in achieving the priorities described in that document, as highlighted below. In general, the reporting period for the accomplishments in this section covers FY 2016 (from October 2015 to September 2016), except where noted. A detailed accounting of progress against *2016 PHEMCE SIP* near-term activities appears in Appendix 5.

MCM Requirements

The PHEMCE approved the Vaccines to Prevent Antimicrobial Resistant (AMR) Infections Product Specific Requirement (PSR), which indicates how vaccines may address priority public health AMR pathogens designated by the CDC in 2013.[14] The PSR articulates the product specifications for vaccine products as required by the National Action Plan for Combating Antibiotic-Resistant Bacteria[15] and serves as a guide by which PHEMCE member agencies can align their research and development efforts in this area. In addition, the PHEMCE approved PSRs for antifungals, antibacterials, and antivirals to define potential needs to treat infections that might arise because of immunosuppression caused by radiation exposure from an improvised nuclear device. These PSRs set the stockpiling goal for antimicrobials to mitigate injuries caused by an improvised nuclear detonation by considering the need for antimicrobials across a large range of scenarios, the ability to use them in an incident, and the threshold and objective product characteristics desired.

Research, Development, and Procurement

Product Approvals

Successful development and FDA approval of safe and effective MCMs is a critical milestone in advancing MCM preparedness.[16] FDA approval is the culmination of many years of dedicated funding, resources, time, and effort from federal agencies across the PHEMCE and in collaboration with private industry. With respect to MCMs to treat disease or conditions caused by CBRN threats in FY 2016, FDA approved ANTHIM® (obiltoxaximab), an anthrax monoclonal antibody to treat inhalational anthrax in combination with appropriate antibacterial drugs, and reduce the risk of inhalational anthrax when alternative therapies are not available or not

14 Centers for Disease Control and Prevention, (2013). Antibiotic Resistant Threats in the United States from https://www.cdc.gov/drugresistance/threat-report-2013/

15 The White House, (2015). National Action Plan for Combating Antibiotic-Resistant Bacteria, from https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

16 For purposes of this document, unless otherwise specified, the terms “approved” product and “FDA-approved” product refer to a product that is approved, licensed, or cleared under section 505, 510(k), or 515 of the FD&C Act or section 351 of the PHS Act, as applicable.

appropriate.[17] FDA also expanded the indication for BioThrax (Anthrax Vaccine Adsorbed) to include post-exposure prophylaxis (PEP) of disease resulting from suspected or confirmed *B. anthracis* exposure, when combined with the recommended course of antimicrobial therapy in persons 18–65 years of age. In addition, FDA approved a new indication for Neulasta (pegfilgrastim), a cytokine product for the treatment of adult and pediatric patients at risk of developing myelosuppression after a radiological/nuclear incident. Neulasta® is a long-acting formulation of Neupogen® that requires less frequent dosing (weekly vs. daily) and represents the dominant product in the commercial market. As a result of this approval, Biomedical Advanced Research and Development Authority (BARDA) is replacing some Neupogen® with Neulasta® in the SNS. For additional information on procurement and/or replenishment contracts, see Table 4b and Table 4c.

In FY 2016, FDA also approved the following medical products to improve our nation's seasonal and pandemic influenza preparedness:

- Vaccines
  - Q-Pan (Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted: FDA extended the indication of the first U.S. licensed adjuvanted pandemic influenza vaccine, Q-Pan, to include persons 6 months and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.[18]
  - FLUCELVAX® Influenza Vaccine: FDA extended the indication for Flucelvax, a cell-based, inactivated seasonal influenza virus vaccine (both trivalent and quadrivalent), to include persons 4 years of age and older, for active immunization of the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.[19]
- Therapeutics
  - Tamiflu® (oseltamivir phosphate): FDA approved the first generic version of oseltamivir, a widely used medication for the treatment of influenza A and B in patients two weeks of age and older who have had influenza symptoms for no more than 48 hours; and prevention of influenza in patients one year of age and older.[20]
- Diagnostics

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[17] U.S. Food and Drug Administration, (2016). *FDA approves new treatment for inhalation anthrax* [Press Release]. From https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm491470.htm

[18] U.S. Food and Drug Administration, (2016). Approval Letter to ID Biomedical Corp. of Quebec for Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted. From https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM520303.pdf

[19] U.S. Food and Drug Administration, (2016). Approval Letter to Seqirus, Inc., for Biologics License Application (BLA) for Influenza Vaccine. From https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM503082.pdf

[20] U.S. Food and Drug Administration, (2016). *The FDA approves first generic version of widely used influenza drug, Tamiflu* [Press Release]. From https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm514854.htm

- FDA cleared three qualitative in vitro diagnostic tests for the detection and differentiation of influenza A, influenza B, and respiratory syncytial viruses [Xpert Flu+RSV Xpress/GeneXpert Xpress System, Cobas Influenza A/B & RSV, and ARIES Flu A/B & RSV Assay]; a qualitative test for the detection and differentiation of influenza A and B viral ribonucleic acid (RNA) [Solana Influenza A + B Assay (September 2016)]; and a multiplexed device for the qualitative detection of influenza A (with sub-type differentiation), influenza B, and other respiratory viruses and bacteria (NxTag Respiratory Pathogen Panel). FDA also approved modifications to nine previously cleared influenza detection *in vitro* diagnostics to improve and/or enhance product efficiency and performance.

These steps forward in influenza prophylaxis, treatments, and diagnostics facilitate preparedness for both seasonal and pandemic influenza, as new tests and technologies apply to emerging pandemic influenza strains once approved for seasonal influenza use.

Product Advancement

In FY 2016, BARDA continued to support Phase 2 clinical studies to advance development of two novel therapeutics for treatment of the severely ill, influenza-infected, and hospitalized patients. Both candidate therapeutics (JNJ-872 under development by Janssen and VIS410 under development by Visterra) have novel and distinct mechanisms of action and are active against neuraminidase inhibitor resistant viral isolates. NIAID has been supporting the development of an influenza broad-spectrum therapeutic (FF-3, sponsored by Autoimmune Technologies, LLC), which entered Phase 2 clinical trials in 2015 and completed the Phase 2 human challenge study in FY 2017.

NIAID continues to support activities to address basic and pre-clinical research into the development of novel vaccines and therapeutics for Middle East Respiratory Syndrome Coronavirus (MERS-CoV). NIAID conducted a Phase 1 clinical trial of a MERS-CoV polyclonal antibody therapeutic (SAB-301, sponsored by SAB Biotherapeutics) at the NIH Clinical Center. The study began in June 2016 and the last subject visit was in April 2017. Trial data analysis is ongoing. Additionally, BARDA supported clinical lot manufacturing and planned Phase 1 and Phase 2 clinical studies to advance the development of SAB-301, as well as two monoclonal antibodies Regeneron is developing to potentially prevent and treat MERS-CoV. Clinical studies in endemic areas of the Middle East are being arranged in collaboration with partners.

The DoD is supporting the development of countermeasures to MERS CoV as well, funding the first-in-human Phase 1 clinical trial of a MERS CoV DNA vaccine in partnership with GeneOne Life Science Inc. The trial being conducted by the Walter Reed Army Institute of Research (WRAIR) at the WRAIR Clinical Trials Center is nearly complete with data analysis and a report for publication.

In FY 2016, BARDA and NIH, with technical assistance from CDC and FDA, collaborated to launch the “Antimicrobial Resistance Rapid, Point-of-Need Diagnostic Test Challenge.” This challenge competition will help stimulate the development of *in vitro* diagnostics for antimicrobial resistance at an earlier stage in the development process than BARDA would traditionally invest

funds. A total of $20 million will be awarded in the competition, which is expected to be completed in the summer of 2020.

Researchers at the NIAID-supported by the Antibacterial Resistance Leadership Group (ARLG) are developing a simple blood test that analyzes patterns of gene expression to determine if a patient's respiratory symptoms stem from a bacterial infection, viral infection, or no infection at all. An ARLG investigator was selected as a semi-finalist in the first stage of the Antimicrobial Resistance Diagnostic Challenge to expand on this work and to adapt BioFire Defense, LLC's FilmArray® technology for gene expression analysis.

To expand its AMR testing portfolio, BARDA initiated a program to develop a targeted sequencing platform based on next generation sequencing technology for use in clinical diagnostic settings. This program will first focus on development of assays for identification of AMR pathogens and will also be able to subtype influenza samples. BARDA also utilized its Other Transaction Agreement with Roche to initiate clinical trials of diagnostic tests for *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA) on Roche's LIAT point of care (POC) instrument.[21]

NIAID supported the advancement of promising broad-spectrum antibacterial therapeutics. To help relieve bottlenecks in therapeutic development, NIAID contracts provided medicinal chemistry and activity testing support for lead candidate identification of broad-spectrum antibacterial drugs. In addition, Phase 1 clinical testing is underway for several products with broad-spectrum activity, including a novel tetracycline used or multidrug-resistant gram-negative pathogens (TP-434/CUBRC sponsored by Tetraphase) and a beta-lactamase inhibitor (VNRX-5133 under development by VenatoRx) used to address beta-lactam antibiotic resistance. BARDA continues to provide significant financial support to the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) program, along with the Wellcome Trust.[22] As of August 2017, CARB-X is supporting 18 different candidates primarily focused on Gram-negative bacteria. The portfolio also expanded to include a rapid point of care (POC) diagnostic tests. BARDA will continue to support additional candidates in FY 2017. In partnership with BARDA, NIAID is contributing to CARB-X efforts by providing streamlined priority access to NIAID pre-clinical services, including *in vitro* and *in vivo* testing and Good Manufacturing Practice (GMP) manufacture of biopharmaceuticals and vaccines to CARB-X product development award recipients.

Defense Threat Reduction Agency (DTRA)/Joint Science and Technology Office (JSTO) funded discovery of multifunctional antibodies at U.S. Army Medical Research Institute of Infectious

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[21] Other Transactions (OTs) are flexible advanced research and development funding instruments, chiefly used to attract nontraditional government contractors to stimulate innovation. They are public assistance agreements other than procurement contracts, grants, or cooperative agreements. OTs allow for greater flexibility on issues related to cost accounting standards, intellectual property rights, changes, certification requirements, and prime-sub relationships. Public Health Emergency, (2017). *Other Transactions for Advanced Research*. from https://www.phe.gov/about/amcg/otar/Pages/default.aspx

[22] Public Health Emergency, (2017). *CARB-X Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator*. from https://www.phe.gov/about/barda/CARB-X/Pages/default.aspx

Diseases (USAMRIID). A single multifunctional antibody binds multiple viral or bacterial pathogens and causes destruction of pathogens. In collaboration with USAMRIID, many Academics and Biopharmas such as AbbVie pharmaceuticals have provided their multifunctional antibodies for evaluation against Ebola virus. Some of these antibodies have shown to protect animals from various pathogens and are on their way to enter pre-clinical stages of development.

In 2016, NIH awarded six projects that use a multi-disciplinary systems biology approach to identify, quantify, model, and predict the dynamics of the molecular interactions of antibiotic-resistant pathogens and their host during disease initiation, progression or in response to treatment. These projects will model the host-pathogen molecular networks for bacteria such as *Staphylococcus aureus*, *Clostridium difficile,* and carbapenem-resistant *enterobacteriaceae* (CRE) using experimental and computational techniques. The resulting network models will provide a comprehensive framework to identify more effective therapeutic targets and strategies for these pathogens.

For FY 2017, FDA granted a request from BioFire Defense, LLC, for the Evaluation of the Automatic Class III Designation for the FilmArray NGDS Warrior Panel, which is the first molecular diagnostic device to assess the presence of B. anthracis, *C. burnetii*, *F. tularensis*, *Y. pestis*, Ebola, and Marburg virus DNA directly from sputum or blood collected from patients suspected of exposure to these agents. FDA approved a CDC Rickettsia Real-time PCR Assay intended for the qualitative detection and differentiation of *R. rickettsii* and *R. prowazekii* DNA extracted from the venous whole blood samples of individuals with signs or symptoms of infection and epidemiological risk factors consistent with exposure. FDA also granted a request from the CDC for the Evaluation of Automatic Class III Designation for the variola virus Real-Time PCR Assay, which is the first molecular assay to assess the presence of variola virus DNA directly from patient samples. The variola assay was designed to increase sensitivity and specificity, to replace the variola virus-specific test previously deployed to Laboratory Response Network (LRN) laboratories. CDC has deployed the assay reagents and verification panels to qualified labs through the LRN, enhancing U.S. government preparedness efforts to quickly detect and respond to a biological attack.

NIAID submitted all data obtained in animal and historic human volunteer clinical studies in support of qualification of a non-human primate model of pneumonic tularemia to FDA under FDA's Animal Model Qualification Program.[23] This FDA program supports development of

[23] U.S. Food & Drug Administration, (2017). *Animal Model Qualification Program*. From https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm284078.htm

therapeutics and vaccines under the Animal Rule and provides a mechanism for the evaluation of product-independent animal models for product development use.[24]

In 2016, NIH transitioned a potential antidote to treat the life-threatening effects of chlorine inhalation (under development by R-107/ Radikal Therapeutics) to BARDA for advanced development. This represents an important step forward in preparedness against this chemical threat, as the only treatment currently available is limited supportive care.

For seven years, BARDA supported two high throughput biodosimetry programs with advanced research and development funds that became sufficiently mature to transition to Project BioShield (PBS) funding in FY 2016. Additional biodosimetry programs are expected to transition to PBS in FY 2017. In 2016, the NIAID awarded a contract to Columbia University to advance the development of a fully automated, robotic platform for high throughput biodosimetry. This technology requires only a finger prick of blood and uses a commercial platform. These biodosimetry assays aim to assess radiation exposure in potentially exposed individuals, and will allow for accurate triage and effective MCM use following a radiation incident.

PHEMCE partners worked quickly to respond to the Ebola outbreak of 2014-2015 by supporting multiple therapeutic, vaccine, diagnostic candidates, and clinical trials in West Africa. The PHEMCE was able to push the development of key candidates and the work continues. In FY 2017, BARDA anticipates transitioning promising candidates to potential PBS contracts. These transitions represent years of work by the PHEMCE partners prior to the epidemic and the continued collaboration after the epidemic waned. The continued development of these critical MCMs could provide licensed or approved products to be available for the next outbreak or intentional release.

Product Extension

Through the Shelf Life Extension Program (SLEP), FDA continues to support the establishment and sustainment of an adequate supply of MCMs. SLEP is a federal fee-for-service program for extending the useful shelf life of military-significant and contingency use medical products, including MCMs that are owned by components of DoD or other federal program participants such as the SNS. FDA designed SLEP to defer drug replacement costs by extending a drug's useful shelf life beyond the manufacturer's original expiration date. Before FDA grants a shelf-life extension, laboratory personnel test and evaluate drugs submitted for shelf-life extension to assure stability and quality. In FY 2016, as a result of SLEP testing that assured drug stability

[24] The Animal Rule states that for drugs developed to ameliorate or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic substances, when human efficacy studies are not ethical and field trials are not feasible, FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans. Drugs evaluated for efficacy under the Animal Rule should be evaluated for safety under the existing requirements for establishing the safety of new drugs. U.S. Food & Drug Administration, (2017). *Animal Rule Summary*. From https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm391665.htm

and quality, FDA granted shelf life extensions for 2,020 lots (batches) of MCM drugs. Furthermore, FDA helped to extend the expiration dates on Atropine, pralidoxime/2-PAM, and Convulsant Antidote for Nerve Agent autoinjectors both through the SLEP and outside of SLEP (i.e., for stakeholders who do not participate in SLEP). This ensured availability of these products while efforts continue to resume manufacturing of these critical MCM treatments against chemical threats. In April 2017, FDA released draft guidance to government public health and emergency response stakeholders on extending the expiration dates of stockpiled doxycycline tablets and capsules for emergency preparedness and response purposes for an anthrax emergency.[25]

Product Enhancement

In FY 2016, BARDA supported the late-stage development and procurement of a next generation anthrax vaccine for post-exposure prophylaxis intended to decrease the number of required doses to elicit potential protective immunity. This will reduce the overall life cycle management cost to stockpile this vaccine. BARDA is working together with CDC to replace the existing anthrax vaccine stockpile in the SNS with this next generation product.

BARDA continued to support the HHS pandemic preparedness posture through contracts with four influenza vaccine manufacturers with licensed products in the U.S. market to support the HHS pre-pandemic vaccine stockpile and response activities if a public health emergency is declared. These projects comprise potency and stability studies that support current and future clinical studies by BARDA and HHS partners to assess product safety and efficacy.

Additionally, BARDA continued to support development of next generation influenza vaccines that can address the perpetual challenge of pandemic and seasonal influenza, which remain a central objective for BARDA. BARDA supported advanced development of an oral recombinant vectored next generation influenza vaccine candidate and completed a large human challenge study to assess the efficacy of this novel oral influenza vaccine; preliminary results are encouraging and final results are expected by late 2017. In addition, BARDA's development partners identified candidate A(H5N1) vaccine viruses that provide antibody responses against antigenically divergent viruses from endemic regions. These vaccine candidates promise to simplify, strengthen and reduce the cost of maintaining the HHS A(H5N1) pandemic preparedness posture.

BARDA initiated a clinical study to assess the current safety and immunogenicity of influenza A(H5N1) virus vaccine administered with or without the adjuvant MF59, stored for over five years in the HHS pre-pandemic vaccine stockpile. The study, designated BARDA Ready in Times of Emergency (BRITE), was a clinical trial to inform management decisions regarding long-term stored A(H5N1) vaccine and adjuvants. The study demonstrated that the A(H5N1) vaccine and MF59 adjuvant stored in the HHS stockpile remain safe and immunogenic.

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[25] U.S. Food & Drug Administration, (2017). *Draft Guidance for Government Public Health and Emergency Response Stakeholders, Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Strockpiles*. From https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM554506.pdf

NIAID has completed enrollment of subjects for two pre-pandemic influenza A(H5N8) and two pre-pandemic A(H7N9) vaccine clinical trials to assess both safety and immunogenicity of various doses and prime-boost vaccination given with and without stockpiled adjuvants. The clinical study results to date continue to demonstrate well-tolerated safety profiles and robust immune responses irrespective of antigen or adjuvant.

There is ongoing interagency coordination and development with GlaxoSmithKline (GSK) for treatment of drug-resistant gonorrhea and complicated urinary tract infection with the novel antibiotic, gepotidacin. The DoD is transitioning gepotidacin, from DTRA-JSTO to advanced development at the JPEO-MCS to treat multidrug-resistant (MDR) *Y. pestis* and *B. anthracis*; non-human primate testing of the product against *Y. pestis* was promising and studies for both *Y. pestis* and *B. anthracis* continue. Manufacturing of drug product to support clinical trial testing is underway via an interagency agreement between the JPEO for Chemical and Biological Defense (JPEO-CBD) and BARDA.

CDC improved analytical diagnostic bioassay tests for radioactive Cesium-137 and Plutonium-239 and made significant progress on developing a diagnostic bioassay test for Iodine-131 and Iodine-125, which can help identify exposed individuals and inform effective use of MCMs during a radiological emergency.

Effective Utilization of MCMs

NIH funded a pre-hospital clinical trial Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) that demonstrated superiority of intramuscular midazolam over intravenous (IV) lorazepam.[26] FDA approved Midazolam as a fast-acting, highly effective pre-operative sedative for adults and children. Although not approved for treatment of seizures, the drug also may stop prolonged seizures, including those caused by nerve agents.[27] A recently published study suggests that the publication of RAMPART results may have altered the national use of midazolam for pre-hospital benzodiazepine-treated seizures.[28]

ASPR and the National Library of Medicine (NLM) continued to collaborate on the Radiation Emergency Medical Management (REMM) and Chemical Hazards Emergency Medical Management (CHEMM) resources to ensure understanding of radiation and chemical incidents and effective utilization of MCMs. REMM and CHEMM also include decision support tools to

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[26] Silbergleit, R., Lowenstein, D., Durkalski, V., and Conwit, R. RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial): A Double-blind Randomized Clinical Trial of the Efficacy of Intramuscular Midazolam Versus Intravenous Lorazepam in the Prehospital Treatment of Status Epilepticus by Paramedics, Epilepsia. 2011 Oct; 52 Suppl 8:45-7.

[27] Silbergleit, R., Lowenstein, D., Durkalski, V., and Conwit, R. (2013). Lessons from the RAMPART study – and which is the best route of administration of benzodiazepines in status epilepticus. Epilepsia, 54(0 6), 74–77. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767187/pdf/nihms488950.pdf

[28] Yu-Cheng Lin - Po-Chien Chou - Stone Cheng. (2010). The Proceedings of the Symposium on the Motion and Vibration Control: 3B12 Combined Dual Plant Modeling and Controller Design with Verification for the Nutator System Retrieved, 2017 Mar 17.

identify type of agent involved in an incident and direct users to appropriate MCMs and other clinical guidance.

CDC completed its first MCM operational readiness review (ORR) process in June 2016. The ORR is a rigorous, evidence-based assessment of a jurisdiction's process to plan and execute a large response requiring MCM distribution and dispensing. CDC assessed 132 jurisdictions (50 state health departments, four directly-funded localities, 70 Cities Readiness Initiative (CRI) local jurisdictions, and eight territories), and state awardees assessed 355 CRI local jurisdictions. This first ORR provided a foundational assessment of the nation's ability to execute MCM plans. The ORR process highlighted strengths and gaps in the current systems, including the need for sustainable staffing to support state and local dispensing operations, especially during a prolonged event, and the need for additional security staffing for state and local dispensing sites. Results also show the majority of states are adequately planning for receiving, cold chain storage and maintenance, transport, tracking, and distribution of MCMs and are routinely exercising those plans.

CDC developed updated Memorandums of Understanding with four states and directly funded localities containing Department of Homeland Security Urban Area Security Initiative jurisdictions to define the specific delivery times for the SNS assets required to conduct mass dispensing for the full population of each city in the event of a biological attack.

CDC provided substantial training to prepare federal, state, and local partners for effective response to public health emergencies. In 2016, CDC conducted 39 objective-based external SNS training courses tailored to specific state and local requirements. CDC also trained 1,893 federal and STLT emergency responders representing 15 different project areas using in-person trainings at STLT locations and the Federal Emergency Management Agency (FEMA) Center for Domestic Preparedness facilities in Alabama, and virtually led training via web meetings.

CDC released the National Institute for Occupational Safety and Health Personal Protective Equipment (PPE)-Info database (https://wwwn.cdc.gov/ppeinfo) to provide an online publically available database containing a compendium of federal regulations and consensus standards for PPE. It contains standard information compiled from the federal government, American National Standards Institute accredited standard development organizations (SDO), and the International Organization for Standardization (ISO), when applicable nationally.

The DoD's MDR Organism Repository and Surveillance Network (MRSN) at the WRAIR remains the only entity dedicated to the large-scale collection and advanced characterization of MDR bacteria from patients treated across the military health system, including organisms of intense public health interest such as CRE, MRSA, *Pseudomonas aeruginosa*, and *Acinetobacter* species. As of FY 2017, the repository contains over 48,000 MDR bacterial isolates. The MRSN provided specific high-priority isolates (e.g., *mcr*-1 E. coli) and panels of isolates to several collaborators within the DoD, other federal agencies (e.g., the NIH and CDC), and academic institutions for use in testing new assays and treatments against MDR bacteria. In addition, the MRSN utilized its high-throughput DNA sequencing capacity to assist six military hospitals and two recruit training facilities (as well as two civilian hospital systems) domestically and abroad with their investigations of suspected outbreaks of bacterial disease, directly impacting infection control practices and patient outcomes at these facilities. MRSN uploaded

1,000 MDR bacterial genome sequences to the NIH National Center for Biotechnology Information for public access and analysis, and additional genomes will be uploaded in the future.

Regulatory Science Management

FDA expanded and sustained MCM regulatory science collaborations in FY 2016.[29] For example, FDA:

- Sponsored the fourth installment of a program with the University of Texas Medical Branch (UTMB) to provide training on best practices to ensure the quality and integrity of data generated in maximum-containment (i.e., Animal Biosafety Level 3 and 4) laboratories used to support product approval under the Animal Rule.
- Supported the Animal Model Qualification Program, which provides a mechanism for the evaluation of product-independent animal models for use in drug and biological product development under the Animal Rule.[30]
- Established and continued to expand a publicly available, well-curated reference database of regulatory-grade sequences from diverse microorganisms. This database, called the "FDA database for Regulatory Grade microbial Sequences" (FDA-ARGOS), will be critical to developers seeking to validate their candidate high-throughput sequencing- based *in vitro* diagnostic assays. The National Center for Biotechnology Information (NCBI), a component of the NLM, hosts this database.[31] The FDA-ARGOS expanded the database to include Ebola-related sequences in 2015, and Zika-related sequences in 2016.
- FDA funded and led several projects to expand efforts to build a national capability to monitor and assess MCMs after they are dispensed or administered in response to CBRN threat or emerging infectious disease.[32]

Emergency Use Authorizations (EUA) and Emergency Use Instructions (EUI)

During FY 2016, FDA continued to work with CDC, BARDA, DoD, and industry on pre-EUA activities for MCMs against a diverse array of threats including smallpox, anthrax, pandemic influenza, Ebola virus, Zika virus, glanders, melioidosis, nerve agents, and nuclear threats. For

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[29] U.S. Food & Drug Administration, (2016). Emergency Preparedness and Response: MCMi Fiscal Year 2016 Program Update. From https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm545369.htm

[30] U.S. Food & Drug Administration, (2017). Animal Model Qualification Program. From https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm284078.htm

[31] U.S. Food & Drug Administration, (2013). Database for Reference Grade Microbial Sequences, NCBI BioProject 231221 (FDA-ARGOS). From https://www.ncbi.nlm.nih.gov/bioproject/231221

[32] U.S. Food & Drug Administration, (2017). Medical Countermeasure Monitoring and Assessment. From https://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/mcmissues/ucm561377.htm

example, during FY 2016 FDA provided feedback to sponsors on 36 pre-EUAs for Zika virus diagnostic tests, and four pre-EUAs for Ebola diagnostic tests.[33] To date, FDA has issued 20 EUAs for Zika virus diagnostic tests and 12 EUAs for Ebola diagnostic tests.

During FY 2016, FDA, upon request by CDC and in coordination with DoD, worked toward issuance of an EUA authorizing CDC and DoD to procure, import, and use an Atropine auto-injector, manufactured by Rafa Laboratories, Ltd. in Israel. This EUA would allow CDC to preposition these products in CHEMPACK containers for the treatment of symptoms of known or suspected poisoning in individuals exposed to nerve agents or certain insecticides (organophosphorus and/or carbamate).[34] This EUA helps alleviate ongoing Atropine auto-injector shortages and allows CDC, DoD and other stakeholders to maintain capability to respond to a chemical nerve agent event in the U.S.

In March 2016, CDC and FDA issued the first "emergency preparedness packages," which include Emergency Dispensing Orders and EUI for both doxycycline and ciprofloxacin for anthrax post-exposure prophylaxis.[35] As with the doxycycline and ciprofloxacin "emergency preparedness packages," when feasible, FDA and CDC will coordinate issuance of emergency dispensing orders (which may include cGMP waivers) and EUI. In addition, CDC continues work with FDA to develop "emergency preparedness packages" for pandemic influenza antivirals, granulocyte/granulocyte-macrophage colony-stimulating factors for treating the hematopoietic syndrome of acute radiation syndrome, and antimicrobials for plague and

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[33] The EUA authority is a legal mechanism that allows FDA to help strengthen the nation's public health protections against CBRN threats by facilitating the availability of MCMs needed during public health emergencies. 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. Under section 564 of the FD&C Act (21 U.S.C. 360bbb-3), the FDA Commissioner can allow either (a) the use of an unapproved medical product (e.g., drug, vaccine, or medical diagnostic device) or (b) the unapproved use of an approved medical product during an emergency to diagnose, treat, or prevent a serious or life-threatening disease or condition caused by a CBRN agent if certain statutory criteria are met. U.S. Food & Drug Administration, (2017). Emergency Use Authorization. From https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm

[34] CHEMPACKs are containers of nerve agent antidotes placed in secure locations at local levels around the country to allow rapid response to a chemical incident. These medications treat the symptoms of nerve agent exposure and responders can use them even when the actual agent is unknown. For information on CHEMPACKs see: Centers for Disease Control and Prevention, "Strategic National Stockpile." 29 Nov. 2017. From https://www.cdc.gov/phpr/stockpile/chempack.htm

[35] For information on the "emergency preparedness packages," see: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm495126.htm#eui. Section 564A of the FD&C Act allows for streamlined mechanisms to facilitate CBRN preparedness and response activities for eligible FDA-approved MCMs without FDA having to issue an EUA. For eligible products, FDA is expressly empowered to extend expiration dating, waive Current Good Manufacturing Practices (CGMP), and allow emergency dispensing and pursuant to delegation from the HHS Secretary, CDC is authorized to facilitate the availability of streamlined information about the MCM's approved conditions of use by creation of EUI, FDA and CDC entered into a Memorandum of Understanding concerning creation of EUI. https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm495126.htm

tularemia. CDC will continue to make finalized EUIs available and host webinars to support pre-event planning by public health STLT stakeholders.

In addition, in April 2016, FDA published draft guidance for industry and other stakeholders with general recommendations and procedures applicable to sections 564 (EUA authorities), 564A (other emergency use authorities), and 564B (MCM prepositioning authorities) of the FD&C Act.[36]

Medical Countermeasures Initiative (MCMi) Regulatory Science Program

In FY 2016, FDA continued to implement the MCMi Regulatory Science Program through both intra- and extramural collaborative research, as well as through partnerships with federal government agencies, academia, and industry. The goal of the MCMi Regulatory Science Program is to develop the tools, standards, and approaches to assess MCM safety, efficacy, quality, and performance and to help translate cutting-edge science and technology into innovative, safe, and effective MCMs.

FY 2016 MCMi Regulatory Science program activities included:

- Completing a project mapping immune responses to certain biothreat agents and MCMs in humans and animal models to create species-specific immune function maps.[37] The MCMi Regulatory Science program received the final report for this project and the data sets are available to the public via a web-accessible database.[38]
- Expanding a database of regulatory-grade nucleic acid sequences to include AMR organisms as well as Ebola- and Zika-related sequences.
- CDC, in collaboration with FDA, has developed a bank of AMR strains and panels for developers of diagnostics and therapies to identify and treat AMR bacteria. The FDA-CDC Antimicrobial Resistance Isolate Bank website contains available information on strains and panels.
- Developing a rapid and comprehensive method for detection of antimicrobial resistance genes in bacterial pathogens in order to treat secondary bacterial infections associated with influenza infection; the studies have been completed and the data are being analyzed.

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[36]The final guidance, "Emergency Use Authorization of Medical Products and Related Authorities" is posted at: https://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/UCM493627.pdf

[37] The project received funds under the extramural MCMi Regulatory Science program and completed in June2016. For more information, see: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm332539.htm

[38] Antibody screening and cross-species datasets are available at: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm332539.htm https://immuneatlas.org/

- Developing and validating assays for Ebola for use outside of specialized, maximum-containment Biosafety Level 4 laboratories.
- Developing mobile device applications to bi-directionally collect and communicate MCM product information and analyze CBRN and emerging infectious disease patterns and clusters in real-time.
- Investigating decontamination and reuse[39] of respirators in public health emergencies, and optimizing respirator decontamination[40] to inform decision-making on the potential for decontamination and reuse of respirators to help maintain adequate supplies in emergency circumstances.
- Developing methods for obtaining safety and limited efficacy data from patients who receive MCMs during a public health emergency through a collaboration with the U.S. Critical Illness and Injury Trials Group (USCIITG) and critical care physicians at 20 hospitals throughout the U.S.[41]
- Developing a toolkit to assess efficacy of Ebola vaccines and therapeutics.[42]
- Conducting survivor studies to understand Ebola's after-effects, and help find new treatments.[43]
- Generating reference materials to standardize and qualify immune assays for Zika detection.[44]

Under the MCMi, FDA established multidisciplinary Public Health and Security Action Teams (Action Teams) as necessary to advance MCMs for priority threats by working with internal and external entities—as appropriate—to identify and catalyze the resolution of regulatory and

[39] FDA funded this project under the extramural MCMi regulatory science program, which was completed in July 2016. For more information, including the final report, see: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm412725.htm

[40] FDA funded this project under the extramural MCMi regulatory science program. For more information, see: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm414974.htm

[41] FDA funded this project under the extramural MCMi regulatory science program. For more information, see: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm414015.htm

[42] This project, initiated in FY 2016, was funded under the extramural MCMi regulatory science program. For more information, see: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm471610.htm

[43] This project, initiated in FY 2016, was funded under the extramural MCMi regulatory science program. For more information, see: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm500274.htm

[44] More information about the Zika virus reference materials is available at: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm494615.htm#panel

scientific challenges to MCM development. Key accomplishments of the Action Teams in FY 2016 include:

- The Acute Radiation Syndrome (ARS)/Biodosimetry Action Team is supporting the development of an ARS Questions and Answers guidance to help sponsors develop products for ARS indications under the Animal Rule and issued final guidance for Radiation Biodosimetry Devices.
- The Warfighter Action Team facilitates the development and regulatory assessment of MCMs and related technologies to support the warfighter, and where appropriate, leverage these activities to similar "counterparts" in the civilian/public health sector, for example, trauma victims of mass casualty events such as the Boston Marathon Bombing. To that end, FDA is considering how to evolve and refine access mechanisms under relevant statutory authorities for critical MCMs that may be necessary for mass casualty events triggered by explosives, burns, and nerve agents. In FY 2016, FDA established a formal fellowship program to support the training of DoD scientific and medical personnel in advanced product development and the FDA regulatory process.

Stakeholder Engagement

FDA continues robust stakeholder engagement through various venues, including direct interactions with sponsors and applicants, issuing guidance documents, and holding advisory committee meetings and public workshops.[45] FDA issued 15 guidance documents (both draft and final) in FY 2016, including Product Development Under the Animal Rule, Post-Market Management of Cybersecurity in Medical Devices, Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax, and Expanded Access to Investigational Drugs for Treatment Use Q&A. Twelve public workshops were hosted (or co-hosted) by FDA in FY 2016, including Clinical Trial Designs for Emerging Infectious Diseases, Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests, and a Medical Devices Panel of the Medical Device Advisory Committee, specifically to discuss diagnostic devices for detection of pathogens causing infectious diseases.

CDC continues to collaborate with commercial supply chain partners to identify and implement opportunities for integrated MCM response planning and assumptions that will enhance cost efficiency and resilient supply chain response capacity. Specifically, CDC hosted a collaborative workshop with the Healthcare Industry Distributors Association (HIDA), convening more than 30 industry partners and providing a conversational forum to discuss anticipated challenges and potential opportunities for improved communication and coordination during a public health emergency response or a period of product shortage.

CDC continues to develop clinical guidance for biological threat agents in collaboration with clinical professional organizations, public health officials and other stakeholders. These

[45] For a complete list of FDA guidance documents and advisory committee meetings, see: https://www.fda.gov/RegulatoryInformation/Guidances/default.htm and https://www.fda.gov/AdvisoryCommittees/default.htm

guidance documents comprehensively review the available scientific data; make recommendations for MCM use for all populations, including the practical implication of MCM use for a specific threat during public health emergencies.

CDC transferred methods for detecting organophosphate nerve agent metabolites in human serum to state and local laboratories participating in the Laboratory Response Network-Chemical, increasing network capability, and capacity to help identify exposed individuals and inform effective use of MCM during an emergency.

In April 2016, the Medical CBRN Defense Consortium (MCDC) formed to establish an Other Transaction Authority (OTA), to include industry, academic, and not-for-profit partners, to work with DoD to develop FDA licensed CBRN MCMs. The MCDC will accelerate MCM development timelines for the DoD by removing barriers and providing the flexibilities for better public-private collaborations.

The DoD continues to procure several MCMs from the SNS for use by DoD personnel to mitigate the risks posed by anthrax and smallpox. In the case of DoD procurement of anthrax vaccines, the DoD is able to leverage the SNS by procuring doses prior to their expiration. Such efforts serve as an example of successful interagency cost sharing and help to ensure MCM availability for both routine and surge requirements.

BARDA hosts an annual BARDA Industry Day; and the 2016 event was the largest to-date with over 600 participants registered.

International Collaboration on MCMs

In 2016, as a continued U.S.-Canada health security collaboration, ASPR's Office of Policy and Planning (OPP), Division of International Health Security (DIHS) continued to work with the Public Health Agency of Canada to identify and address barriers relating to the rapid deployment of MCMs across the U.S.-Canada border during a public health emergency. Specifically, DIHS worked with Canada to further develop a bilateral toolkit for the deployment of MCMs that outlines the processes by which the U.S. and Canada can request MCMs from their respective national stockpiles and rapidly deploy them across the U.S.-Canada border in anticipation of or in response to a public health event that requires mutual assistance and joint actions to protect regional health security.

Additionally, DIHS collaborated with Canada to develop a white paper summarizing the key challenges to the rapid cross-border deployment of MCMs and proposing recommendations to address these challenges. DIHS shared this paper with Mexico under the North American Plan for Animal and Pandemic Influenza (NAPAPI), so Mexico can develop and frame the regional problem and contribute to trilateral solutions. Throughout 2016, DIHS also hosted several technical exchanges with NAPAPI partners at the working level to share information relating to availability and access to pandemic influenza MCMs, including by exchanging best practices for stockpiling, deployment, and supply-chain preparedness.

In April 2016, ASPR hosted a trilateral exercise under NAPAPI that convened government representatives from the health, security, agriculture, and foreign affairs sectors of the U.S.,

Canada, and Mexico, to discuss plans and challenges associated with ensuring robust and resilient supply chains for critical products during an influenza pandemic.

DIHS also served as chair of the Global Health Security Initiative (GHSI) Medical Countermeasures Task Force, which brings together representatives from the group of seven countries, Mexico, the World Health Organization (WHO), and the European Commission to identify and address the legal, regulatory, funding, and logistical barriers to the international deployment of MCMs. In 2016, through the MCM Task Force, GHSI has worked with the WHO to develop a framework to guide the international deployment of MCMs. In complement to this work, ASPR provided support to the WHO to develop processes to facilitate emergency regulatory review and approval of MCMs during public health emergencies.

In addition to supporting ASPR and collaborating with PHEMCE partners on the above efforts, FDA established agreements in FY 2016 with its international counterparts to foster information sharing and collaboration, and help the international regulatory community prepare and respond to future public health emergencies. For example, in October 2015, FDA and the Saudi Food and Drug Authority (SFDA) signed reciprocal confidentiality commitments to help facilitate communications between the two agencies on medical products used, or proposed to use, for MERS-CoV as part of cooperative regulatory activities. In April 2016, FDA and the Brazilian Health Regulatory Agency signed a joint statement of continued cooperation to offer mutual support and to collaborate to address the public health emergency presented by the Zika virus disease outbreak in the Americas. Furthermore, FDA worked with the relevant national regulatory authorities throughout the FY 2016 Ebola and Zika virus responses to facilitate MCM import/export and other issues related to expanded access and EUA mechanisms to make available unapproved MCMs in the affected nations.

Finally, ASPR and CDC continue to co-chair the International Sharing of MCMs Policy Group to implement and improve policies and procedures for responding to international requests for MCMs from the U.S. SNS. The Group's policies and research contributed to approximately 30 international requests to date.

Zika Virus Response[46]

The PHEMCE continued its integrated response to Zika virus, a vector-borne, emerging infectious disease. Since 2015 and through 2016, all PHEMCE partners contributed to this response. Due to these efforts, the PHEMCE agencies and their external partners achieved important public health milestones. The PHEMCE continues efforts to safeguard against the Zika virus outbreaks and monitor new cases. Below are highlights of PHEMCE accomplishments in FY 2016, except where noted.

[46] U.S. Department of Health and Human Services. Determination and Declaration Regarding Emergency Use of In Vitro Diagnostic Tests for Detection of Zika Virus and/or Diagnosis of Zika Virus Infection. 81 Fed. Reg. 10878 (March 2, 2016). On February 26, 2016, the HHS Secretary determined that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad and that involves Zika virus.

The CDC Emergency Operations Center, in response to Zika virus outbreaks, activated on January 22, 2016 and CDC was heavily involved in multiple areas of the Zika virus response effort.[47] In addition to the specific examples of MCM-related activities noted here, a full account of this work is on the CDC website.[48]

CDC, BARDA, NIH, and FDA collaborated to obtain, characterize, and distribute Zika positive specimens for industry throughout this response. These specimens helped commercial manufacturers validate their diagnostic tests and develop other MCMs.

Under BARDA's National Medical Countermeasure Response Infrastructure, core services continue to play an important role in MCM development and response. The Centers for Innovation and Advanced Development and Manufacturing (CIADM) accelerated the Zika virus response by conducting a variety of studies to move candidates quickly through early stages of vaccine development and submitted an Investigational New Drug (IND) request to FDA to begin clinical studies. To further speed development time, the CIADM utilized a vaccine technology similar to that used in vaccines developed to protect against similar viruses, such as dengue. BARDA's Division of Quantitative Analysis (DQA) worked with CDC SMEs in the Zika virus response providing computational modeling for the crisis in Puerto Rico and the southern U.S. he Fill and Finish Manufacturing Network expanded to include two contract manufacturing organizations that can enhance our live vector vaccine filling capability. The core services supported product development, product evaluation, and response efforts and remain a vital component of BARDA's mission.

NIAID is currently leveraging its previous experience with mosquito-borne viral diseases to respond to the Zika virus. Focusing on several research priorities, NIAID is conducting basic and clinical research to study the biology of the virus and understand how it causes disease in animal models and in humans. NIAID is partnering with the National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, and the Brazilian research institute, the Oswaldo Cruz Foundation (Fiocruz) in the largest natural history study in humans to examine the link between Zika virus infection and adverse pregnancy outcomes. The Zika in Infants and Pregnancy study is a multi-center, international, prospective study of up to 10,000 pregnant women in six different Zika virus-affected regions including Puerto Rico. This study collects data that informs our understanding of Zika virus-related congenital disease (microcephaly, and various neurological outcomes). Over 5,600 women early in their pregnancy enrolled in the study, and their children will be followed for at least one year after birth. NIAID is also playing a central role in vaccine development, and conducting basic and translational research on a number of candidates, including several designed by our intramural and Vaccine Research Center scientists. In 2016, NIAID awarded a task order under the Animal Models of Infectious Disease Indefinite-Delivery/Indefinite-Quantity (IDIQ) contract to Southern Research Institute to establish a Zika virus infection model in Indian-origin rhesus

[47] See: https://www.cdc.gov/mmwr/volumes/65/wr/mm6552e1.htm

[48] For more information of CDC MCM related information, see: https://www.cdc.gov/zika/about/whatcdcisdoing.html

macaques. This model is currently in use to evaluate vaccine and therapeutic candidates targeting Zika virus infection.

FDA is actively supporting the national and international response to Zika virus by engaging and advising product developers and providing technical assistance to federal government partners, including expedited feedback on vaccine development and first-in-man clinical protocols. As of late September 2016, FDA mobilized more than 400 staff members to support the agency's critical contributions to the federal government's Zika virus response.[49] FDA worked on and provided advice on novel issues related to the Zika virus response, such as ensuring FDA regulations do not interfere with programs to provide FDA-approved long-acting reversible contraception to Puerto Rico, regulation of genetically engineered mosquitoes, and ensuring the safety of the blood supply.

DIHS led the federal government's Sample Sharing Working Group, which coordinated the federal government's efforts to identify, acquire, and distribute domestic and international sources of Zika virus and related specimens to support government and industry development and validation of serological and molecular diagnostics, vaccines, and other MCMs. Of note, the group developed an "Emergency Use Sample Letter Agreement" (EUSLA), the terms of which allowed the sharing of Zika virus-related material with any entity using it for any legitimate purpose required to rapidly prevent, detect, prepare for, and respond to the spread or transmission of Zika virus. Between February and September 2016, a number of entities, including CDC, NIH, and the biorepository BEI Resources used EUSLA. This resulted in the sharing of hundreds of Zika virus samples and spurring diagnostic and vaccine development efforts. Following the success of sharing Zika virus samples during the response, DIHS began developing a federal government framework for the rapid sharing of biological material related to non-influenza pathogens with the potential to cause a public health emergency of international concern to formalize the processes, procedures, and considerations used during that response.

Zika Virus Diagnostics

To date, FDA authorized the emergency use of 20 Zika virus diagnostic tests; with 19 *In vitro* diagnostic (IVD) tests for Zika virus currently available. In addition, several amendments were granted that allowed additional specimen types, extraction methods and instruments to be used with authorized devices. Prior to the Zika virus outbreak in the U.S. and Puerto Rico, CDC developed two diagnostic assays (one molecular, one serologic) capable of detecting Zika virus. Utilizing the EUA process, FDA authorized both assays as the first FDA-authorized assays for detection of Zika virus in FY 2016. The molecular assay simultaneously detects Zika virus, dengue, and chikungunya viruses, transmitted by the same mosquito. CDC distributed the molecular diagnostic assay throughout the U.S. and to more than 100 countries. CDC also supported the use of the serologic assay and provided critical reagents for its use. Before CDC distributed assays to requesting laboratories, CDC provided validation panels with each

[49] View the latest updates on FDA's Zika virus response at: https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm

requesting lab to ensure proficiency. CDC also administered a series of proficiency panels to the labs conducting FDA-authorized tests to ensure proficiency with the CDC IVD assays over time. As of January 2017, CDC performed more than 179,000 assays on over 165,000 specimens. To support testing by laboratories in commercial and public sectors, CDC performed serologic confirmatory testing using the Plaque Reduction Neutralization Test (PRNT). As of August 2017, only CDC and three Laboratory Response Network (LRN) laboratories had the capacity to perform this complex test."

To stimulate the rapid development of needed diagnostics for the Zika virus, FDA proactively reached out to numerous test developers, and BARDA held a summit where assay developers, sample collectors, and researchers in the flavivirus field came together to discuss, share knowledge, and network on ways to improve diagnostic tests for the Zika virus. FDA established a comprehensive Zika Virus Diagnostic Development website that provides information to product sponsors regarding reference materials, regulatory support (including EUA templates), and important points of contact.

BARDA initiated four development programs for development of serologic diagnostics for Zika virus, including both point of care and laboratory-based tests. FDA issued an EUA for one of the laboratory methods arising from these programs and by the end of FY 2016 it was being used by some health care laboratories to inform the care of people in the U.S. with recent Zika virus infections.

Additionally, BARDA initiated two programs for development of high throughput laboratory tests for screening the U.S. blood supply. One of these tests was instrumental in blood collection in Puerto Rico during the early phases of the Zika virus outbreak, allowing the expensive airlift of blood from the U.S. mainland to Puerto Rico to cease. By the end of FY 2016, based on FDA-issued recommendations and guidance for universal blood screening nationwide, these tests were under an IND application to ensure the safety of U.S. and Territorial blood supplies in Zika virus-affected areas. Implementation of a nationwide Zika virus blood supply screening was accomplished in early FY 2017 using these two tests, which are working toward FDA-clearance.

Also to support Zika virus diagnostic test development, BARDA funded the collection of patient samples from people with active or prior Zika virus infection, collaborated with CDC to have these samples characterized, and then distributed them to diagnostic test developers. Public health workers collected 100 samples from Zika virus convalescent patients in Puerto Rico and the continental U.S. While screening donor blood collected in Puerto Rico, 50 samples that tested positive with Zika virus RNA provided to BARDA assisted developers working on Molecular Zika virus tests.

NIAID is supporting the development of improved Zika virus diagnostic tests, and working closely with the CDC, BARDA, and FDA, to better detect acute and previous infections. Currently, NIAID is focusing research efforts on improving the serological tests to discriminate between past exposures to Zika virus versus other related viruses like dengue. In addition, NIAID is developing improved multiplex molecular diagnostic tests and acquiring critical reagents, like panels of characterized Zika virus serum and recombinant proteins, to help companies and investigators properly develop and validate new diagnostic tests for Zika virus. Vaccine Research Center (VRC),

In addition, to help Zika virus diagnostic manufacturers assess the traceability of their tests (a requirement under EUA use), FDA developed and made available in May 2016 the FDA Zika Virus Reference Materials for nucleic acid testing (NAT)-based *in vitro* diagnostics devices, available upon request to Zika virus device developers who have a pre-EUA submission with the agency and established the analytical and clinical performance of their assay.[50]

Zika Virus Vaccines

NIAID supported Phase 1 trials for a DNA vectored Zika virus vaccine candidate developed at the NIAID VRC. The first Phase 1 trial launched in August 2016, and a second Phase 1 trial testing an optimized vaccine design launched in December 2016. In early 2017, vaccinations began in a multi-site Phase 2/2b clinical trial testing this vaccine. The trial aims to enroll at least 2,490 healthy volunteer participants in areas of confirmed or potential active mosquito-transmitted Zika infection, including the continental U.S. and Puerto Rico, Brazil, Peru, Costa Rica, Panama, and Mexico.

The DoD, specifically WRAIR and its partners at NIAID and BARDA, advanced the WRAIR-produced Zika Purified Inactivated Virus (ZPIV) vaccine candidate and are supporting Phase 1 clinical trials in humans. Phase 1 trials are currently ongoing at multiple locations including WRAIR, the NIAID Vaccine and Therapeutics Evaluation Unit (VTEU) at Saint Louis, NIAID VRC (as a boost to the VRC developed DNA Zika virus vaccine), Beth Israel Deaconess Medical Center, and a site in Puerto Rico through the Saint Louis VTEU. Initial results from 55 vaccine and 12 placebo recipients demonstrated that ZPIV was well-tolerated and generated immune responses that met or exceeded those benchmarks that protected rhesus macaques in experimental challenge experiments. Data pertaining to long-term durability, optimized dose and schedule, and the impact of pre-existing flavivirus exposure will be available over the next eight months.

Scientists in NIAID's Laboratory of Infectious Diseases are developing a live-attenuated chimeric vaccine, which is designed to protect against Zika virus and the closely related dengue virus. The dengue components of the investigational vaccine are currently being evaluated in a large Phase 3 study in Brazil. A monovalent version of the investigational vaccine that is designed to protect solely against Zika virus will enter a Phase 1 trial at Johns Hopkins University in Baltimore and University of Vermont in early 2018. The Zika/dengue version of the vaccine candidate may enter clinical testing in early 2018. NIAID is working with Brazil's Butantan Institute and the University of Sao Paolo to plan later-stage trials.

Through a Preclinical Services contract with Battelle, NIAID is funding the development and qualification of a series of assays used for the evaluation of the effectiveness of Zika virus vaccine candidates in clinical trials. These include microneutralization assay, plaque reduction neutralization assay (PRNT), RVP-based flow-neutralization assay, enzyme-linked

[50] An infographic about these reference materials is available at: https://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/UCM507010.pdf

immunosorbent assay (ELISA), and quantitative reverse transcriptase polymerase chain reaction.

In FY 2016, BARDA expanded support for three Zika virus vaccine development programs to conduct Phase 1 clinical studies and advance manufacturing and characterization of the vaccine product including optimization of processes and manufacturing at scale to improve production yields. These projects are part of the HHS strategic MCM portfolio to mitigate the threat of the Zika virus. BARDA also provided funds and subject matter expertise to Instituto Butantan in Sao Paulo, Brazil, to assist in the international response and development of vaccine candidates.

Zika Virus Therapeutics

NIAID maintains an active program to screen for antiviral drugs with activity against flaviviruses, including dengue, West Nile, yellow fever, and Japanese encephalitis viruses. NIAID enhanced these efforts with the development of an *in vitro* assay to test compounds for antiviral activity against Zika virus, and made this test available to the broader research community. As of November 2017, NIAID has completed 1,015 in vitro tests of antiviral molecules and has identified 54 molecules with high or moderate activity against Zika virus. This assay identified promising drug candidates proposed for tests in a small animal model of Zika virus infection developed with NIAID support.

NIAID evaluated BCX4430 (galidesivir), a broad-spectrum antiviral drug candidate discovered at USAMRIID with support from DTRA/JSTO for Ebola and Marburg viruses (Biocryst Pharmaceuticals), and found that the drug also protected immune-deficient mice infected with Zika virus.

Ebola Response

In FY 2016, as part of this global fight against the Ebola virus disease, PHEMCE partners made significant contributions toward MCM research, development, acquisition, and effective utilization planning.

Ebola Diagnostics

OraSure Technologies, Inc., through a BARDA-funded program obtained an EUA from FDA for use of its POC Ebola diagnostic test for use with oral fluid samples. Previously, in FY 2015, the program obtained an EUA for use of the test with whole blood samples. An important need to minimize the spread of Ebola virus disease in Western Africa is the ability to determine the cause of a death by testing a cadaver. Traditional burial practices can continue if death was due to causes other than the Ebola virus disease. Oral fluid is an easy sample to collect in cadavers. The program continues to work toward FDA's 510(k) approval for this test.

FDA issued two EUAs for an Ebola and Ebola-Malaria Rapid Diagnostic Tests (RDT), in coordination with DoD and CDC.

CDC, in conjunction with NIAID is working on deep sequencing analysis of the Ebola virus isolates and clinical material for microvariant genotypes of virus isolates from the West African

outbreak. Over 100 complete Ebola virus genomes from clinical specimens (West Africa) and semen specimens (U.S. and Sierra Leone) were sequenced (Illumina, MisSeq).[51]

Ebola Vaccines

NIAID supported Phase 1 trials of chimp adenovirus (cAd3) vectored Ebola vaccine candidate for Ebola virus and Sudan virus (the Ebola virus monovalent portion known as cAd3-ZEBOV, GlaxoSmithKline), which is completed. These trials demonstrated the safety and immunogenicity of a single vaccination.[52]

Merck/Newlink, BARDA, NIAID, and DoD (DTRA-JSTO and JPEO-MCS) successfully advanced the V920 Ebola vaccine (rVSV∆G-ZEBOV-GP) through Phase 3 trials, manufacturing validation, assay validation, and are funding final pre-licensure fielding studies.

A subsequent NIAID funded randomized, placebo-controlled Phase 2 trial of cAd3-ZEBOV and rVSV∆G-ZEBOV-GP, conducted under the Partnership for Research on Ebola Vaccines in Liberia, or PREVAIL I, enrolled 1,500 subjects. Publication of the results in the *New England Journal of Medicine* in October 2017 indicated these two investigational vaccines were well-tolerated and induced immune responses among vaccinated participants that persisted for at least a year.

NIAID supported preclinical, manufacturing and Phase 1 clinical trials in the U.S. of other Ebola vaccine candidates, including a heterologous prime-boost combination of adenovirus 26-vectored investigational vaccine Ad26.ZEBOV (Crucell/Janssen/Johnson & Johnson) with modified vaccina ankara (MVA) vectored vaccine (MVA.BN.Filo, Bavarian Nordic), and heterologous prime-boost combination of Ad26.Filo (Crucell/Janssen/Johnson & Johnson) with MVA-vectored vaccine (MVA.BN.Filo, Bavarian Nordic). Phase 1 trials for Ad26.ZEBOVare complete while Phase 1 trials with MVA.BN.Filo alone and in the prime-boost combination with Ad26.ZEBOV are ongoing.

BARDA continues to support three Ebola Zaire vaccine candidates; Merck, GSK, and Janssen/Bavarian Nordic. BARDA continues to support manufacturing activities, non-clinical, and clinical studies. BARDA anticipates transitioning Ebola vaccine candidate(s) to late-stage development and potential procurement under PBS in FY 2017.

NIAID supports the Partnership for Research on Ebola VACcination (PREVAC), a Phase 2 clinical trial investigating the safety and immunogenicity of three different investigational vaccine regimens. PREVAC launched in Guinea (March 2017) and Liberia (April 2017) with plans to launch in Sierra Leone and Mali in 2018. The randomized, placebo-controlled trial will evaluate two prime-boost regimens: the first includes an adenovirus-vectored prime followed by a MVA-vaccine boost (Ad26.ZEBOV + MVA-BN-Filo); the second includes prime and booster immunizations with rVSV∆G-ZEBOV-GP4. The study also will evaluate a single immunization

[51] Dudas, G. et al. (2017) "Virus genomes reveal factors that spread and sustained the Ebola epidemic," Nature 544(7650):309-15.

[52] Ledgerwood, Julie E. D.O., DeZure, Adam D., M.D., Stanley, Daphne A. M.S., et al., Chimpanzee Adenovirus Vector Ebola Vaccine, New England Journal of Medicine, 2017; 376:928-938).

with rVSVΔG-ZEBOV-GP. The PREVAC trial is a result of a research partnership that involves INSERM, NIH, the London School of Hygiene and Tropical Medicine, and the ministries of health of the host countries.

The Filovirus Animal Nonclinical Group (FANG) is an interagency group, co-chaired by the DoD and NIAID with BARDA and FDA as core team members that focuses on product development tools and other interagency product development issues relevant to FDA approval of Filovirus MCM. In September 2016, FDA indicated that the DoD-led FANG assay to measure Ebola antibodies in human sera from clinical trials is suitable for its intended use to evaluate vaccine immunogenicity.

Through a Preclinical Services Contract with Battelle, NIAID is funding a series of vaccine dose-down and filovirus challenge studies to support filovirus vaccines from three product developers: Janssen, Profectus Biosciences, and Novavax. These studies aim to increase the size of the dataset to support immunobridging of non-human primate immunogenicity and survival data to human clinical immunogenicity to support licensure of these vaccines under FDA Animal Rule. Through same Preclinical Services contract, NIAID is also funding development of exploratory immune assays, some of which may serve useful as surrogate biomarkers or correlates of protection.

NIAID is also supporting the development of an oronasal filovirus challenge model in ferrets as a model that represents natural route of infection. NIAID will use this model for testing of Ebola vaccine candidates.

The Joint Vaccine Acquisition Program (JVAP) at DoD also funds, in part, a large multi-site, multi-country Phase 2 study of a Janssen sponsored multivalent Ebola vaccine based on a platform of non-replicating modified Vaccinia Ankara virus and Adenovirus serotype 26 vectors expressing Filovirus glycoprotein antigens. The Military Human Immunodeficiency Virus (HIV) Research Program/WRAIR at the WRAIR Clinical Trials Center and its international sites in East and West Africa is conducting the study.

Ebola Therapeutics

Throughout the epidemic response, CDC studied the pathogenic properties of the new West African Ebola virus isolates compared with previous outbreak isolates and supported the rapid assessment of promising antiviral therapeutics. The CDC designed and validated a high-throughput assay to test compounds for antiviral activity against Ebola. HHS and DoD use the assay to assess panels of nucleoside analogue drugs from three different academic laboratories, with some identified active compounds.[53, 54]

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[53] Warren, TK; Jordan, R; Lo, MK; Flint, M; McMullan, LK; Chen, SS; Fearns, R; Swaminathan, S; Mayers, DL; Spiropoulou, CF; Lee, WA; Nichol, ST; Cihlar, T; Bavari, S. 2016. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature. 531(7594):381-5.

[54] McMullan, LK; Flint, M; Dyall, J; Albariño, C; Olinger, GG; Foster, S; Sethna, P; Hensley, LE; Nichol, ST; Lanier, ER; Spiropoulou, CF. 2016. The lipid moiety of brincidofovir is required for in vitro antiviral activity against Ebola virus. Antiviral Res. 125:71-8.

USAMRIID, in response to DTRA/JSTO and JPEO-MCS BD-Tx call to action, continued to expand its drug discovery and development portfolio and initiated several Collaborative Research and Development Agreements (CRADA) with multiple large pharmaceutical industries such as Merck, Pfizer, GSK, Astra Zeneca, AbbVie pharmaceuticals. USAMRIID screened all the chemical libraries that provided from these companies and found 128 compounds with drug-like properties. Many of these compounds advanced assets and came with large pharmacology data sets. Some of these compounds proved to be highly active as broad-spectrum therapeutics for many highly deadly viruses were found to have activity against multiple viruses in the screening assays and might have potential for development as broad spectrum therapeutics.

In FY 2016, the JPEO-MCS BD-Tx used OTA to fully partner with Gilead Sciences, Inc. on development of GS-5734, an IND therapeutic product to treat the Ebola virus. DTRA-JSTO funded the evaluation of GS-5734 by USAMRIID and the product transitioned to JPEO-MCS for advanced development in FY 2016. JPEO-MCS is cost sharing with Gilead Biosciences for continued development of this product. USAMRIID documented the broad-spectrum antiviral activity of GS-5734 against multiple pathogenic RNA viruses, including filoviruses, arenaviruses, and coronaviruses (such as MERS-CoV), suggesting the potential for wider medical use. GS-5734 proved to be amenable in large-scale production and clinical studies investigating the drug safety and pharmacokinetics are ongoing.

NIAID Division of Clinical Research under the Liberia-U.S. Joint Clinical Research Partnership is conducting a double blind, randomized, two-phase, placebo-controlled, Phase 2 trial of GS-5734 to assess the antiviral activity, longer-term clearance of Ebola virus, and safety in male Ebola survivors with evidence of Ebola viral persistence in semen. The intended sample size is between 60-120 subjects. The study began in Liberia in July 2016 and has 32 subjects to date with plans to open in Guinea in the first quarter of 2018. The NIAID institutional review board, the Liberian National Ethics Review Board, and the NIAID data and safety monitoring board with Liberian representation oversee the study.

NIAID continues to support preclinical and clinical development of a viral RNA polymerase inhibitor BCX4430 (BioCryst Pharmaceuticals, Inc.), which shows therapeutic efficacy antiviral activity in non-human primate models of Ebola infection. The results demonstrated tolerability and safety of BCX4430 Intramuscular (IM) formulation in a completed Phase 1 trial. BioCryst filed the IND for BCX4430 as an IV formulation. The Phase 1 trial for the IV formulation will begin in mid-2017.

BARDA continues to support three therapeutic candidates. BARDA is working in collaboration with NIAID to support manufacturing activities for BCX4430. BARDA is also working with Mapp Biopharmaceuticals to continue development of ZMapp™ and worked with FDA and the sponsor establishing an expanded access protocol (EAP) at the 10 Ebola treatment centers in the U.S. and the NIH Clinical Center. BARDA is currently working with the sponsor to implement the EAP in Sierra Leone, Liberia, and Guinea. Finally, BARDA continues to work with Regeneron to support its candidate product that is also a combination cocktail of monoclonal antibodies. BARDA anticipates the transition of therapeutic candidate(s) to late-stage development and potential procurement under PBS in FY 2017.

SECTION 2: NEW ACTIVITIES SINCE THE 2016 PHEMCE SIP

This section describes activities the PHEMCE is currently undertaking, which were not included in the *2016 PHEMCE SIP*. These are new, forward-looking activities; plans to pursue and accomplish the activities detailed depend on federal funding levels. Timeframes for these activities match the *2016 PHEMCE SIP*: near-term (FY 2017-2018), mid-term (FY 2019-2020), and long-term (FY 2021 and beyond). PHEMCE agencies are still pursuing activities described in the *2016 PHEMCE SIP* as PHEMCE priorities unless updated in this section or in Appendix 5.

Ebola Preparedness and Response

(T.E.22) The DoD JPEO-CBD is standing up a mobile clinical capability in Uganda to rapidly execute clinical trials for DoD-funded Ebola therapeutics in an outbreak setting to generate data that may support FDA approval of MCMs and/or augment data, and provide risk mitigation, for better understanding of the role and effects of such products and their contribution to human treatment outcomes. The Joint Mobile Emerging Disease Intervention Clinical Capability (JMEDICC) conducted its Initial Operational Capability Phasing and Capability Exercises at Fort Detrick, Maryland, in April 2016. In July 2017, JMEDICC successfully demonstrated the capability to conduct clinical research at the "hub" clinical site based at the Fort Portal Referral Hospital in Uganda. JMEDICC will exercise the mobile "spoke" capability in early 2018 at a distant site in Uganda. JMEDICC is coordinating with FDA, the Ugandan National Drug Authority, the WHO, and other U.S. and international experts.

The DoD also invested in establishing a new strategic initiative called the Joint West Africa Research Group, that initially used re-programmed funds from the DoD response to the 2014 West African Ebola outbreak and now has created a program of memorandum to leverage existing research platforms and relationships to improve biopreparedness in the region. This new program is a collaboration between WRAIR and the Navy Medical Research Center. Partners will build upon existing programs in Nigeria, Ghana, and Liberia with initiatives focused on lab strengthening, biosurveillance, and countermeasure development.

Bacterial Threats

(T.OB.17) In March 2017, BARDA and NIH launched the CARB-X program to address the threat of antibiotic resistance that will complicate any public health emergency. CARB-X is one of the world's largest public-private partnerships focused on preclinical discovery and development of new antibacterial products to help address the threat of antibiotic resistance. CARB-X is supporting 11 candidate products.

(T.OB.18) In March 2017, the DoD DTRA-JSTO kicked off a multi-year effort in collaboration with the Biological Defense Research Directorate/Naval Medical Research Center, the Naval Medical Research Unit 2 (NAMRU-2), the U.S. Marine Corps, and the Menzies School of Health Research in Australia to determine the frequency and immune characteristics of exposure to *Burkholderia* species among Marines deployed to Darwin, Australia. Early estimates indicate seroprevalence among post-deployment forces at up to 11 percent and data will inform potential future vaccine trials.

(T.OB.19) In the mid-term, DHS and HHS will conduct an Material Threat Assessment (MTA) 2.0 assessment for *Burkholderia*. *(T.OB.20)* ASPR will include MCM response strategies for plague and tularemia in addition to response strategies for other threats identified in the *2016 PHEMCE SIP* (under activity code 3.2.5); and will prioritize these with other MCM response strategies in appropriate timeframes based on available resources. *(T.OB.21)* NIAID and USAMRIID are discussing existing data from animal studies of doxycycline for plague with FDA, and possible additional studies are under discussion in order to update the doxycycline indication for plague. FDA will consider an updated doxycycline indication for plague, if appropriate, after review of animal study data provided by NIH. *(T.OB.22)* CDC and FDA will develop PHEMCE-wide consensus on the appropriate duration of PEP for plague and reflect this guidance on the CDC plague website. *(T.OB.23)* ASPR will discuss with FDA the possible basis for seeking an indication for ciprofloxacin for tularemia PEP.

Improvised Nuclear Device

The PHEMCE will undertake several initiatives to address the threat of an improvised nuclear device. In the mid-term ASPR will develop: *(T.RN.16)* a national operations coordination framework and system in the long-term and *(T.RN.17)* an MCM response strategy for a nuclear detonation in the near-term. *(T.RN.18)* BARDA will test cytokine-based drugs, which restore immune cell populations destroyed during radiation exposure, to determine the operational window for administration to be effective still. *(T.RN.19)* ASPR will develop an Integrated Capabilities Document (ICD) to assess the operational capacity to administer cytokines in response to an improvised nuclear device detonation. *(T.RN.20)* In addition, ASPR will analyze the transportation and evacuation needs/capabilities for severely ill patients.

Chemical Threats

(T.C.13) The CDC is collaborating with external and internal partners to implement a drop shipment delivery method for product sustainment of CDC's CHEMPACK program. Drop shipment is the delivery, replacement, documentation, and return process of CHEMPACK assets conducted in coordination with the recipient, as arranged by stockpile personnel, designated overnight package delivery companies, and executed on site by CHEMPACK cache site personnel or other recipient representatives. Drop shipment reduces program costs to sustain the more than 1,900 CHEMPACK caches fielded across the nation for rapid local response to nerve agent exposure or organophosphate poisoning, as well as reducing time commitments for federal, state, and local program participants.

Advanced Development and Manufacturing

(C.CIADM.6) In October 2016, the DoD initiated the Advanced Development and Manufacturing of Antibody Technologies (ADAMANT) program to establish a monoclonal antibody (mAb) platform capability to respond to recognized, emerging, and engineered threats. The ADAMANT mAb Platform is first being established at the DoD ADM facility through development and manufacture of a mAb MCM against botulinum neurotoxin serotypes A and B. The aim of the ADAMANT platform capability is to rapidly and cost-effectively generate data on safety and

efficacy appropriate to support applications/supplements for FDA licensure while enhancing the warm-base mAb development capability of the DoD ADM for other biological threats.

CONCLUSION

This *2017-2018 PHEMCE SIP* records progress made by the PHEMCE in the past year and updates the priorities included in the *2016 PHEMCE SIP* for federal MCM research, development, acquisition, stockpiling, distribution, dispensing, and monitoring programs. ASPR will continue to track execution of these priorities and provide periodic updates 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. The PHEMCE will publish a *2018-2019 PHEMCE SIP* to report on progress and provide other updates as needed to this report.

APPENDIX 1: ACRONYMS

AAP	American Academy of Pediatrics
Ad4	Adenovirus Serotype 4
ADAMANT	Advanced Development and Manufacturing of Antibody Technologies
AMR	Antimicrobial Resistant
ARD	Advanced Research and Development
ARLG	Antibacterial Resistance Leadership Group
ARS	Acute Radiation Syndrome
ASPR	Assistant Secretary for Preparedness and Response
ASTHO	Association for State and Territorial Health Officials
AVA	Anthrax Vaccine Adsorbed
BAA	Broad Agency Announcements
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
BRITE	BARDA Ready in Times of Emergency
cAd	Chimp adenovirus
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CBD	Chemical and Biological Defense (Division) (at DHS)
CBRN	Chemical, Biological, Radiological, and Nuclear
CDC	Centers for Disease Control and Prevention
CERC	Crisis and Emergency Risk Communication
CIADM	Centers for Innovation in Advanced Development and Manufacturing
CLIA	Clinical Laboratory Improvement Amendments of 1988
DHS	U.S. Department of Homeland Security
DIHS	Division of International Health Security (at ASPR)
DoD	U.S. Department of Defense
DSLR	Division of State and Local Readiness (at CDC)
DSNS	Division of the Strategic National Stockpile (at CDC)
DTRA	Defense Threat Reduction Agency (at DoD)
EID	Emerging Infectious Diseases
ELISA	Enzyme-Linked Immunosorbent Assay

EUA	Emergency Use Authorization
EUI	Emergency Use Instructions
FANG	Filovirus Animal Nonclinical Group
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDA-ARGOS	Database for Regulatory Grade Microbial Sequences
FEMA	Federal Emergency Management Agency
FMS	Federal Medical Station
FY	Fiscal Year
GHSI	Global Health Security Initiative
GSK	GlaxoSmithKline
HHS	U.S. Department of Health and Human Services
HIV	Human Immunodeficiency Virus
ICD	Integrated Capabilities Document
IND	Investigational New Drug
IPT	Integrated Program Team
IV	Intravenous
IVD	*In vitro* diagnostic
JSTO	Joint Science and Technology Office (at DoD)
LRN	Laboratory Response Network
mAb	Monoclonal Antibody
MA IPT	MCM Monitoring and Assessment IPT
MCM	Medical Countermeasures
MCDC	Medical Countermeasures Defense Consortium
MCMi	Medical Countermeasures Initiative (at FDA)
MDR	Multi-Drug Resistant
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MOP WG	MCM Operational Planning Working Group
MTA	Material Threat Assessment
MVA	Modified Vaccinia Ankara (smallpox vaccine)
MYB	Multiyear Budget

NACCHO	National Association of County and City Health Officials
NAPAPI	North American Plan for Animal and Pandemic Influenza
NBSB	National Biodefense Science Board
NCBI	National Center for Biotechnology Information
NGDS	Next Generation Diagnostics System
NGO	Non-Governmental Organizations
NIAID	National Institute of Allergy and Infectious Diseases (at NIH)
NIH	National Institutes of Health
NIVDP	National Influenza Vaccination Disparities Partnership
NLM	National Library of Medicine
NPRSB	National Preparedness and Response Science Board
OEM	Office of Emergency Management (at ASPR)
On-TRAC	Online Technical Resource and Assistance Center (at CDC)
OPHPR	Office of Public Health Preparedness and Response
OPP	Office of Policy and Planning (at ASPR)
OPT	Office of Pediatric Therapeutics (at FDA)
OMB	Office of Management and Budget
ORR	Operational Readiness Review
OTA	Other Transaction Authority
PAHPA	Pandemic and All-Hazards Preparedness Act
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act (Public Law 113-5)
PBS	Project BioShield
PEP	Post-Exposure Prophylaxis
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PHEP	Public Health Emergency Preparedness
PHS Act	Public Health Service Act
POD	Point-of-Dispensing
PMC	Post-market commitment
PPE	Personal Protective Equipment
PSR	Product Specific Requirement
RMP	Regulatory Management Plan

RNA	Ribonucleic Acid
rPA	Recombinant (anthrax) Protective Antigen
rVSV	Recombinant Vesicular Stomatitis Virus
S&T	Science and Technology Directorate (at DHS)
SIP	Strategy and Implementation Plan
SLEP	Shelf Life Extension Program
SNS	Strategic National Stockpile (at CDC)
SRF	Special Reserve Fund
STLT	State, Tribal, Local, and Territorial
TAR	Technical Assistance Review
TRACIE	Technical Resources, Assistance Center, and Information Exchange
U.S.	United States
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
VA	U.S. Department of Veterans Affairs
VSV	Vesicular Stomatitis Virus
VTEU	Vaccine and Therapeutics Evaluation Units
WRAIR	Walter Reed Army Institute of Research
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 STLT, regional, international, industrial, and professional society stakeholders. These interactions shape federal MCM planning and identify new ways to address national MCM needs.

In January 2016, the PHEMCE hosted a two-day PHEMCE Stakeholders Workshop, which highlighted past progress and future directions in developing, stockpiling and effectively utilizing MCMs. ASPR and CDC continue to work closely with STLT stakeholders through the National Association of County and City Health Officials (NACCHO) and the Association for State and Territorial Health Officials. For example, multiple STLT collaboration sessions took place in conjunction with the 2017 Public Health Preparedness Summit in April 2017. These included an ASPR-hosted PHEMCE learning session and a CDC/NACCHO co-hosted MCM Link Session. CDC also continues to work directly with STLT partners to support assessment and capability enhancement for MCM preparedness (specific examples are noted in the accomplishments section of this report).

CDC collaborated with ASPR on six MCM Dispensing Planning Regional Summits conducted in August and September 2016. The promising best practices identified during the summits were gathered and tested as part of a National Virtual Tabletop Exercise. CDC participated in the interactive polling sessions in October 2016 and the virtual tabletop in November 2016.

Each year, BARDA holds BARDA Industry Day and the 2016 was the largest event to-date with over 600 participants registered. BARDA also works closely with professional societies and end user professionals such as the American Burn Association, the Infectious Disease Society of America, Radiation Injury Treatment Network, American Association of Blood Banks, and state and local first responders.

CDC's Division of State and Local Readiness (DSLR) provides a monthly webinar series, Second Wednesday Webinar that focuses on MCM promising practices. For example, in October 2016, the webinar focused on CDC's new Online Technical Resource and Assistance Center (On-TRAC). On-TRAC supports state and local public health in preparing for public health emergencies related to MCM distribution and planning. It provides a central, online website to request technical assistance and access a wide range of resources.

CDC engaged in a yearlong effort to develop an online data collection system for the ORR. As part of the rollout of the ORR online system, CDC hosted a workshop for the 62 Public Health Emergency Preparedness grant recipient MCM coordinators in June 2017.

In January 2017, CDC hosted a workshop, Medical Countermeasure Operational Resource Guide Stakeholder Meeting. The goal of the workshop was to provide an opportunity for various state, tribal, and local planners, including the health care sector, to discuss the content and format of the MCM Operational Resource Guide. The resource guide is still under development and will be available to STLT when completed.

Furthermore, CDC conducted a pilot in June 2016 of the StopAnthrax™ mobile messaging program with 17 local health departments and one hospital in Wisconsin and Illinois. StopAnthrax™ is an automated two-way text-messaging program aimed at providing health messages about MCM protocols during an anthrax emergency. A total of 240 people across the test sites participated in the 10-day pilot.

CDC redesigned two MCM dispensing courses: the Mass Antibiotic Dispensing workshop and the Train-the-Trainer course. CDC renamed the new courses POD Essentials and POD Essentials Train-the-Trainer. POD Essentials is an introductory-level course for individuals who will work in a point-of-dispensing (POD) site during a public health emergency. It provides context for a POD within the larger emergency response, outlines roles performed within a POD, teaches specifics of the greeting/triage, screening, and dispensing roles through activity-based learning, and identifies strategies to mitigate responder health and safety risks. The POD Essentials Train-the-Trainer course will prepare federal, state, local, tribal, and territorial public health instructors for implementation of the POD Essentials course in their state or jurisdiction.

The POD Essentials Train-the-Trainer was pilot tested with MCM trainers from Region 10 in Portland, Oregon, in May 2017. POD Essentials is currently undergoing revisions to incorporate pilot feedback with finalization planned for the beginning of 2018. CDC delivers POD Essentials Train-the-Trainer four times a year at the Center for Domestic Preparedness (CDP) in Anniston, Alabama. Additionally, CDC teaches regionally scheduled trainings throughout the year to state and local MCM trainers.

CDC also offers the RealOpt© PODs virtual, instructor-led training once a month. RealOpt© PODs are a staff optimization tool for PODs to improve dispensing efficiency. Students learn to manipulate existing models, run and interpret reports, discover how to build their own models to maximize staff usage, eliminate bottlenecks, and determine processing times. The training is typically two to three hours in length depending on the number of participants. Students can register for the course through CDC TRAIN.

In addition to in-person, instructor-led training, CDC also provides online learning through CDC TRAIN:

- *The Strategic National Stockpile (SNS) Overview* course provides federal, state and local agencies information on how to manage deployed SNS materiel during an event of public health significance.
- *Mass Dispensing Overview: A Stockpile Perspective* introduces students to the terminology and concepts of mass dispensing at the community level. “Mass dispensing” refers to the delivery of medications or vaccines to the public to address a public health threat; other terms used to describe this activity include “MCM dispensing” and “mass prophylaxis”. Public health threats could include a bioterrorism event such as a release of anthrax into a community or a naturally occurring event such as a novel disease outbreak
- *Closed POD Considerations: A Stockpile Perspective* provides state and local agencies with information to manage Closed POD sites during a public health emergency. It covers planning functions for designing a system to dispense prophylactic medications to the employees and their families.

- *The Receive, Stage and Store (RSS) Warehouse Floor Marking Video* is a quick learn lesson that provides an easily accessible reference for those who need to effectively prepare their warehouse to receive SNS products during an emergency. The information will enhance the speed with which live-saving medications or supplies can be dispensed to the public, while maintaining property accountability.
- *Safe Handling of 12-hour Push Package Containers in the Stockpile* is another quick learn lesson to provide an accessible reference for those who need to effectively prepare their warehouse to receive SNS products during a public health event. The information will introduce safe handling practices for 12 Hour Push Package Containers while working in a warehouse during a public health event.

CDC also maintains webinars on TRAIN to assist STLT planners with using materiel provided by CDC during an event of public health significance:

- *The Strategic National Stockpile (SNS) Formulary Update* provides public health partners with an overview of the Strategic National Stockpile (SNS) formulary.
- *Extending Expiration Dates of Stockpiled Doxycycline for Anthrax Preparedness: Overview of FDA Guidance for Government Stockpiles* provides stakeholders an overview of the U.S. Food and Drug Administration's (FDA) April 2017 draft guidance, Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Stockpiles: Draft Guidance for Government Public Health and Emergency Response Stakeholders. The draft guidance provides information for government stakeholders on laboratory testing used to extend the expiration dating of their stockpiled doxycycline tablets and capsules for anthrax emergency preparedness.
- *Introduction to CDC's Strategic National Stockpile* is a learning webcast that will familiarize partners and stakeholders with the Centers for Disease Control and Prevention's (CDC) Strategic National Stockpile (SNS). The SNS is the nation's largest supply of potentially life-saving pharmaceuticals and medical supplies for use in a public health emergency severe enough to cause local supplies to run out.
- *Maximizing MCM Shelf Life and Mitigating Public Health Concerns* is one in a series of DSNS information sharing events designed to familiarize partners and stakeholders with critical SNS concepts. This informational webinar will help participants better understand the importance of shelf life and the impact of this dynamic on medical countermeasure (MCM) preparedness planning capabilities.
- *DSNS Pharmaceutical Supply Chain Webinar Series*. This Health Care Ready sponsored webinar series is designed to familiarize partners and stakeholders with critical concepts related to the pharmaceutical supply chain and the role of the Strategic National Stockpile.
- *Navigating the Pharmaceutical Supply Chain* webinar includes a discussion on the interconnected nature of the pharmaceutical supply chain and an overview of pharmaceutical supply chain logistics. Discussion includes third-party logistics, just-in-time inventory, and the complexities of forecasting demand and allocation.
- *The Partnering with the Pharmaceutical Supply Chain* webinar helps participants understand the value of building relationships between public health and the private-sector pharmaceutical supply chain. Speakers discuss the complex nature of these kinds of partnerships and describe common components for restoration of services for supply chain components following a disaster.

- *The Principles of Pharmaceutical Regulation* webinar will help participants better understand pharmaceutical regulation in the United States, supply chain protection and mitigation programs in place, and regulatory processes related to Strategic National Stockpile products.
- *Understanding Drug Shortages* webinar will help participants understand drug shortages, why they occur and current trends. Speakers will also discuss how the Food and Drug Administration and drug manufacturers work to prevent and mitigate drug shortages.

NIAID held a meeting in August 2016 to address the need to harmonize radiation dosimetry across their research program. In addition, the Radiation Injury Treatment Network co-sponsored a conference in July 2016, to highlight the need to refine the study of animal models to match operational needs for radiation medical management. Manuscripts are in preparation to share the outcomes from both meetings in peer-reviewed journals.

ASPR and NLM continued to disseminate REMM and CHEMM to a variety of stakeholders so that emergency responders and healthcare providers are aware of and have immediate access to information regarding the use of MCMs for radiation/nuclear and chemical incidents. NLM developed a course on CBRN incidents that includes instruction on how to use REMM, CHEMM, and other CRBN resources such as NLMs Wireless Information System for Emergency Responders.

FDA holds Advisory Committee Meetings and public workshops as part of its usual efforts to obtain independent input and expert advice on scientific, technical, and policy matters to facilitate MCM development.

Key meetings and public workshops held during FY 2016 include:

- October 13-14, 2015 – Public workshop – Physiological Closed-Loop Controlled (PCLC) Devices – A workshop to discuss the challenges related to the design, development, and evaluation of critical care PCLC devices. This workshop focused on the design, development, and performance evaluation of PCLC systems intended for use in critical care environments. Such devices include closed-loop anesthetic delivery, closed-loop vasoactive drug and fluid delivery, and closed-loop mechanical ventilation.
- October 16, 2015 – Public workshop – Non-Microbial Biomarkers of Infection for *In Vitro* Diagnostic Device Use – A workshop to receive input from stakeholders and discuss approaches to establish the performance of non-microbial biomarker assays for differentiating viral from bacterial infections and for diagnosis and assessment of sepsis.
- October 27-28, 2015 – Public workshop co-sponsored by NIST and FDA – Standards for Pathogen Detection Via Next-Generation Sequencing (NGS) - A workshop to receive input from stakeholders and discuss how to define reference materials, reference data, and reference methods for assessing analytical sensitivity, specificity, and relative performance of NGS-based pathogen detection devices/assays.
- November 9-10, 2015 – Public workshop – Clinical Trial Designs for Emerging Infectious Diseases – A workshop to explore the ethical and methodological assumptions behind the choice of different trial designs, describe different types of emerging infectious diseases of concern, and explore several clinical trial designs for both vaccines and therapeutic products.

- November 12, 2015 – Public workshop – Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing *In Vitro* Diagnostic Tests – A workshop to obtain feedback on possible analytical standards and approaches to develop or build on existing standardization efforts in order to optimize FDA's regulation of NGS-based IVDs.[55]
- January 20-21, 2016 – Public workshop – Moving Forward: Collaborative Approaches to Medical Device Cybersecurity – A workshop to highlight past collaborative efforts, increase awareness of existing maturity models (i.e., frameworks leveraged for benchmarking an organization's processes), used to evaluate cybersecurity status, standards, and tools in development, and to engage the multi-stakeholder community in focused discussions on unresolved gaps and challenges that hamper progress in advancing medical device cybersecurity.[56]
- March 3, 2016 – Public workshop – Advancing the Development of Biomarkers in Traumatic Brain Injury – A workshop to examine potential biomarkers, discuss the challenges and solutions related to biomarker development methodologies, and establish strategies for data standardization, sharing, and analysis of big data sets for traumatic brain injury.
- March 28-29, 2016 – Zika Virus in the Americas: An HHS Expert Consultation to Accelerate the Development of Countermeasures – Co-sponsored by HHS, NIH, CDC, BARDA, and FDA, a workshop to review current information about epidemiology of Zika virus, and clinical manifestations and pathogenesis of Zika virus. Participants also discussed strategies to accelerate the development of vaccines, diagnostics, therapeutics, and novel vector control methods and ensure blood supply safety.
- April 5-6, 2016 – Public workshop – Proposed Pilot Project(s) under the Drug Supply Chain Security Act – to discuss proposed design objectives of pilot projects that will explore and evaluate methods to enhance the safety and security of the pharmaceutical distribution supply chain.
- April 14-15, 2016 – Public workshop – Developing an Evidentiary Standards Framework for Safety Biomarkers Qualification – co-hosted by FDA and the NIH Biomarkers Consortium, a workshop to elaborate a general framework for biomarker qualification along with specific application to different contexts of use related to drug safety, including assessment of several specific case studies involving qualifying clinical markers of toxicity in different organ systems.
- August 16, 2016 – Advisory Committee meeting – Microbiology Devices Panel of the Medical Devices Advisory Committee – to discuss and make recommendations regarding the appropriateness of clearing or approving over-the-counter diagnostic tests for the detection of pathogens causing infectious diseases, focusing on respiratory and sexually transmitted infections.
- September 23, 2016 – Public Workshop – Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests –A workshop to obtain feedback on two FDA draft

[55] For more information, see the FDA Voice blog post *FDA Taking Genomic Testing to the Next Level*, available at: https://blogs.fda.gov/fdavoice/index.php/2015/09/fda-taking-genomic-testing-to-the-next-level/

[56] More information about cybersecurity of medical devices is available at: https://www.fda.gov/MedicalDevices/DigitalHealth/ucm373213.htm

guidance documents, Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics (IVDs) Used for Diagnosing Germline Diseases and Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics that describe new approaches to regulate NGS-based tests.

- January 25-26, 2017 – MCM Operational Resource Guide Stakeholder Meeting - The goal of the workshop was to provide an opportunity for various state, tribal, and local planners, including the health care sector, to discuss the content and format of the MCM Operational Resource Guide. The resource guide is still under development and CDC will make the guide available to STLT when completed.

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

Since the release of the *2016 PHEMCE SIP*, the PHEMCE made significant progress in addressing the MCM needs of at-risk[57] populations. As required by section 2811(d) of the PHS Act,[58] selected highlights of this progress are below.

Table 2: Progress in Addressing At-Risk MCM Needs

PHEMCE Mission Component[59]	Progress
Requirements Setting	• The PHEMCE MCM requirements include consideration of at-risk population needs. The Pediatrics and Obstetrics Integrated Program Team (IPT) reviews all requirements documents to provide perspectives in addressing pediatric and obstetric population needs. • The Pediatrics and Obstetrics IPT has been and will continue to consult with BARDA's DQA when modeling scenarios are developed and applied involving MCM scenarios for the pediatric and obstetric populations.
Advanced Development/ Manufacturing	• BARDA has ongoing efforts to develop MCMs for pediatric and geriatric populations. • BARDA continued development of vaccine and therapeutic candidates to address at-risk population needs. These included Prussian blue (radiocesium decorporation), smallpox and influenza vaccines, and influenza antiviral drugs. • BARDA-supported program for MVA completed enrollment of its Phase 3 clinical trial in 2016. The Biologics license application (BLA) submission is projected for 2018. • BARDA is also developing an IV formulation of a smallpox antiviral drug to be able to treat the pediatric population and those unable to swallow an oral medication. • NIAID, in conjunction with several Institutes and centers, will continue to support both in vitro and in vivo screening of therapeutic candidate compounds, antibodies, and peptides to identify those with antiviral activity against the Zika virus. • NIAID supported the licensure of Neulasta ® to increase survival in adult and pediatric patients acutely exposed to myelosuppressive doses of radiation. • NIAID co-funded several grants with the NIH National Institute of Aging to study age-related differences in responses to radiation and medical countermeasures.

[57] 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

[58] 42 U.S.C. 300hh-10(d)

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

Regulatory Science Management	• FDA-supported researchers are exploring potential lessons from animal models for understanding pharmacokinetics of MCMs during pregnancy. • NIAID extended support of the Armed Forces Radiobiology Research Institute for juvenile models to include consideration of juvenile nonhuman primates. In addition, mixed field irradiation models for these species are under development, as well as cutaneous and radiation combined injuries in minipig models.
Procurement / Inventory Management / Stockpiling	• PHEMCE will continue to ensure pediatric formulations (e.g., suspensions) or suitable alternatives of antimicrobials products stockpiled in the SNS. • Pediatrics and Obstetrics IPT actively participates in the SNS Annual Review to identify and prioritize pediatric and obstetric MCM gaps. • The SNS holds more than enough smallpox vaccines for the entire U.S. population, including millions of regimens of the unlicensed MVA vaccine that CDC may be able to use in an emergency under an EUA in individuals of all ages with HIV or atopic dermatitis, including nursing and pregnant women.
Deployment / Distribution / Dispensing / Administration	• CDC published a guidance document, Clinical Framework and Medical Countermeasure Use During an Anthrax Mass-Casualty Incident, for the utilization and prioritization of MCMs after a mass casualty anthrax incident. CDC engaged the American Academy of Pediatrics (AAP) in developing this guidance to address pediatric needs. • CDC is examining how to incorporate at-risk population needs into the MCM ORR evaluation tool. • The AAP, with support from the Health Resources and Services Administration's Maternal and Child Health Bureau and ASPR, launched the AAP Project ECHO Zika Telementoring Learning Community. This innovative telementoring project uses a combination of didactic methods from experts across the U.S. and case-based learning, including what we know about the Zika virus and its effect on fetuses and newborns, and the Zika virus outbreak specific to the U.S. Territories. This is a series of virtual clinics designed to build a learning community of primary care pediatric providers in the U.S. Territories interested in learning how to manage their patients that may have been exposed to the Zika virus. • CDC's SNS developed, packaged, and deployed Zika Prevention Kits (ZPK) to meet the needs of populations in specific jurisdictions experiencing mosquito borne transmission of the virus. In 2016, CDC deployed 31,389 ZPKs for pregnant women in U.S. states and territories and associated island nations.

Additionally, the PHEMCE coordinated with FDA's Office of Pediatric Therapeutics (OPT), to identify and address the needs of pediatric and maternal populations. The OPT works closely with FDA review divisions who are responsible for facilitating the development and availability of MCMs for children. For example, OPT works with FDA scientists to provide regulatory advice and guidance to product developers and PHEMCE partners to assure enrollment of children only in clinical studies that are scientifically necessary and ethically appropriate. The OPT also works with the review divisions to ensure that any pediatric studies for MCMs are rigorously designed and conducted in accord with the 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; 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.

ASPR published the 2014-2015 Report of the Children's HHS Interagency Leadership on Disasters Working Group: Update on the Department Activities in April 2017. The report covers activities in progress from 2014 through 2015, including those that originated in years prior. Each area of focus includes background information and a description of programs, activities, and research, including governmental and NGO collaboration. The report details departmental updates within the following six themes: (1) behavioral health; (2) MCMs; (3) child physical health, EMS, and pediatric transport; (4) child care, child welfare, and human services; (5) pregnant and breastfeeding women and newborns; and (6) children at heightened risk.

APPENDIX 4: ADVANCED RESEARCH AND DEVELOPMENT AND PROCUREMENT

Project BioShield Authorities and Reporting Requirements

The PBS Act of 2004 amended the PHS Act and the 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 gives the government the authority to quickly authorize such MCM use during emergencies. The law further delineates, clarifies, expands, and extends these authorities in the Pandemic and All-Hazards Preparedness Act (PAHPA) and PAHPRA. Section 5 of the PBS 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 PBS Act, as enacted in 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 (SRF)** – Section 3 of the PBS Act enacted Section 510 of the Homeland Security Act (6 U.S.C. 321j) to authorize the appropriation of up to $5.593 billion over the period of FY 2004 through FY 2013 in a SRF for the procurement of security countermeasures that may be placed in the SNS. Furthermore, Section 3 of the PBS 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.
- **EUA for Medical Countermeasures** – Section 4 of the PBS Act, as enacted under Section 564 of the FD&C Act (21 U.S.C. 360bbb-3), and amended by PAHPRA and the 21st Century Cures Act, Pub. L. No. 114-255. The law enables the FDA Commissioner[60] to issue an EUA to authorize the use of certain unapproved medical products, or to authorize certain unapproved uses of approved medical products,[61] 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 is issued, FDA must conclude that the product meets 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 there are no adequate, approved, available alternatives).

[60] The HHS Secretary has delegated most authority under this statute, including the authority to issue an EUA to the FDA Commissioner.

[61] This authority is limited to products to respond to emergencies that involve biological, chemical, radiological, or nuclear agents.

Reporting is required on emergency uses of certain biologicals, drugs and devices, emergency declarations, and conditions of authorization.

Authority Usage

In FY 2016, 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. HHS deemed the standard Federal Acquisition Regulation practices to be adequate for acquisition activity in 2016.

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

BARDA will continue to provide monthly reports to the authorizing and appropriating committees detailing expenditures under ARD and PBS. BARDA vets potential PBS procurements through the PHEMCE leadership and are consistent with the annual PHEMCE SIP goals and objectives.

Table 3a: FY 2016 Advanced Research and Development Contracts

Threat / Portfolio Area	Time from Submission to Award	FY 2016 Award Amount ($ million)	Benchmarks / Milestones
Anthrax	Phase 4 PMC and Clinical Study of AVA and Raxibacumab (GlaxoSmithKline) – 5 months	$2	Conduct an FDA-requested drug/vaccine interaction clinical study as part of the post licensure agreement between GSK and FDA.

Threat / Portfolio Area	Time from Submission to Award	FY 2016 Award Amount ($ million)	Benchmarks / Milestones
Broad-Spectrum Antimicrobials	CARB Accelerator (Boston University) – 6 months	$30	CARB-X brings together BARDA, NIAID, Wellcome Trust, Boston University and 3 non-profit life science accelerators to identify, select, and manage a portfolio of early stage antibacterial candidates.
	OTA for Antimicrobials and Diagnostics (Hoffman-LaRoche) – 9 months	$35	Support the establishment and advanced research and development of a dynamic portfolio of novel antibacterial products.
	OTA for Antimicrobials (Medicines Company) – 180 days	$32	Support the establishment and advanced research and development of a dynamic portfolio of novel antibacterial products.
	Development of Ceftobiprole (Basilea) – 5 months	$20	Support the Phase 3 clinical development, evaluation and regulatory approval of ceftobiprole for the treatment of skin, lung and blood infections due to MRSA when polymicrobial infections are suspected.
Chemical	R-107 for Treatment of Acute Chlorine Inhalational Lung Injury (Radikal Therapeutics) – 142 days	$16	Further develop R-107, a pro-drug nitric oxide donor, to treat chlorine-induced inhalational lung injury. Work in the base period focuses on refinement of the synthesis of API and demonstration of safety and efficacy in large and small animal models.
Diagnostics	Development of an Anthrax Point of Care Diagnostic Assay System (SRI International) – 84 days	$2.5	Development, clinical evaluation, FDA 510(k) clearance and CLIA waiver of an anthrax lethal factor assay for use at point of care.
	Development, Validation and FDA Clearance for a Simplified Next Generation Nucleotide Sequencing Platform and Relevant Analysis Tools for the Use in a CLIA Regulated Lab (DNAe) – 51 days	$8.6	Development, clinical studies, and FDA 510(k) clearance of their targeted sequencing instrument along with molecular antibiotic resistance and influenza subtyping assays.
Innovation	N/A	N/A	N/A

Threat / Portfolio Area	Time from Submission to Award	FY 2016 Award Amount ($ million)	Benchmarks / Milestones
Respiratory Protective Devices	Surge Production Capacity of Respirators (Halyard Health) – 120 days	$1.6	Determine the feasibility of development of a respirator manufacturing line capable of producing 1.5 million or more respirators per day.
Influenza	Physical Chemistry Testing of H7N9 Vaccine (GlaxoSmithKline) – 90 days	$0.2	Physical and compatibility testing between vaccine and adjuvant
	ResPECT Study (Johns Hopkins University, Bloomberg School of Public Health) – 86 days	$0.4	Data analysis and publication of data previously collected in federal government-funded studies in order to support recommendations for respiratory protection in outpatient settings in the event of an influenza pandemic, or other infectious disease epidemics.
	Advanced Development of SAB-301 (SAB Biotherapeutics) – 90 days	$2.4	Enable the sponsor to complete the analytical testing of samples from the Phase 1 safety study and to manufacture additional doses for a Phase 2 study.
	Advanced Development of REGN 3048/3051 (Regeneron) – 120 days	$9	Enable the sponsor to develop the analytical assays needed to test samples from the Phase 1 safety study and to complete manufacturing of final drug product for use in clinical trials.
Radiological/Nuclear	Mirostal Treatment of Platelets (Terumo) – 89 days	$17.47	Determine the clinical effectiveness of Mirasol-treated platelets. The Mirasol System is being developed to increase the safety and availability of platelet products required under emergency condition.
	Clinical Study to Evaluate Intercept System in Puerto Rico (Cerus) – 75 days	$31	Advance Cerus' INTERCEPT Pathogen Reduction Technology to treat red blood cells to protect the blood supply, to conduct a clinical study with the INTERCEPT System in Puerto Rico where Zika is prevalent.

Threat / Portfolio Area	Time from Submission to Award	FY 2016 Award Amount ($ million)	Benchmarks / Milestones
Viral Hemorrhagic Fever	Expanded Access Protocol in U.S. and West Africa (Mapp Biopharmaceutical) – 87 days	$13	Establish a regulatory mechanism to make ZMapp available to the 10 Ebola treatment centers and NIH hospital in the U.S. and Liberia, Guinea, and Sierra Leone if needed to treat individuals with Ebola disease.

Threat / Portfolio Area	Time from Submission to Award	FY 2016 Award Amount ($ million)	Benchmarks / Milestones
Zika Virus	Clinical Trial for Puerto Rico Blood Supply Testing (Roche) – 6 days	$0.4	Screening of Blood units from an area where Zika transmission is rampant (Puerto Rico), Collection of sufficient reactive units to support BLA filing. Indirectly ensuring safety of the PR blood supply during the study.
	Zika Elisa (InBios) – 65 days	$5	Development, Emergency Use Authorization, clinical studies, and 510(k) clearance of a Zika IgM diagnostic assay for use in clinical laboratories.
	Detection of Zika Antibody Response in Patients (ChemBio) – 89 days	$6	Development, Emergency Use Authorization, clinical studies, and 510(k) clearance of a Zika IgM diagnostic assay for use in clinical laboratories.
	Zika Lateral Flow (Orasure) – 145 days	$7	Development, Emergency Use Authorization, clinical studies, 510(k) clearance and CLIA waiver of a Zika IgM diagnostic assay for at point of care.
	Development of LIAISON Zika Virus Assays (DiaSorin) – 118 days	$2.7	Development, Emergency Use Authorization, clinical studies, and 510(k) clearance of an automated Zika IgM diagnostic assay for use in clinical laboratories.
	Advanced Development of mRNA-1325 (Moderna) – 54 days	$8	Enable sponsor to manufacture and evaluate a recombinant mRNA-based vaccine in a Phase 1 clinical trial and to conduct a developmental and reproductive toxicology study.
	Whole Inactivated Zika Virus Vaccine (Takeda) – 93 days	$20	Enable sponsor to manufacture and evaluate an inactivated, whole-virus Zika vaccine in a repeat-dose toxicology study and a Phase 1 clinical trial.
	Whole Inactivated Zika Virus Vaccine (Sanofi Pasteur) – 90 days	$43	Enable sponsor to manufacture and evaluate an inactivated, whole-virus Zika vaccine in a repeat-dose toxicology study and a Phase 2 clinical trial, and conduct a case definition/ surveillance study in Latin America.

Threat / Portfolio Area	Time from Submission to Award	FY 2016 Award Amount ($ million)	Benchmarks / Milestones
Total[62]	--	$313.3	--

Table 3b: FY 2016 Project BioShield Procurement Contracts

Threat / Portfolio Area	Time from Submission to Award	FY 2016 Award Amount ($ million)	Benchmarks / Milestones
Anthrax	Enhanced Anthrax Vaccine (Emergent) – 5 months	$199	Enable the sponsor to complete all remaining Phase 3 development activities required for FDA licensure and provide an initial procurement of product to begin stockpiling of the vaccine within the Strategic National Stockpile.
Botulism	N/A	N/A	N/A
Broad-Spectrum Antimicrobials	N/A	N/A	N/A
Chemical	N/A	N/A	N/A

[62] These are FY 2016 funds, which do not include FY 2017 supplemental funds.

Threat / Portfolio Area	Time from Submission to Award	FY 2016 Award Amount ($ million)	Benchmarks / Milestones
Diagnostics	Late Stage Development of Arad High Throughput Biodosimetry Test Validation Device (MRIGlobal) – 113 days	$21	Validation, clinical and animal model studies, FDA Pre-EUA approval, FDA 510(k) clearance of biodosimetry assays, and manufacturing preparations and stockpile deliveries of Biodosimetry assay kits for use in clinical laboratories.
	Late Stage Development of Arad High Throughput Biodosimetry Test Validation Device (DxTerity Diagnostics) – 113 days	$22	Validation, clinical and animal model studies, FDA Pre-EUA development, FDA 510(k) clearance of biodosimetry assays, and manufacturing preparations and stockpile deliveries of Biodosimetry assay kits and sample collection vials for use in clinical laboratories.
Plague	N/A	N/A	N/A
Radiological/Nuclear	N/A	N/A	N/A
Smallpox	N/A	N/A	N/A
Total	--	$242	--

Table 3c: FY 2016 Strategic National Stockpile (SNS) Procurement / Replenishment Contracts [63]

Threat / Portfolio Area	Actual FY 2016 ($ million)
Anthrax	$184.6
Botulism	$0
Burkholderia	$5.9
Chemical	$3.1
Influenza	$7.0
Plague	$0
Radiological/Nuclear	$13.6
Smallpox	$42.7
Tularemia	$0
Federal Medical Station (FMS)	$0.2
Medical Supplies and Ancillary Items (MS&AI) and non-MS&AI[64]	$67.4
Total	$324.5

Projected PHEMCE Funding by Threat Area

The PHEMCE Multiyear Budget (MYB) Report captures five-year cost projections associated with the research, development, procurement, and stockpiling of MCMs for use against CBRN threats and emerging infectious diseases. ASPR delivered the PHEMCE MYB FYs 2015-2019 report to Congress in April 2016. The FY 2016-2020 MYB, which provides five-year spending

[63] DSNS bases contracts for the stockpile on factors that vary from year to year. These include PHEMCE recommendations and priorities (as established for example through the SNS Annual Review process), expiring product, replenishment decisions, procurement costs and availability, shelf life extension, and available funding.

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

estimates for research, development, procurement and stockpiling of MCMs against potential CBRN and emerging infectious disease threats, is under development.

APPENDIX 5: PROGRESS TOWARDS NEAR-TERM *2016 PHEMCE SIP* MILESTONES (as of FY 2016 unless otherwise noted)

Table 4: Progress towards Near-Term 2016 PHEMCE SIP Activities

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
1.1.2	Submit the annual MYB report to Congress.	ASPR	FY 2016-2018	ASPR delivered the PHEMCE MYB FY 2015-2019 report to Congress in April 2016. The MYB FY 2016-2020, which provides five-year spending estimates for research, development, procurement and stockpiling of MCMs against potential CBRN and emerging infectious disease threats, is in progress.
1.1.5	PHEMCE IPTs will complete preparedness assessments for all SNS holdings in the near-term.	ASPR	FY 2018	The PHEMCE conducted preparedness assessments for MCMs to address anthrax, botulism, glanders, melioidosis, plague, tularemia, cesium-137, and improvised nuclear devices. Additional assessments are ongoing and the PHEMCE will use ICDs to inform the analysis.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
1.1.7	Engage with appropriate subject matter experts, both within the federal government and externally, to evaluate operational and response planning for MCM preparedness assessments.	ASPR, CDC	FY 2018	1) The PHEMCE stood up, and ASPR and CDC are co-leading, a new MCM Operational Planning Working Group (MOP WG) within the PHEMCE to support coordination and alignment of the operational aspects of MCM emergency response across federal agencies and provide broad-based expertise on MCM operational, and utilization issues associated with PHEMCE products. The MOP WG will serve as an interagency community of practice for vetting and input on the development, coordination, standardization, and assessment of civilian MCM response plans and guidance. 2) The PHEMCE is standing up a new PHEMCE advisory body (the Enterprise Executive Committee – Intergovernmental) that will directly include STLT public health representatives in the PHEMCE federal MCM governance process. 3) SMEs engaged in exercises such as Gotham Shield (April 2017), Tranquil Shift (April 2017), and collaboration with Technical Resources, Assistance Center, and Information Exchange (TRACIE).

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
1.1.8	ASPR and CDC will work to incorporate data from CDC's DSLR ORR evaluation process to inform assessment of the national operational capacity to use MCMs.	ASPR, CDC	FY 2018	CDC reviews capacity annually. Prior to 2015, the technical assistance review (TAR) assessed planning capability only. In 2015-16, CDC implemented a new process to assess not only planning but also operational capacity via the MCM ORR. This is now an ongoing process, and, beginning in 2017-18, CDC will review 50% of state, local, and territorial jurisdictions every year. CDC will use Information obtained from these reviews to form a national picture of operational capacity to use MCMs, with plans to incorporate this info into PHEMCE preparedness assessments. CDC also uses data to TAR to localities with gaps.
1.2.4	Develop and implement a risk assessment methodology and process through which the PHEMCE will determine which EID threats require PHEMCE response.	ASPR	2016	COMPLETED – The EID Working Group developed a risk assessment framework for guiding discussions through 16 topics that should be considered when assessing an emerging threat. The Enterprise Executive Committee piloted the framework during a table top exercise in July 2016.
1.2.5	PHEMCE leadership will determine, utilizing this framework, which emerging infectious diseases to add to the list of PHEMCE high priority threats (see Box 1).	ASPR	FY 2018	PHEMCE leadership will determine how to implement the EID risk assessment framework to identify high-priority threats.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
1.2.7	Develop or update MCM requirement documents for CBRN threats, as well as requirements that address multiple threats, as detailed in Objective 1.2, Table 3 of the *2016 PHEMCE SIP*.	ASPR	FY 2018	The ASPR signed PSRs completed by the PHEMCE for antifungals, antibacterials, and antivirals to treat that might arise because of immunosuppression caused by radiation exposure from an improvised nuclear devices and vaccine to prevent AMR infections. The PHEMCE is in the process of finalizing Filovirus Point-of-Care and Lab-based Diagnostic PSRs and an Anthrax Scenario-Based Analysis. Other PSRs are on target for projected completion date.
1.2.9	Complete an assessment of economic consequences of terrorism threats.	DHS	FY 2017	The updated economic consequence model will be complete once the Terrorism Risk Assessment (TRA) economic expert group has a chance to review and comment. Following its review, DHS will implement the model for CBRN attacks.
1.2.10	Complete an Adversary Decision Model, which incorporates input from the intelligence community to provide frequency probabilities, and incorporate it into the final Biological Terrorism Risk Assessment (BTRA) 5.0 report.	DHS	FY 2018	The Undersecretary of DHS S&T signed the BTRA 5.0 report in May 2017. DHS briefed the results to the National Security Council and Office of Science and Technology Policy in June 2017 and posted to the BTRA's Intellipedia page.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
1.3.5	In 2015, NIH released a Broad Agency Announcement (BAA) entitled "Development of Therapeutic Products for Biodefense and Emerging Infectious Diseases" with awards to be made in FY 2016.	NIH	FY 2016	COMPLETED – In 2015, NIAID issued BAA-NIAID-DMID-NIH-AI-2015037, "Development of Therapeutic Products for Biodefense and Emerging Infectious Diseases that focuses on the development of promising lead therapeutic candidates/products that demonstrate broad spectrum therapeutic activity including activity against AMR bacteria." In September 2016, NIAID funded a contract to VenatoRx for the development of an orally bioavailable, broad-spectrum small molecule beta-lactamase inhibitor (VNRX-7145) in combination with a licensed beta-lactam antibiotic to be used for treatment of infections caused with Gram-negative bacteria resistant to beta-lactam antibiotics. NIAID also awarded a contract to AbViro for development of a broad-spectrum monoclonal antibody AV-1 for treatment of dengue fever. This antibody may potentially be developed for treatment of Zika virus and other flavivirus infections.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
2.3.1	The MCM Monitoring and Assessment (MA) IPT will evaluate current MCM preparedness assessment capabilities and develop a strategy for a PHEMCE-wide comprehensive capability to facilitate a timely and appropriate assessment of MCMs during a public health emergency.	FDA	FY 2018	The MA IPT established workgroups to review and consider, in-depth, a proposed scenario/case study and to develop potential strategies for data collection and analysis in order to monitor and assess MCMs during a PHE with specific regards to safety, effectiveness/efficacy, clinical outcomes, and compliance. The IPT plans to analyze the workgroups' findings and recommendations to identify and propose requirements for monitoring and assessment to provide to the Enterprise Executive Committee. For further information on FDA's progress, see the MCMi Program Update – Fiscal Year 2016.[65]

[65] https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm545369.htm

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
2.3.2	The MA IPT will identify enhancements to current drug and vaccine safety monitoring systems and the potential to leverage clinical information from electronic health records that could help to assess MCMs deployed in a public health emergency.	FDA	FY 2018	The MCM MA IPT created an Anthrax Workgroup to assess the landscape of current planning for the administration of vaccines and dispensing of oral antibiotics in response to a wide area anthrax emergency (i.e., for PEP). In that response context, the workgroup reviewed opportunities for, and challenges associated, with monitoring and assessing the use of such MCMs for safety, compliance, and clinical benefit. The workgroup also explored potential systems and tools that may enhance MCM data collection including CDC's Inventory Management and Tracking System, Medical Countermeasure Electronic Request and Information System, and Countermeasure and Response Administration to understand whether such systems could support, or be leveraged to support, monitoring and assessment efforts following the dispensing or administration of anthrax MCMs.
3.1.1	Submit to Congress the SNS Annual Review report.	HHS	FY 2016-2018	The 2015 SNS Annual Review which provides policy recommendations for FY 2018, was completed on time in August 2016. PHEMCE leadership has approved the recommendations for the 2016 SNS Annual Review (FY 2019 Plan) and ASPR is developing the report.
3.1.2	The PHEMCE will re-visit the appropriate roles and responsibilities of the SNS, based on progress made to date, future opportunities, and in consideration of the need for long-term sustainability of this critical national asset.	ASPR, CDC	FY 2018	CDC's Division of Strategic National Stockpile (DSNS) is considering a number of options that include future appropriations, cost savings measures, and partnerships.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
3.2.2	OEM and DSNS will evaluate whether FMS or other temporary beds could be used in response to a CBRN incident to expand operational capacity. The evaluation will include needs and requirements for staff and supplies.	ASPR, CDC	FY 2018	HHS capabilities resource document updated July 2016 outlines the FMS capacity during incident support. ASPR provides the operational program support and supplemental logistical support, and coordinates federal staffing, while DSNS procures and maintains the FMS caches of equipment and supplies. Caches are met at delivery by a FMS Strike Team of 2-4 personnel from the DSNS, who provide technical guidance to local volunteers (a labor pool of approximately 12 personnel is one element of the required wrap around services) who lay out and set up the FMS. Upon reaching operational status, FMSs are logistically resupplied through prime vendors. Federal FMS staffing is typically a Rapid Deployment Force of U.S. Public Health Service Commissioned Corps Officers, augmented by a small National Disaster Medical System task force from a Disaster Medical Assistance Team. Federal staffing may also be provided by the Veterans Health Administration or Department of Defense (DoD).
3.2.3	ASPR and CDC will lead PHEMCE evaluation of cross-threat constraints on emergency preparedness posed by IV MCM formulations and identify initiatives to address these gaps, leveraging existing efforts by CDC to evaluate ancillary supplies.	ASPR, CDC	FY 2018	The IV ICD is being developed to estimate the operational capacity to administer IV products. Once completed, an assessment of threat-specific considerations will be conducted to identify any threat-specific differences, and provide recommendations.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
3.2.6	Develop clinical practice guidelines for MCMs to address botulism (FY 2017) and ARS-associated neutropenia (FY 2018), and chemical agents (FY 2019)	ASPR, CDC	FY 2017-2018	A CDC review of clinical guidance information available to inform use of the MCMs against chemical agents determined that sufficient guidance existed (e.g., through the ASPR/NLM Chemical Hazards Emergency Medical Management (CHEMM) website at https://www.chemm.nlm.nih.gov/) and no additional products were needed at this time. Clinical information to support the use of MCMs for ARS-associated neutropenia is being developed by CDC. Systematic literature reviews of the available information on the clinical features, evaluation, and treatment of botulism (e.g., clinical use of botulism antitoxins) have been completed and are in CDC clearance. A meeting of experts was held in 2016 to seek individual input on CDC guidelines for the clinical evaluation and management of botulism and the use of botulism antitoxin. Clinical guidance is being drafted.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
3.2.13	The PHEMCE, through collaboration with finance, budget, and contract management partners, will identify strategies to accelerate the MCM-related administrative decision-making processes.	ASPR	2017	Through the Health Resources Priorities and Allocation System, HHS addresses health resources pursuant to the authority under Section 101(c) of the Defense Production Act as delegated to HHS by Executive Order 13603. Section 101 of the Defense Production Act provides the President with authority to require acceptance and priority performance of contracts and orders (other than contracts of employment) to promote the national defense over performance of any other contracts or orders, and to allocate materials, services, and facilities as deemed necessary or appropriate to promote the national defense to a number of agencies. The delegated authority is given to the HHS Secretary with respect to health resources; including drugs, biological products, medical devices, materials, facilities, health supplies, services, and equipment required to diagnose, mitigate or prevent the impairment of, improve, treat, cure, or restore the physical or mental health conditions of the population.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
3.2.20	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 Border Initiative, and as called for in NAPAPI.	ASPR	FY 2018	DIHS shared, with Canada, a draft U.S.-Canada bilateral toolkit for the deployment of MCMs, which is working to add elements to the document based on how Canada would receive U.S. MCMs or deploy its own MCMs to the U.S. After Canada provides feedback, both countries will work together to finalize the toolkit. In addition, DIHS is leading work with Canada and Mexico on describing the legal, regulatory, and logistical challenges of deploying MCMs among the three countries. Next, DIHS will work with Canada and Mexico to develop a trilateral white paper, which will outline recommendations for addressing these shared challenges.
3.3.1	In 2016-17, DSLR will provide targeted technical assistance to address operational gaps identified during the MCM ORR site visits in 2015-16.	CDC	FY 2018	Based on MCM ORR site visits in 2015-2016, 100% of technical assistance action plans have been completed for 62 awardees and the local planning jurisdictions in the 72 CRI jurisdictions for the first three quarters of the current budget period. Each action plan captures targeted technical assistance provided by CDC and improvement plans completed by health departments. CDC has completed action plans for the last quarter of the budget period, which ended on June 30, 2017.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
3.4.3	Update 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	FY 2018	The CERC Program provided online training courses, 15 in-person sponsored training to external organizations, 7 CDC University courses to CDC staff, and 23 presentations to audience types including state officials, public information officers, and other health communicators. These trainings and presentations reached, respectively: 1) In-Person Sponsored Training: 724 total participants. 2) CDCU Courses: 123 total participants. 3) Presentations: 2,061 total participants. 4) Online Training: 2,043 total participants.
4.2.5	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	FY 2018	BARDA' supported program for MVA completed enrollment of its Phase 3 clinical trial in 2016. BLA submission is projected for 2018.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
T.A.1	Obtain results from preliminary studies into various technologies for temperature stabilization and alternative routes of delivery for next-generation anthrax vaccines.	NIH	FY 2018	A next generation, lyophilized adjuvanted Anthrax Vaccine Adsorbed (AVA) vaccine, Thermostable AV7909 candidate (Emergent BioSolutions) is currently under formulation development, manufacturing scale up and preclinical testing (supported by NIAID, DoD, and BARDA). Several anthrax vaccines are currently under investigation for immunogenicity, efficacy, and stability. These include a subcutaneous pellet vaccine composed of recombinant protective antigen (rPA) expressed from *Pseudomonas fluorescens* to be delivered via a Glide SDI system with or without an adjuvant (Pfenex), an intranasal anthrax vaccine based on the Public Health England, 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; and a plant-based *B. anthracis* Protective Antigen (PA83) formulated with a saponin-cholesterol adjuvant (Fraunhofer). Stability of lyophilized rPA vaccine (Pharmathene) is currently under evaluation. Different regimens of rPA- adenovirus serotype 4 (Ad4), replication competent, oral Ad4 vectored vaccines expressing *B. anthracis* protective antigen rPA (PaxVax), with or without the licensed AVA, were evaluated in a Phase 1 clinical trial.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
T.A.10	Submission for FDA review of animal efficacy studies of antimicrobials currently approved for other indications to support approval under the "Animal Rule" for use against inhalational anthrax.	NIH	FY 2016	Anthrax: NIAID is obtaining additional data (pharmacokinetic and in vitro) requested by FDA to support a regulatory decision on the efficacy of amoxicillin and amoxicillin/clavulanate for prophylaxis of anthrax. Anticipate final submission in FY 2018. Plague: NIAID and USAMRIID have been actively discussing doxycycline studies data with FDA. Final study report is planned for summer 2017 and additional studies are under discussion for execution in FY 2018. Tularemia: Doxycycline data is complete and will be submitted to FDA by the end of 2017. The ciprofloxacin study is completed; NIAID is evaluating whether additional data are required prior to submission to FDA.
T.A.12	ASPR and CDC will lead analysis of the optimal ratios of products for oral antimicrobial PEP for anthrax, considering resistance, tolerability, cost, and fluctuations in market availability.	ASPR, CDC	FY 2018	COMPLETED – In November 2016, the PHEMCE adjusted the ratio of doxycycline and ciprofloxacin to 80:20 for SNS holdings for oral PEP for anthrax. This decision included consideration of a request from local jurisdictions, safety profile of ciprofloxacin, and usability in pediatric populations.
T.OB.2	Qualify animal models for anthrax, plague, and tularemia in support of PEP and treatment indications, through FDA's Animal Model Qualification Program.	NIH	FY 2018	Anthrax: NIAID is taking the lead regulatory role in completing this activity. Submission of a briefing package for qualification of the rabbit model is planned for the end of 2017. Plague: Statistical analysis is nearly complete and briefing package submission is anticipated by end of 2017. Tularemia: All data have been submitted and NIAID is proceeding to preparing the final qualification package.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
T.OB.10	Continue testing of candidate products against *Burkholderia pseudomallei* and *Burkholderia* mallei.	BARDA	FY 2018	CLOSED – Reports of naturally occurring human disease caused by *B. pseudomallei* suggest incidence sufficient to support informative human clinical trials. As a result, approval for antibiotics for *B. pseudomallei* would not occur under the Animal Rule. Clinical trials in endemic areas would be required. BARDA developed a strain panel and a nonhuman primate model for *B. pseudomallei*. This work was discontinued. For *B. mallei*, BARDA was unable to develop a non-human primate model with a reliable primary endpoint (e.g., mortality).
T.OB.12	CDC will develop and FDA will review a pre-EUA package for meropenem, trimethoprim/sulfamethoxazole, and amoxicillin/clavulanate for the treatment of melioidosis and glanders.	CDC, FDA	FY 2018	CDC submitted a Pre-EUA submission to FDA in June 2016 for meropenem IV for the treatment of melioidosis and glanders and recently received FDA's review comments; CDC developed a Pre-EUA for SMZ-TMP with target submission to FDA before the end of FY 2017. CDC also initiated development of a Pre-EUA package for amoxicillin/clavulanic acid and will submit it to FDA to coincide with the stockpiling timeframe.
T.S.5	The PHEMCE will assess policy implications of the use of antivirals.	ASPR, CDC	FY 2018	The National Center for Emerging and Zoonotic Infectious Diseases' Division of High-Consequence Pathogens and Pathology is conducting a systematic review of the literature for smallpox antivirals to provide the evidence base for policy assessments and decisions. Further planning for the smallpox antiviral policy assessment by the Smallpox IPT is currently underway.
T.S.6	Complete delivery to the SNS of the required treatment courses of the smallpox antivirals currently under contract.	BARDA	FY 2018	BARDA successfully completed delivery of 2 million treatment courses of Tecovirimat to the SNS.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
T.PI.3	Develop procedures to ensure that public information in future pandemics is provided in accessible and alternative formats.	CDC	FY 2018	CDC continues to use multiple platforms for including traditional, web, social media, and mobile messaging for the delivery of public health messages to the public. The National Center for Immunization and Respiratory Diseases' Influenza Division and Office of Public Health Preparedness and Response's (OPHPR) Emergency Risk Communications Branch develops strategies for communicating to the general public in advance of and during pandemics.
T.PI.4	Refine and implement partnership strategies to improve communication with hard-to-reach and at-risk populations.	CDC	FY 2018	For the 2015-16 flu season, members of the CDC-sponsored National Influenza Vaccination Disparities Partnership (NIVDP) hosted flu vaccination promotion events in 47 cities, including events for Hispanic/Latino and African American communities. During this season, 116 new partners were recruited (for a total of 902 partners), and 36 connections were made between health departments and immunization coalitions. In total, over 81,000 vaccinations were provided nationwide. Starting in 2016-17, NIVDP began to focus its efforts on three geographic areas - Atlanta, GA, Trenton, NJ, and Houston, TX. In order to create a partnership model, NIVDP targeted work in these areas to develop sustainable partnerships between state/local health departments and grassroots partners and key influencers within each jurisdiction. Research, needs assessments, and hands-on work in these three areas should result in a partnership model that can replicate.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
T.PI.6	Develop an approach, definitions, tools, and models for a risk communication response plan.	CDC	FY 2018	COMPLETED – CDC continues to work with internal and external federal public health preparedness and response partners to update risk communication plans. OPHPR updated the Joint Information Center 101 training. CDC updated its Operations Plan to include a Joint Information Center structure, standard operating procedures, and functional roles/responsibilities. The Office of the Associate Director for Communication continues to coordinate with HHS and the White House to exercise risk communication plans for all-hazards preparedness, including pandemic influenza.
T.PI.8	Maintain and update the existing stockpile of novel influenza viruses and pre-pandemic vaccines and adjuvants as needed.	BARDA	FY 2018	The preliminary results of the BRITE study indicated that vaccines in the stockpile remain safe and effective after long-term storage. BARDA is now working closely with FDA to develop innovative approaches to support a regulatory pathway for the use of vaccines stored for more than five years in the pre-pandemic stockpile.
T.PI.9	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	FY 2018	With support from BARDA, CDC has made progress on synthetic vaccinology. The BioXp 3200 biosynthesizer machine (Synthetic Genomics Inc.) has been tested and found to be unsatisfactory for the current needs. CDC will continue to work with the company to optimize speed and conditions. Additionally, CDC is developing alternative strategies for the production of reverse genetics constructs, including synthetic genomics and rapid polymerase chain reaction mutagenesis.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
T.PI.10	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	FY 2018	CDC's National Center for Environmental Health and Influenza Division is investigating isotope dilution mass spectrometry as an alternative to the current potency testing method (single radial immunodiffusion assay) for pandemic and seasonal influenza vaccines. BARDA is tabulating all data from various sources including other partners.
T.PI.14	Initiate preclinical development of novel viral antigen and universal influenza vaccine concepts.	NIH	FY 2018	NIH continues to support the development of a chimeric hemagglutinin universal vaccine candidate targeting the chimeric hemagglutinin stem. This candidate is currently in the clinical concept development phase.
T.PI.17	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	FY 2018	Partner laboratories developed ELISA, surface plasmon resonance, total organic carbon, initial calibration verification - and size exclusion chromatography - isotope dilution mass spectrometry assays. The laboratory assessment including all U.S. licensed influenza vaccine manufactures revealed feasibility of ELISA-based assays. FDA studies indicated feasibility of surface plasmon resonance for monovalent (pre-pandemic vaccines). International Federation of Pharmaceutical Manufacturers and Associations, FDA's Center for Biologics Evaluation and Research and BARDA established an alternative potency assay working group. Recommendations to WHO Essential Regulatory Laboratories and industry are due in July 2017. Follow-on studies are being planned.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
T.PI.21	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	FY 2018	BARDA is supporting the advanced development of a monoclonal antibody to treat hospitalized patients. This therapeutic is currently undergoing Phase 2 clinical testing. BARDA is also supporting the advanced development of a small molecule PB2 inhibitor for the treatment of hospitalized patients. This therapeutic completed Phase 2 clinical trials and is scheduled to begin Phase 3 clinical trials in December 2017.
T.PI.23	Develop new plans for antiviral distribution and dispensing.	CDC	FY 2018	CDC conducted an assessment of feasibility and acceptability of new concepts. CDC is establishing contractual mechanism for operations. Once contracts are in place, operational guidance will be developed and a pandemic influenza response plan will be updated accordingly.
T.PI.26	Continue supporting development of diagnostics to inform seasonal and pandemic influenza treatment with an emphasis on higher quality and faster testing at the POC.	BARDA	FY 2018	BARDA continues to support development of Influenza diagnostics through the Influenza BAA. BARDA is currently funding development of an influenza point of care multiplexed molecular platform and two influenza subtyping tools. BARDA is in discussions with multiple organizations to support development of home use molecular flu diagnostics. Through a BARDA-funded cooperative agreement, Johns Hopkins University developed a screening and diagnostic testing strategy to improve antiviral use. The clinical decision guideline and workflow within the emergency department developed by Johns Hopkins University resulted in rapid screening and testing of all patients thought to be infected with influenza. This triage protocol combined with rapid diagnostic testing resulted in a 55 percent increase in antiviral use.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
T.B.1	NIH will continue to evaluate a collection of next-generation botulism antitoxin mAbs. Botulism serotype B&E cocktails will be in Phase 1 trials in 2016. Serotypes C&D cocktail is nearing completion of IND-enabling activities. Serotype F&G candidates are undergoing final selection.	NIH	FY 2018	NIH support initiation of a Phase 1 clinical trial for a botulism serotype B antitoxin mAb cocktail was initiated in October 2016; botulism serotype E antitoxin mAb cocktail is expected to enter a Phase 1 trial in 2017. IND-enabling studies for a serotypes C/D anti-toxin mAb cocktail were completed in 2016; a Pre-IND meeting (written responses) occurred November 2016 and NIH anticipates a Phase 1 clinical trial in 2017. Serotype F&H anti-toxin mAb candidates were undergoing final maturation and selection in 2016.
T.B.2	NIH will continue to support the manufacture of a newly identified botulinum toxin, Bot A/F, to enable PHEMCE partners to test efficacy of licensed botulism antitoxin therapeutic, and candidate anti-botulism monoclonal antibodies that are currently in development.	NIH	FY 2018	To address technical challenges, NIH decided to switch host strains for the manufacture of botulinum toxin, Bot A/F, from the parent producing two toxins to a derivative producing only the desired toxin. Multi-party intellectual property issues were addressed in 2016.
T.RN.3	Conduct market analyses on antimicrobials and other products needed to respond to the public health and medical consequences of radiological or nuclear threats.	HHS	FY 2018	CLOSED – This not planned due to resource constraints. HHS will leverage the antimicrobial MCMs currently held in the SNS for a radiological or nuclear response, in alignment with current clinical guidance.
T.RN.10	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	FY 2018	ASPR completed the economic risk assessment in 2016 and briefed it to the CDC. CDC identified that additional information needed to provide a more complete understanding of the impact of limiting testing capacity. Work is ongoing within CDC and with BARDA modelers to provide additional information that would inform the scale and scope of the testing needed.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
C.D.4	CDC with support from other agencies (e.g., FDA and DHS) will help to coordinate the development of highly sensitive, specific, and robust assays for high-priority biological threat agents (i.e., bacterial, viral, and toxins) in accordance with the LRN Design Control Process.	DHS, CDC	FY 2018	CDC continues to work with other agencies to develop assays for biological threat agents. For example, the LRN obtained from FDA two Emergency Use Authorizations for assays to detect Zika virus that were deployed to LRN labs enabling rapid testing capabilities for this emerging infection.
C.D.5	Develop additional pre-EUA assays for Joint Biological Agent Identification and Diagnostic System for Pan-*Burkholderia* and Ebola Bundibugyo.	DoD	FY 2018	COMPLETED – DoD completed the studies required for an Ebola Bundibugyo pre-EUA. CLOSED – DoD did not advance *Burkholderia* assays due to poor performance during validation studies.
C.D.6	Develop FDA-approved IVD capabilities for anthrax and smallpox as part of the NGDS Increment 1 platform.	DoD	FY 2018	The NGDS FilmArray Warrior panel for the detection of *B. anthracis, C. burnettii, F. tularensis, Y. pestis*, Ebola and Marburg detection from whole blood was FDA cleared in February 2017 through the de novo process. The Warrior panel was also cleared by FDA for the detection of *B. anthracis* and *Y. pestis* in blood culture in February 2017. A 510(k) for the clearance of the Warrior panel for the detection of *Y. pestis* and *F. tularensis* in sputum was submitted to FDA in March 2017 and is currently under review. The feasibility of adding to the Warrior panel additional agent detection assays including smallpox has not been determined.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion Date	Progress
C.CIADM.1	BARDA will support completion of the construction of critical infrastructure within the CIADMs. The Centers will provide MCM development and manufacturing capabilities to address public health threats as needed.	BARDA	FY 2018	In June 2012, BARDA entered into novel public-private partnerships with industry and academia to establish three CIADMs. The Center in North Carolina completed construction of a Tech Services Support building and a Clinical Trial Manufacturing suite with vial filling, syringe filling, and lyophilization filling capabilities. The suite is finishing qualification activities and scheduled to be completed by the third quarter of 2017. The Center in Maryland is nearing completion of a manufacturing facility that includes GMP manufacturing space for an influenza candidate, quality control laboratories, and a warehouse. A ribbon cutting took place in May 2017. The Center in Texas has completed three construction projects: 1) a renovation to a modular, small scale lab and manufacturing facility; 2) Construction of a new pandemic manufacturing facility with equipment procurement and qualification ongoing throughout 2017; and, 3) Construction of a new modular live virus manufacturing facility with installation and qualification of five modular clean rooms to occur in 2017.

2016 Activity Number	Milestone Description	Lead Agency	Projected Completion 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	FY 2018	The Center in North Carolina already had a licensed influenza vaccine and is successfully working towards a process improvement initiative under the CIADM contract that will increase yields for many of its demonstrated strains thus far. The Centers in Maryland and Texas both faced major obstacles when their influenza partners programs for developing an influenza vaccine failed. Both have spent considerable effort throughout 2016 in partnering with another influenza partner, with minimal results as of year-end.
C.CC.2	Establish an Innovation Modeling Hub to provide analytic decision support and access to real-time modeling capabilities to senior decision-makers within ASPR and the PHEMCE.	BARDA	FY 2017	The BARDA Modeling and Visualization Hub is the Innovation Modeling Hub that will provide analytic decision support and access to real-time modeling capabilities for senior decision makers. BARDA will install the Modeling and Visualization Hub in the second quarter of FY 2017 and will be operational after third party information security testing required in order to receive HHS OCIO Authority to Operate.
C.CC.3	BARDA is working on developing a matrix to determine high-priority programs for inclusion in the Regulatory Management Plan (RMP) mandated under the FD&C Act, as amended by PAHPRA.	FDA / BARDA	FY 2018	BARDA/RQA will work with FDA to complete RMPs if and when necessary. To date, BARDA and FDA agree that there are no MCMs that require an RMP.
C.CC.4	Establish an MCM advanced development and manufacturing facility.	DoD	FY 2018	During FY 2016, fit out and Commissioning, Qualification and Validation continued and was near completion. Incremental capabilities came on line starting in the third quarter of FY 2016, with full capability forecast for early FY 2017.

APPENDIX 6: PHS ACT REQUIREMENTS

Table 5: 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 1: Accomplishments in FY 2016 Maintained from *2016 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 in FY 2016 Appendix 3: Progress In Addressing At-Risk Population Medical Countermeasure Needs Appendix 5: Progress Towards Near-term 2016 PHEMCE SIP Milestones
Identify and prioritize near-, mid-, and long-term needs with respect to such countermeasures or products to address a CBRN threat(s).	Maintained from *2016 PHEMCE SIP;* • Section 1:Activities to Achieve Strategic Goals and Objectives • Section 2: Threat-based Approaches • Section 3: Capabilities-based Approaches Section 2: New Activities Since the 2016 PHEMCE SIP Appendix 5: Progress Towards Near-term 2016 PHEMCE SIP Milestones
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)).	Development of the 2017-2018 PHEMCE SIP – Consideration of Perspectives from National Advisory Committees

PHS Act Information Requirements	Location in *PHEMCE SIP*
Report on the amount of funds available for procurement in the PBS SRF 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
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;	Maintained from 2016 PHEMCE SIP Section 1: Activities to Achieve Strategic Goals and Objectives, Goal 4 Appendix 3: Progress In Addressing At-Risk Population Medical Countermeasure Needs Appendix 5: Progress Toward Near-Term 2016 PHEMCE SIP Milestones

PHS Act Information Requirements	Location in *PHEMCE SIP*
Identify the use of certain authorities and activities added to the PHS Act by the PBS 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 the Office of Management and Budget); – The number of persons paid $50,000 and the number of persons paid $100,000 under personal services contracts.	Section 1: Accomplishments in FY 2016, Regulatory Science Management Appendix 4: Advanced Research and Development and Procurement
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. DoD (and other interagency) coordination is highlighted throughout this document.