U.S. Department of Health and Human Services

Public Health Emergency Medical Countermeasures Enterprise

Multiyear Budget

Fiscal Years 2017-2021

Saving Lives. Protecting Americans.

ASPR

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Executive Summary

The Public Health Service (PHS) Act, as amended by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), requires the Office of the Assistant Secretary for Preparedness and Response (ASPR) to lead the development of a coordinated five-year budget plan for medical countermeasure (MCM) development and to update the plan annually. This Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Multiyear Budget Report (MYB) is the fourth submission in response to that requirement. This report includes the multiyear budgets for the Department of Health and Human Services (HHS) entities, or their divisions, that are members of the PHEMCE: the National Institutes of Health (NIH), ASPR's Biomedical Advanced Research and Development Authority (BARDA), the Strategic National Stockpile[1], and the Food and Drug Administration (FDA).

For the five-year period Fiscal Years (FYs) 2017–2021, this report provides estimates for HHS total spending which would be $24.8 billion, a $4.4 billion, or 22 percent, increase compared with the projection for FYs 2016–2020, which was $20.4 billion. The five-year funding total aggregates MCM-related spending estimates for NIH, BARDA, SNS, and FDA (Table 1).

Table 1 Estimated Total PHEMCE Spending by HHS Division and Fiscal Year (Dollars in Millions)

Division	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	Total	Change Over FYs 2016-2020
NIH	$2,007	$2,213	$1,972	$2,027	$2,084	$10,303	$2,136
BARDA	$1,339	$1,490	$1,517	$2,665	$2,964	$9,975	$1,413
SNS	$575	$610	$575	$1,206	$810	$3,775	$858
FDA	$136	$140	$151	$172	$177	$775	$24
Total	**$4,058**	**$4,452**	**$4,215**	**$6,069**	**$6,035**	**$24,828**	**$4,431**

This year's report uses the same methodology as the previous report for the costs to maintain or baseline scenario. This year's report includes an estimate of funding needed to replenish products held in the SNS that were originally purchased by Project BioShield but are anticipated to be approved or licensed by the FDA prior to FY 2022. The previous report mentioned these product transitions but detailed contract information was not available. This report includes estimates of these replenishment costs, would be incurred by the SNS beginning in FY 2020. This change accounts for approximately $900 million of the estimated total $4.4 billion increase described below.

This report developed the spending estimates as follows. For FY 2017 and FY 2018 the enacted annual appropriation levels were used and for FY 2019 the President's Budget was used. The out-year funding levels (FY 2020 and FY 2021) for NIH, BARDA, SNS, and FDA were developed without regard to the competing priorities considered in the budget development process and that must be considered as Congressional budget submissions are developed. These estimates are subject to change in the future.

Within individual threat areas or portfolios across the PHEMCE, this total reflects estimated budget increases in pandemic influenza, NIH's cross-cutting science and Other Threats portfolios, filoviruses, smallpox, chemical threats, radiological and nuclear threats, broad spectrum antimicrobials, botulinum, anthrax, and plague and tularemia. Portfolios with net decreases include: BARDA's proposed emerging infectious disease program, non-procurement costs at BARDA and SNS, and biological threat diagnostic. The following summary describes estimated spending by threat for the cumulative five-year period and the change relative to the last year's report for FYs 2016–2020:

Pandemic Influenza: $4.3 billion, an increase of $1.2 billion (+40 percent), to support the early and advanced development as well as the procurement of vaccines, therapeutics, and diagnostics, along with infrastructure capacity-building (e.g., vaccine stockpiling, vaccine manufacturing, and the Fill Finish Manufacturing Network). Separately, a portion of this increase also supports replenishment of expiring material in the SNS.

Broad Spectrum Antimicrobials: $3.5 billion, an increase of $237 million (+7 percent), for new products to address gaps in antimicrobial needs for threats caused by gram

[1]As stated in the FY 2019 President's Budget, ASPR began managing the SNS in FY 2019 including the procurement, maintenance, and deployment of SNS medical countermeasures. For this and future reports, activities funded from appropriations made to SNS are labeled as SNS. Certain non-MCM procurement activities are funded from these appropriations and are referenced in the CDC chapter. These activities will remain at CDC in the future. CDC will continue to participate on the PHEMCE. However, with the move of SNS to HHS in FY 2019, CDC funding and activities will be reported elsewhere.

negative bacteria (broad-spectrum antimicrobials). These investments are consistent with objectives in the National Strategy for Combating Antibiotic-Resistant Bacteria.

NIH Cross-Cutting Science Portfolio: $3.0 billion, an increase of $765 million (+34 percent), for National Institute of Allergy and Infectious Diseases (NIAID) research activities that cannot be assigned to a specific threat, but augment preparedness and response as overarching capabilities. These investments support such necessary investment areas as animal model development, diagnostics, sequencing facilities, reagent manufacturing, clinical training programs, epitope mapping, biosafety lab support, and computational biology.

NIH's Other Threats Portfolio: $2.6 billion, an increase of $640 million (+33 percent), for investments at the NIAID that support activities against threats such as arboviruses (including Zika virus), MERS-CoV, waterborne and foodborne pathogens, tuberculosis, and activities investigating fundamental aspects of the human immune system.

Anthrax: $2.0 billion, an increase of $170 million (+9 percent). This portfolio supports the development, procurement and licensure of the next-generation anthrax vaccine, NuThrax, as well as anthrax therapeutics. The increase in funding supports the replenishment of anthrax therapeutics and antimicrobials.

Radiological and Nuclear Threats: $1.8 billion, an increase of $332 million (+22 percent) for basic and advanced research into products to address Acute Radiation Syndrome (ARS) and procurements of antineutropenic cytokines, biodosimetry devices, and multiple candidate products for the treatment of thermal burns.

Filoviruses (including the Ebola virus): $1.6 billion, an increase of $550 million (+52 percent), to support a variety of activities. These activities include: the manufacturing of clinical investigational lots, clinical trials to be conducted in the U.S. and West Africa that are essential for FDA approval or licensure, attaining the ability to manufacture these MCMs at commercial scale, and ultimately procurement of vaccine and therapeutic MCMs. BARDA anticipates transition of additional vaccine and therapeutic candidates to Project BioShield in FY 2018 which accounts for a portion of the increase.

Smallpox: $1.2 billion, an increase of $366 million (+43 percent), for the procurement of a next-generation vaccine against smallpox, potentially providing greater shelf-life and lower sustainment costs, along with the replenishment of current vaccine and immunoglobulin stockpiles.

Chemical Threats: $1.2 billion, an increase of $337 million (+41 percent), to support the development of safe and more effective therapeutics to treat exposure to nerve agents, vesicating chemicals, pulmonary agents, and toxic industrial chemicals.

Botulinum: $382 million, an increase of $207 million (+119 percent), for the sustainment of the hBAT (botulinum antitoxin, heptavalent) program which includes processing additional hyperimmune plasma into finished product.

The remaining funds ($3.2 billion) for the five-year period are allocated to: SNS Non-Procurement Costs (including those that support CDC preparedness activities), FDA Regulatory Science, BARDA's Emerging Infectious Disease program, Multiplex Diagnostics, BARDA's Management and Administration, BARDA's Medical Countermeasure Innovator Program, MCM for plague and tularemia, MCM for glanders and melioidosis, BARDA's Innovation program and SNS's Federal Medical Stations. More information is available in the section on PHEMCE-Wide Findings.

The FYs 2017-2021 report complements the annual PHEMCE Strategy and Implementation Plan, which further describes the mechanisms and detailed interagency planning for a coordinated, life-cycle approach to MCM development. These coordinated efforts guarantee the PHEMCE's responsible stewardship of taxpayer dollars and that its goals and objectives are attained. The PHEMCE has built an Advanced Research and Development pipeline with more than 200 products, stockpiling 14 countermeasures in the SNS that are available during a public health emergency and achieving FDA approval of 38 products since 2007.

As stated in the FY 2019 President's Budget, ASPR began managing the SNS in FY 2019 and engage in the procurement, maintenance, and deployment of SNS medical countermeasures. In previous reports, appropriations made to SNS were labeled as CDC. Although not strictly procurement or replenishment, some critical MCM-related activities are funded from these appropriations and are referenced in the CDC chapter. Transitioning SNS from CDC to ASPR will consolidate strategic decision-making around the development and procurement of medical countermeasures and streamlines leadership to enable nimble responses to public health emergencies. CDC will continue to maintain a critical role in the PHEMCE process and the SNS will continue to support CDC's subject matter experts on work related to USG smallpox research agenda to ensure efficacy and safety data of smallpox related antivirals and vaccines, developing and executing Emergency Use Instructions (EUIs), Emergency Use Authorizations (EUAs), etc.

In coordination with the PHEMCE, the SNS will continue to develop strategies to meet the national priorities for federal stockpiling, to maintain and improve SNS capabilities, and to address inventory gaps. The sustainment of the SNS is

a critical challenge facing the PHEMCE in the future. Each product developed and acquired under BARDA's Project BioShield program both increases national preparedness and increases the resource needs to maintain these capabilities in the SNS over time. Beyond the costs of product procurement itself, the SNS assumes financial responsibility (e.g., storage, security, overhead, etc.) for products stored at the SNS. Additionally, these spending estimates do not include the additional resources that would be needed to support large-scale deployment and use of SNS assets in event of a public health emergency.

Introduction

The Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) is an interdepartmental governance structure overseen by the U.S. Department of Health and Human Services (HHS) for the research, advanced development, procurement, stockpiling, and development of plans for effective use of medical countermeasures (MCMs)—needed to respond to infrequent but high-consequence public health events. These events may result from intentional, accidental, or natural occurrences. The PHEMCE is led by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and includes three primary HHS internal partners: the Strategic National Stockpile (SNS), the Food and Drug Administration (FDA), the National Institutes of Health (NIH). Several interagency partners are also active within the PHEMCE, including the U.S. Department of Defense (DoD), the U.S. Department of Veterans Affairs (VA), the U.S. Department of Homeland Security (DHS), and the U.S. Department of Agriculture (USDA).

This report, *the FYs 2017–2021 Public Health Emergency Medical Countermeasures Enterprise Multiyear Budget*, describes the five-year interagency budget plan for the basic research, advanced research and development, regulatory review and approval, procurement, stockpiling, and replenishment of the United States government's civilian medical countermeasure enterprise.[2] The report consolidates PHEMCE budget forecasting into one document and complements the PHEMCE Strategy and Implementation Plan (SIP), fostering program alignment, harmonization, and synergy across threats or portfolios. This report provides an update for Fiscal Years (FYs) 2017–2021 of PHEMCE budget priorities across chemical, biological, radiological, and nuclear (CBRN) threats, pandemic influenza, and other emerging, or re-emerging, infectious diseases. Further, it details the ongoing work of the PHEMCE and how member agencies leverage their resources to implement the coordinated investment strategy from requirements setting to advance research and development and procurement.

Background on Medical Countermeasure Development

The development of MCMs is a time-intensive, risky, and expensive endeavor, requiring substantial coordination among federal departments and agencies, and the concerted efforts of commercial partners. Prioritizing federal funding across portfolios and the stages of MCM development is fundamental to achieving the PHEMCE's goals. Successful coordination requires strategic planning that incorporates discrete funding streams into a coherent plan spanning many years.

The PHEMCE and its members are guided by the need to develop responses to novel threats and to develop more cost-efficient methods to protect the nation, and all populations, against existing threats. This report reflects the importance of programs that address specified intentional threats identified through DHS's Material Threat Determination process. It also demonstrates the need to evolve into a more flexible "capabilities-based" system that reflects the realities of the omnipresent threats we face. Novel technologies and the rapid movement of people and materials around the world have created new and dynamic threats to national health security. These threats include emerging infectious diseases such as new pandemic strains of respiratory viruses, epidemics involving hemorrhagic fever viruses, and new mosquito-borne diseases. Additional threats include the use of pathogens customized through new genetic manipulation capabilities, and the marketing of radiological materials for use by transnational terrorist groups. Finally, the rise of antibiotic-resistant bacteria, especially in a community setting, reminds us of the critical function of antibiotics and the need for novel antimicrobial agents, and the important role that effective antibiotics would play in response to a variety of the threats mentioned above.

The PHEMCE's success is demonstrated by the products that evolved across programs, achieved regulatory approval, and were purchased for stockpiling in the SNS. Currently, HHS's Advanced Research and Development (ARD) pipeline contains more than 200 products. The PHEMCE stockpiled 14 countermeasures in the SNS that are available for use during a public health emergency. Since 2007, the FDA has approved 38 products for CBRN threats and pandemic influenza supported by the Biomedical Advanced Research and Development Authority (BARDA).

This report forecasts that 12 MCM candidates will transition from procurement under BARDA's Project BioShield (PBS) to stockpiling in the SNS by 2021. These MCMs would not yet have achieved FDA approval or licensure at the time of initial shipment to the SNS but could potentially be used under the FDA provisions for Emergency Use Authorization, as needed, and authorized under the Federal Food, Drug and Cosmetic (FD&C) Act.[3] SNS will be responsible for the

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

[3]The Project BioShield Act of 2004, [PL 108-276], amended the Federal Food Drug and Cosmetic Act, which was further amended by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 [PL 113-5], to give authority to the Secretary of HHS to declare that circumstances exist that justify the emergency use authorization, and for FDA to grant emergency use authorization, of certain MCMs that are not approved, or for uses for which the MCMs are not approved, in emergencies under certain terms and conditions [21 USCS § 360bbb-3]. An emergency use authorization does not require the declaration of a public health emergency under section 319 of the PHS Act.

replenishment costs of those MCMs procured by BARDA under PBS once these products achieve FDA approval or licensure. The SNS also procures commercially available, FDA-approved or licensed materials that meet identified PHEMCE MCM requirements. As such, a primary budgetary issue facing the PHEMCE is the relative financial resource requirements for PBS and SNS.

The Constitution states that one of the federal government's fundamental responsibilities is to provide for the common defense—to protect the American people, our homeland, and our way of life. The strength of our nation's public health and health infrastructure, and the capabilities necessary to quickly mobilize a coordinated national response to emergencies and disasters, are foundational for the quality of life of our citizens and vital to our national security. Threats facing the United States during the 21st century are increasingly complex and dangerous. Therefore, improving national readiness and response capabilities for 21st century health security threats is a national security imperative.

The nation is witnessing the impacts of naturally occurring outbreaks such as influenza, Ebola, Zika, and Severe Acute Respiratory Syndrome. The PHEMCE currently monitors potential emerging infectious diseases that could cause a pandemic, such as the H7N9 influenza strain circulating in China. The year 2018 marks the 100-year anniversary of the 1918 influenza pandemic, which killed more people than World War I. During that pandemic, more than 25 percent of the U.S. population became sick and 675,000 Americans, many of them young, healthy adults, died from the highly virulent influenza virus and pneumonia due to secondary infection by bacteria. This was in the time before antibiotics and pneumonia was often fatal.

ASPR has four key priorities for building readiness and response capabilities for 21st century health security threats, one of which is: advance an innovative medical countermeasures enterprise by capitalizing on additional authorities provided in the 21st Century Cures Act, as well as advances in biotechnology and science to develop and maintain a robust stockpile of safe and efficacious vaccines, medicines, and supplies to respond to emerging disease outbreaks; pandemics; and chemical, biological, radiological, and nuclear incidents and attacks. This report reflects this priority and provides a road map for progress in achieving PHEMCE's goals and objectives for MCM development, procurement, and deployment.

Background on the Multiyear Budget

The Multiyear Budget Report (MYB) fulfills the requirement to "Develop, and update on an annual basis, a coordinated five-year budget plan based on the medical countermeasure priorities," in section 2811(b)(7) of the Public Health Service (PHS) Act added by section 102 of the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013. This report provides cost estimates for the HHS PHEMCE offices and agencies based on enacted appropriations in FY 2017 and FY 2018, and the FY 2019 President's Budget. For FYs 2020 and 2021, funding estimates are to support MCM-related activities, including research, development, or procurement of MCMs.[4] Each office and agency developed its own methodology for providing estimates for this report. The estimates for procurement costs are point-in-time estimates and could change in future reports to reflect current market prices. NIH assumed an inflationary increase in the out-years indexed to the Biomedical Research and Development Price Index. BARDA assumed levels consistent with authorization contained in section 319F-2 of the PHS Act, as amended by PAHPA and PAHPRA.

The FY 2019 President's Budget moved the SNS from CDC to ASPR. In the previous reports the estimated funding described for SNS was labeled as CDC. In this and future reports, the funding estimates are labeled as SNS. In prior reports, CDC assumed funding levels necessary to maintain the current SNS inventory, including replenishment of all FDA approved or licensed MCMs, including those originally acquired by PBS. For this report SNS used the same assumption. Also, SNS includes an estimate of the funding that will be needed in out-years to replenish products originally purchased by PBS that are not yet FDA approved or licensed, but which are forecast to become so and require replacement in those years. The previous report mentioned these product transitions but detailed contract information was not available previously. This report includes estimates of these replenishment costs, would be incurred by the SNS beginning in FY 2020. This change accounts for approximately $900 million of the estimated total $4.4 billion increase described above.

FDA assumed a three percent increase for each of FY 2020 and 2021. The out-year funding levels (FY 2020 and FY 2021) for NIH, BARDA, SNS, and FDA, were developed without regard to the competing priorities considered in the budget development process and that must be considered as Congressional budget submissions are developed. These estimates are subject to change in the future.

[4]CDC budget requirements to support PHEMCE and MCM-related activities in FYs 2020 and 2021 will not be funded through direct appropriations and fiscal support, for these activities are uncertain going forward. The FY 2019 President's Budget moved the SNS to ASPR. Future reports will need to reassess how to describe MCM-associated activities outside of the SNS.

Multiyear Budget: PHEMCE-Wide Findings

In coordination with its interagency partners, the PHEMCE's investments and accomplishments are the result of the actions of NIH, ASPR, SNS[5], and FDA. This section provides, first, an overview of spending across HHS Divisions, and second, a more granular level to highlight accomplishments and projections over the course of the five-year period. Congress does not appropriate funding directly to the PHEMCE, but the PHEMCE, led by ASPR, helps to coordinate those appropriations to achieve the PHEMCE's goals and objectives.

Overview

In total, the four HHS Divisions spent $4.1 billion on MCMs and MCM-related activities in FY 2017. Estimated spending across the divisions is delineated in Table 2. The Spend Plan Tables in Appendix A provide additional detail for each Division. Under the Baseline scenario, PHEMCE investments for the five-year period total $24.8 billion, a $4.4 billion or 22 percent, increase compared with the projections in the FYs 2016–2020 Report. The five-year funding total includes aggregated MCM-related spending estimates for the NIH, $10.3 billion, a $2.1 billion or 26 percent increase; ASPR's BARDA, $9.9 billion, a $1.4 billion or 16 percent increase; the SNS, $3.8 billion, a $858 million, or 29 percent increase; and the FDA, $755 million, a $24 million or 3 percent increase; as compared to the FYs 2016–2020 Report.

Table 2 Estimated Total PHEMCE Spending by HHS Division and Fiscal Year (Dollars in Millions)

Division	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	Total	Change Over FYs 2016-2020
NIH	$2,007	$2,213	$1,972	$2,027	$2,084	$10,303	$2,136
BARDA	$1,339	$1,490	$1,517	$2,665	$2,964	$9,975	$1,413
SNS	$575	$610	$575	$1,206	$810	$3,775	$858
FDA	$136	$140	$151	$172	$177	$775	$24
Total	**$4,058**	**$4,452**	**$4,215**	**$6,069**	**$6,035**	**$24,828**	**$4,431**

This year's report includes an estimate of funding needed to replenish products held in the SNS that were originally purchased by Project BioShield but are anticipated to be approved or licensed by the FDA prior to FY 2022. These are new cost estimates that were not previously available or too preliminary to include in the previous report. The replenishment costs of these products would be incurred by the SNS beginning in FY 2020. This change accounts for approximately $900 million of the estimated total $4.4 billion increase described below.

Threat-Based Approaches

PHEMCE recognizes the need to address high-priority threats. While PHEMCE is evolving toward a capability-based approach across threats, it proposes to maintain key threat-based approaches to address national health security.

Figure 1 depicts estimated PHEMCE spending by portfolio for FYs 2017–2021. As ranked by cumulative estimated spending, PHEMCE's investments reflect the priorities established in the 2017–2018 PHEMCE SIP. (Increases and decreases noted below are changes from the estimates contained in the FYs 2016–2020 Report).

Across NIH, BARDA, SNS, and FDA, estimated spending on pandemic influenza is $4.3 billion over the five-year period, which represents an increase of $1.2 billion (+40 percent). This increase is critical to support achievement and sustainment of pandemic preparedness. The 2017 Pandemic Influenza Plan Update establishes as one of the key actions that HHS will "support innovation in influenza vaccine production for improved efficiencies to enable the production and distribution of final presentation vaccines for pandemic response within 12 weeks from the declaration of an influenza pandemic."[6] To achieve this, BARDA supports the advanced development of cell- and egg-based vaccine manufacturing and infrastructure capacity. Infrastructure capacity is critical to maintaining domestic vaccine manufacturing capability, and includes ongoing vaccine and adjuvant stockpiling programs, including storage, stability, and testing. These funds will also provide continued support for advanced development of therapeutics and novel antiviral drugs for severely ill and hospitalized patients,

[5]ASPR began managing the SNS in FY 2019 and engage in the procurement, maintenance, and deployment of SNS medical countermeasures. In previous reports, activities funded from appropriations made to SNS were labeled as CDC. Certain non-MCM procurement activities are funded from these appropriations and are referenced in the CDC chapter. These activities will remain at CDC in the future.

[6]https://www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf

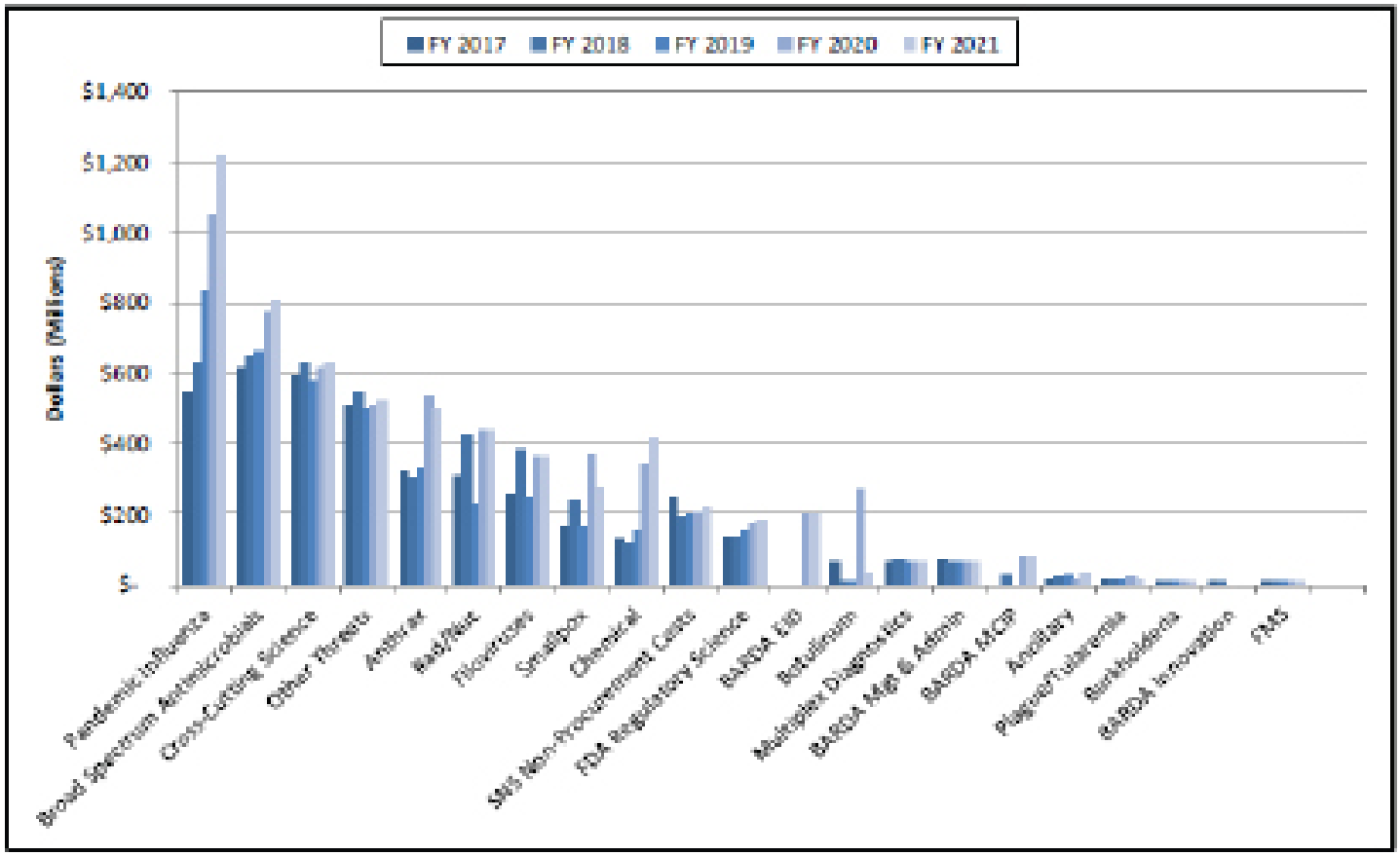


Figure 1: Estimated PHEMCE Spending by Portfolio and Fiscal Year

universal influenza vaccines, home-use diagnostics, as well as reusable respirators, and universal portable ventilators.

Consistent with the National Strategy for Combating Antibiotic-Resistant Bacteria, one of the largest spending estimates is for new products to address gaps in the Broad-Spectrum Antimicrobial portfolio for threats caused by gram-negative bacteria (broad-spectrum antimicrobials), totaling $3.5 billion over five years, which represents an increase of $237 million (+7 percent).

Cross-Cutting Science portfolio includes the National Institute for Allergy and Infectious Diseases (NIAID) research activities that cannot be assigned to a specific threat. These investments support capabilities such as animal models, diagnostics, sequencing facilities, reagent manufacturing, clinical training programs, epitope mapping, biosafety lab support, and computational biology. The five-year budget plan estimate for this portfolio is $3.0 billion, which represents an increase of $765 million (+34 percent).

The NIH's Other Threats portfolio is the next largest area of estimated spending and includes investments at NIAID that support activities against threats such as arboviruses, waterborne and foodborne pathogens, tuberculosis, and activities investigating fundamental aspects of the human immune system. Total five-year spending on these investments is estimated to be $2.6 billion, which represents an increase of $640 million (+33 percent).

The next largest threat-specific investment is the anthrax portfolio, with total estimated spending of $2.0 billion over the five-year period, which represents an increase of $170 million (+9 percent). This portfolio supports the development, procurement, and approval of the next-generation anthrax vaccine, NuThrax, as well as anthrax therapeutics. NuThrax will potentially lower future stockpiling and replenishment costs by reducing the number of doses of vaccine and antibiotic needed to treat patients. The increased spending estimate also supports the replenishment of anthrax therapeutics and antimicrobials by the SNS.

Spending on MCMs against radiological and nuclear threats, the next largest investment for this five-year period, totals $1.8 billion, which represents an increase of $332 million (+22 percent). This investment includes spending for basic and advanced research into products to address Acute Radiation Syndrome (ARS) and the Delayed Effects of Acute Radiation Exposure (DEARE), as well as procurements for antineutropenic cytokines, biodosimetry devices, and

artificial skin for the treatment of thermal burns.

In the filovirus portfolio, the PHEMCE estimates it would spend $1.6 billion, which represents an increase of $550 million (+52 percent). This increase supports the late-stage development and procurement of MCMs against the Ebola virus. The PHEMCE would continue to support activities associated with the transition of MCM candidates from early development supported by the NIH and the Department of Defense (DoD) into advanced development at BARDA and towards FDA approval and licensure. These activities include: the manufacturing of clinical investigational lots, clinical trials to be conducted in the U.S. and West Africa, development of the ability to manufacture these MCMs at commercial scale, and ultimately procurement of vaccine and therapeutic MCMs.

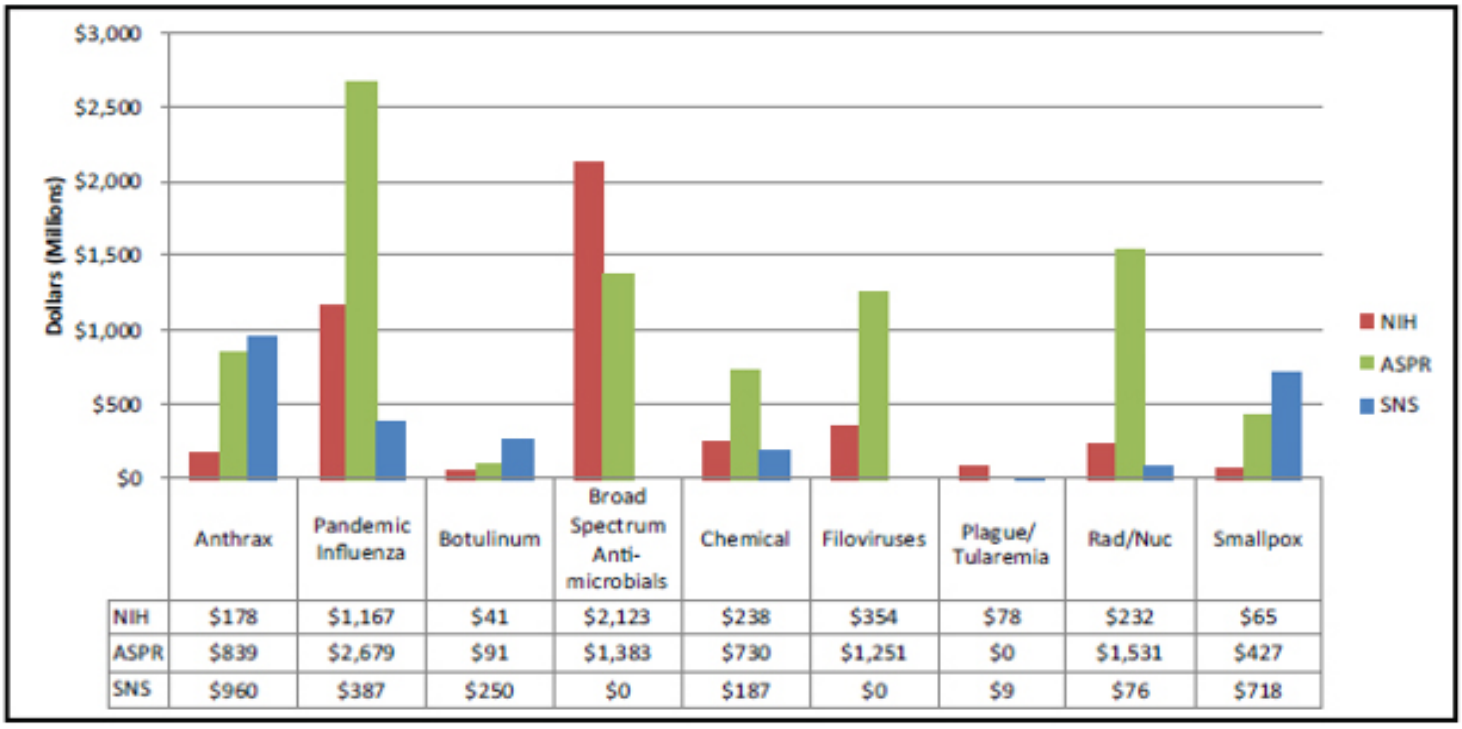
Investment in MCMs to mitigate smallpox is forecasted to have a five-year total of $1.2 billion, which represents an increase of $366 million (+43 percent). This increase reflects the investment in a lyophilized formulation of IMVAMUNE, a non-replicating smallpox vaccine being developed for individuals at risk for adverse events from replicating smallpox virus; a mandate under the PAHPA. Future investments are expected to decrease over this period due to the availability of a next-generation vaccine against smallpox, potentially providing greater shelf-life and, therefore, lower replenishment costs.

Spending on MCMs to mitigate chemical threats is forecasted to have a five-year total of $1.2 billion, which represents an increase of $334 million (+41 percent). The chemical threats portfolio includes research at NIAID, the National Institute of Neurological Disorders and Stroke (NINDS), and other NIH institutes on the development of safe and more effective therapeutics for exposures to nerve agents, vesicating chemicals, pulmonary agents, and toxic industrial chemicals.

Portfolio Investments across HHS Agencies

Funding for MCM development varies depending on the stage of development with greater investment per product being needed as development proceeds. Furthermore, to ensure success of at least one MCM to address a threat, it is necessary to fund more than one candidate product at earlier stages of development. In addition, a product that has been procured, licensed, and stored in the SNS will eventually expire, and the SNS, or in rare instances BARDA, would need to fund replenishment of the product.

Figure 2 shows total five-year spending by agency for high-priority threats. No single factor drives spending at an agency within any one portfolio, and each portfolio may contain several types of MCMs (e.g., vaccine, therapeutic, and diagnostic, etc.). Relatively more mature portfolios require sustained investment by SNS in replenishment costs (e.g., anthrax, pandemic influenza, chemical, nerve



	Anthrax	Pandemic Influenza	Botulinum	Broad Spectrum Anti-microbials	Chemical	Filoviruses	Plague/ Tularemia	Rad/Nuc	Smallpox
NIH	$178	$1,167	$41	$2,123	$238	$354	$78	$232	$65
ASPR	$839	$2,679	$91	$1,383	$730	$1,251	$0	$1,531	$427
SNS	$960	$387	$250	$0	$187	$0	$9	$76	$718

Figure 2: MCM Estimated Spending by High-Priority Portfolio and HHS Division for FYs 2017–2021

agent, and smallpox). Relatively less mature portfolios will show an absence of SNS spending (e.g., broad-spectrum antimicrobials, filoviruses, and radiological or nuclear threats). A significant investment by BARDA may lead to a novel MCM that could be procured and stockpiled by the SNS during this report's timeframe.

Product Transitions

Transition of candidate or approved or licensed products across the PHEMCE partners is a key indicator of success of the PHEMCE. Coordination among the partners is central to efficient use of funding for this purpose. The MYB provides a long-range forecast of when projects may be available for transition to the next stage (i.e., to the next PHEMCE partner or the next source of funding) for development or procurement. It may also inform decision-making around PHEMCE activities such as the SNS Annual Review.

During FYs 2017–2021, BARDA anticipates 12 MCM product transitions from Project BioShield (PBS) to SNS. Transitioning these products will increase the need for funding in the SNS budget to support replenishment of expiring MCMs. Replenishment costs arise from products purchased previously by BARDA or SNS that expire and need to be restocked. A total of $899 million is needed to support replenishment of MCMs by SNS. Table 3 details the products expected to transition from PBS to SNS and the associated two-year replenishment costs.

Future Challenges

The primary challenge faced by the PHEMCE is the sustainability of the MCM response capabilities and capacities of the SNS built through Project BioShield. Successful procurement of an MCM obligates SNS to expend additional funding for sustainment. First, SNS faces replenishment requirements upon expiration for products added to the SNS by BARDA through PBS contracts. PBS funding used for initial MCM procurement rarely supports ongoing maintenance and replacement of the products after it is approved or licensed by FDA. In the past, these additions necessitated tradeoffs determined and reported through the PHEMCE SNS Annual Review when available SNS funds were insufficient to both maintain current capabilities and absorb these additional products. These tradeoffs translated to increasing levels of risk across the threat portfolios and potentially jeopardizing the nation's ability to realize the full benefits of prior research and development investments. Prior SNS Annual Reviews proposed reducing anthrax vaccine holdings and in 2015 proposed reducing both anthrax vaccine and antibiotics to meet budget constraints. The 2016 SNS Annual Review

Table 3: Estimated SNS Spending Needed for MCM Product Replenishment of Products Achieving FDA Approval or Licensure Previously Procured by BARDA, FYs 2017–2021

Medical Countermeasure	Estimated Transition Timeframe (FY)	Estimated Cost FY 2020 & FY 2021 (dollars millions)
Anthrax Therapeutic	2019	$222.3
Anthrax Therapeutic	2020	$80.0
Anthrax Therapeutic	2020	TBD[1]
Botulinum Antitoxin	2020	$250.0
Smallpox Vaccine	2020	$144.0
Smallpox Antiviral	2020	$202.7
Chemical Anticonvulsant	2020	TBD[2]

[1]Cost estimate pending policy review of anthrax antitoxin stockpiling requirements.

[2]Cost estimate pending FDA review of product.

reported that the SNS inventory was below the established stockpiling goals for several types of MCMs.

Beyond these immediate stockpiling challenges, the PHEMCE must address the entire range of capabilities required to effectively use stockpiled MCMs in response to a public health emergency or natural disaster. These include: the ability to rapidly and accurately detect an incident has occurred that requires MCM assets; appropriate regulatory strategies in place to support emergency use of MCM; availability of evidence-based guidance on the appropriate use of these MCMs in all populations; ability to monitor efficacy and safety of MCMs in all populations, the ability of state and local partners to receive, distribute, dispense MCMs; and ability to assess the risks and benefits of MCM during and after an emergency to inform future actions. These capabilities, whose costs are only partially reflected in this report, are as important as establishing and maintaining a complete inventory of the appropriate pharmaceuticals and medical supplies.

Multiyear Budget: NIH

NIH leads basic research towards a comprehensive understanding of the scientific and medical aspects of potential chemical, biological, radiological and nuclear (CBRN) threat agents including emerging infectious disease agents like the Zika virus, Ebola virus and the Middle East Respiratory Syndrome coronavirus (MERS-CoV). NIH support includes the development and maintenance of research resources, such as genomic centers and preclinical services to facilitate the eventual production of countermeasures for CBRN and emerging infectious disease threats. NIH supports translational and product development efforts through Phase 2 clinical trials to maximize the potential for scientific discoveries and novel concepts to become innovative countermeasures.

NIH/NIAID Accomplishments

In FY 2017, NIAID made significant progress in advancing medical countermeasures (MCMs) to protect against emerging infectious diseases, biodefense pathogens, and chemical, radiological, and nuclear threats.

Vaccines

Zika (Other Threats)

NIAID is supporting a multifaceted approach to the development of a vaccine against the Zika virus. NIAID's Vaccine Research Center (VRC) developed a DNA vaccine candidate that entered Phase I clinical trials at the NIH in August of 2016 and launched a multinational Phase 2/2b study in Zika-endemic, or potentially endemic, countries in March 2017. Scientists at NIAID's intramural division are also developing a live attenuated Zika vaccine candidate using technologies based on the NIAID dengue vaccine candidate currently in phase 3 testing. In addition, NIAID worked with Walter Reed Army Institute of Research, BARDA, and Sanofi Pasteur, to develop a Zika purified inactivated virus vaccine candidate. NIAID VRC also collaborated with multiple vaccine developers in conducting preclinical studies of Zika mRNA vaccine candidates. A Phase 1 clinical trial of the pharmaceutical company SEEK's universal vaccine candidate against mosquito borne diseases, including Zika, that targets mosquito saliva is being conducted by NIAID. Several additional candidates are in preclinical development.

NIAID also is supporting the development of two novel Zika vaccine/adjuvant formulations through its Adjuvant Discovery contract program. One contract, to Oregon Health & Science University, is developing a Zika vaccine using a virus-like particle platform adjuvanted with cyclic-dinucleotide. The second contractor, located at University of Minnesota, has engineered a recombinant Zika vaccine based on the surface-expressed E glycoprotein formulated

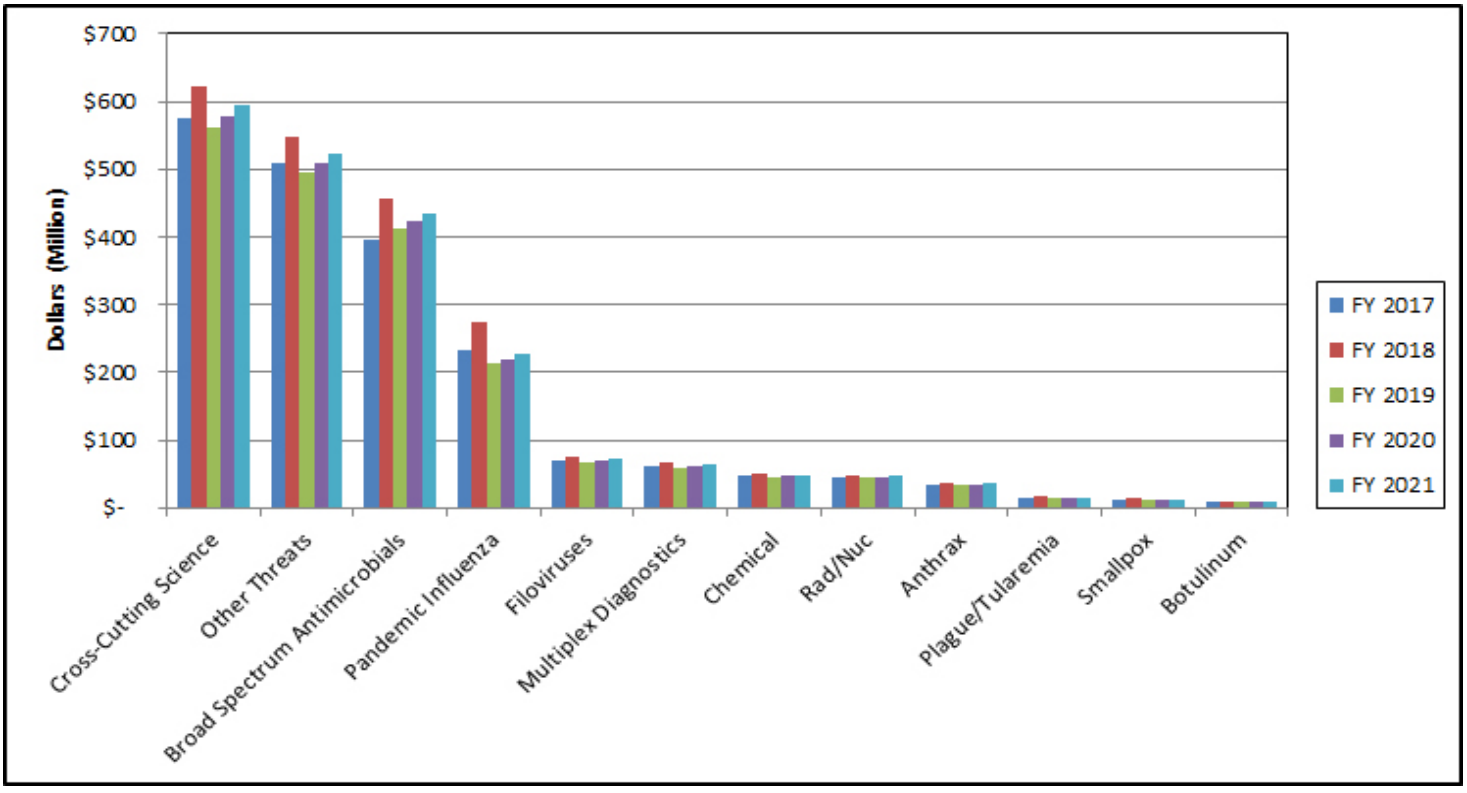


Figure 3: Estimated NIH MCM Spending by Fiscal Year

with a novel small-molecule TLR7 agonist conjugated to hyaluronic acid, which mediates high adjuvant efficacy while preventing reactogenicity.

Ebola

NIAID completed Phase 1 clinical trials of recombinant Vesicular Stomatitis Virus (rVSV) and Chimp Adenovirus type 3 (ChAd3) candidate Ebola vaccines developed by Merck and GlaxoSmithKline (GSK) respectively. These candidate vaccines are in the one-year safety and immunogenicity monitoring period. Additionally, NIAID initiated two Phase 1 clinical trials of Janssen's vaccine, recombinant adenovirus serotype 26-prime with a Modified Vaccinia Ankara boost [Ad26/MVA]. This multivalent vaccine candidate is ready for transfer to BARDA.

NIAID's efforts were the basis for, and continue to support, other clinical efforts in Europe, the UK and Africa using the Merck and Janssen vaccines. Additionally, NIAID's efforts support continued vaccine development activities at the Department of Defense. Clinical trials were also conducted globally, including the ongoing Partnership for Research on Ebola Vaccines in Liberia (PREVAIL I) Phase 2 study, a randomized, placebo-controlled study evaluating two vaccine candidates "(ChAd3 and rVSV) that demonstrated both vaccines were 1safe and immunogenic, eliciting antibody responses after one month. Results were reported in the *New England Journal of Medicine* (N Engl J Med 2017; 377:1438-1447). Additionally, NIAID conducted preclinical development and two Phase 1 clinical trials of Janssen's, recombinant adenovirus serotype 26-prime with a Modified Vaccinia Ankara boost [Ad26/MVA] Ebola vaccine. Phase 2/3 trials are ongoing. This monovalent Ebola vaccine candidate transitioned to BARDA for manufacturing and further advanced development. NIAID continues to advance a trivalent filovirus vaccine (i.e., Ebola, Sudan, and Marburg) based on Janssen's Ad26/MVA platform, and to this end, conducted preclinical development and a Phase 1 clinical trial.

NIAID awarded two contracts to support the development of multi-component vaccine candidates against Ebola, Sudan, Marburg, and Lassa fever viruses. One contract, to Profectus Biosciences, Inc., is for the advanced development of a multivalent vaccine candidate that is being produced in lyophilized form to allow distribution without a cold chain, and to enable routine mass immunization. The second, to Thomas Jefferson University, is to develop, manufacture and test a tetravalent vaccine formulation that is based on an inactivated rabies virus vector combined with a TLR4 agonist as adjuvant (GLA-SE).

Anthrax

NIAID continued its support of a third-generation anthrax vaccine, Thermostable AV7909, a lyophilized formulation of AV7909 being developed by Emergent BioSolutions. The dry formulation vaccine is anticipated to have more permissive storage conditions and increased shelf life, and the potential for significant cost savings for USG stockpiling and deployment. Currently, the final formulation is being evaluated in animals for efficacy, and the process is being transferred to a clinical manufacturing organization (CMO) for scale up. Manufacturing is anticipated to begin in 2018. NIAID plans to support a head-to head comparison of liquid AV7909 and Thermostable AV7909 in a Phase I clinical trial through its Vaccine and Treatment Evaluation Units (VTEUs).

NIAID is supporting the development of an intranasal rPA-based anthrax vaccine candidate at Porton Biopharma Limited (PBL). The vaccine candidate is combined with BlueWillow Biologic's novel nanoemulsion adjuvant W805EC technology component, to be administered using the Pfeiffer Bidose nasal sprayer. The vaccine candidate has shown efficacy in a rabbit model. A toxicology study in rabbits is underway. Currently, the vaccine and nanoemulsion components are being manufactured under current Good Manufacturing Practices (cGMP) conditions. Plans are to evaluate the vaccine candidate in a Phase I clinical trial starting in FY 2019.

Ricin (Other Threats)

NIAID is supporting development, by Soligenix, of a thermostable lyophilized formulation of a ricin vaccine, RIVAX. This dry formulation technology would accommodate elevated room temperature storage and enable increased shelf life as well as cold-chain transport resulting in cost savings. The vaccine is currently being evaluated in a nonclinical efficacy study and cGMP processes for vaccine manufacturing are under development. A Phase1 clinical trial is anticipated to start in FY 2019.

Influenza and Universal Influenza Vaccine

Several NIAID supported candidates are currently advancing toward clinical evaluation, including a novel replication-deficient live virus vaccine and a chimeric hemagglutinin (HA) vaccine candidate designed to focus the immune response against the conserved HA stem domain. NIAID VRC launched a Phase 1 clinical trial for an HA-ferritin vaccine candidate, alone or in prime-boost regimens with an influenza DNA vaccine, in healthy adults in September 2017. The study is currently open to accrual. NIAID's virus-like particles (VLP)-based influenza vaccine candidate was shown to provide significant protection in mice following

challenge with influenza viruses. Preclinical VLP vaccine studies in mice and ferrets continue along with evaluation of immune correlates of protection. NIAID is also supporting development of a broadly protective influenza virus vaccine candidate based on the highly conserved stalk domain by using chimeric HA constructs that express unique head and stalk combinations; GSK is planning to test this candidate in a Phase 1 clinical trial within two years. NIAID-funded investigators at FluGen have developed a novel vaccine virus which induces strong cross-protective immunity against multiple subtypes of influenza. In FY 2017 NIAID supported basic research and preclinical toxicology for an ongoing Phase 1 clinical trial by FluGen.

Furthermore, NIAID-funded investigators developed the Computationally Optimized Broadly Reactive Antigen (COBRA) universal influenza vaccine approach using bioinformatics to design conserved HA head regions. COBRA vaccine candidates with efficacy against diverse H5 or H1 subtypes are in preclinical development at Sanofi Pasteur, moving toward Phase I clinical trials.

In 2017, NIAID also initiated funding of research towards development of antigenically advanced vaccine candidates for pandemic and seasonal influenza strains. This strategy will broaden immune responses to past and future strains, improve seasonal vaccine strain selection and efficacy and inform pandemic stockpiling. The investigators will be using computational techniques to predict antigenic evolution and then develop vaccination strategies that take advantage of previous influenza exposures.

In 2016 and continuing in 2017, NIAID conducted a clinical trial to evaluate the safety and immunogenicity of an inactivated H5N8 influenza vaccine candidate in collaboration with BARDA. The trial is evaluating two doses of the investigational vaccine administered with and without adjuvants in healthy adults In addition to the trials to evaluate H5N8, NIAID is enrolling participants into protocols to evaluate multiple H7N9 vaccine candidates against the 2017 strain. The trials will evaluate the safety and immunogenicity of the vaccine candidates, in the presence or absence of an adjuvant, in healthy adults, the elderly, children, and pregnant women. NIAID evaluated a candidate pandemic live attenuated influenza vaccine (pLAIV) for H7N9 and observed a rapid and robust immune response after a boost with a pandemic inactivated H7N9 influenza vaccine.

Through its Vaccine Adjuvant contract programs, NIAID supports the discovery and development of several novel compounds and formulations that improve the efficacy of seasonal, pandemic, and universal influenza vaccines for different target populations, including newborns and the elderly. The lead adjuvant from these programs, Advax, a carbohydrate-based adjuvant, enhances immunity and is anti-inflammatory. When Advax was added to a seasonal influenza vaccine, it was shown to reduce the incidence of adverse events."

MERS-CoV

NIAID-funded researchers developed and tested an investigational vaccine for the MERS-CoV that fully protects rhesus macaques from disease when given six weeks before exposure. A DNA vaccine candidate for MERS-CoV developed by NIAID intramural researchers is now part of a CEPI-funded project with a projected start date in 2018.

Respiratory Syncytial Virus

NIAID scientists are leveraging recent advances in structural biology to elucidate the atomic structure of viruses and inform the design of structure-based vaccine candidates. Using this technology, NIAID VRC scientists created a respiratory syncytial virus (RSV) vaccine candidate based on a single structurally engineered protein from the surface of the virus. This vaccine candidate is currently being tested in a Phase 1 clinical trial that began in February 2017 at the NIH Clinical Center.

Platform Technologies

NIAID supports the development of vaccine platform technologies that could be used to generate candidate vaccines against multiple different established or emerging pathogens. These platforms include: gene-based vaccination systems such as viral vectors (e.g., MVA), plasmid DNA, and mRNA; single-use manufacturing technologies; and stabilization technologies (e.g., dry versus liquid formulations). In addition, NIAID is supporting programs for the discovery and development of adjuvants to enhance the efficacy of vaccines. These programs have yielded several novel formulations that are in the late stages of preclinical and early stages of clinical development. These novel adjuvants have been tested in more than 20 clinical trials and can be used to enhance the efficacy of a wide variety of vaccines.

Therapeutics

Zika (Other Threats)

NIAID is investigating promising therapeutics, screening small-molecules for activity *in vitro* and *in vivo* against Zika virus, supporting isolation and evaluation of monoclonal antibodies, and supporting the development of standardized assays and cell banks.

Filoviruses - Ebola/Marburg

PREVAIL II, a randomized controlled study comparing ZMapp to optimized standard of care in Liberia, Sierra Leone, Guinea, and the United States indicated that ZMapp was well-tolerated and showed promise as a treatment for Ebola. NIAID VRC scientists have begun planning of a clinical trial for the first-in-human Phase I study to examine safety, tolerability, and pharmacokinetics of the monoclonal antibody (mAb) Mab114 in healthy adults. The study is anticipated to begin enrollment in 2018.

NIAID continues to support the preclinical and clinical development of BCX4430 (Galidesivir) for treatment of Ebola and Marburg. Multiple NHP efficacy studies have demonstrated that BCX4430 was effective in protecting animals from lethal infection when initiating treatment up to three days post infection. Additional delay-time-to-treatment studies are being considered. The single and multiple ascending dose Phase I trials for the intramuscular formulation have been completed. The intravenous infusion formulation of the drug is being developed and Phase I trials are planned for 2018. NIAID also continues to support the clinical development of another broad-spectrum RNA polymerase inhibitor, GS-5734, for treatment of Ebola infection. PREVAIL IV, a study to assess the antiviral activity, longer-term clearance of Ebola virus, and safety in male Ebola survivors with evidence of Ebola virus persistence in semen, is on-going.

Botulism

NIAID continues to support the development of potent monoclonal anti-toxins for botulism. A Phase I clinical trial for a botulism serotype B anti-toxin mAb cocktail was initiated in October 2016 with NIAID support; subject dosing was completed in January 2017, and clinical sample analysis is expected to be completed in 2018. A serotype E anti-toxin mAb cocktail is expected to enter a Phase I trial in 2018. A Phase I clinical trial of a serotype's C/D anti-toxin mAb cocktail was initiated and dosing completed in 2017. Clinical sample analysis is expected to be completed in early 2018. Multiple serotype F anti-toxin mAb candidates completed final maturation and selection in 2017. Work is continuing for the selection of final serotype H anti-toxin candidates.

Broad Spectrum Antimicrobials

NIAID also joined BARDA in supporting the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), lending subject-matter expertise and support via its preclinical services program. In FY 2017, NIAID provided preclinical services for two novel beta-lactamase inhibitors and three efflux pump inhibitors for use with existing antibiotics in Gram-negative infections; a polymyxin analog with activity against Gram-negative bacterial pathogens; two candidate compound series to confer Gram-negative activity to existing Gram-positive drugs; and two broad-spectrum antibiotic candidates. To help relieve bottlenecks in therapeutics development, NIAID contracts provide medicinal chemistry and activity testing support for lead candidate identification of broad-spectrum antibacterial drugs.

In addition, Phase I clinical testing is underway for several products with broad-spectrum activity, including a novel tetracycline and beta-lactamase inhibitor. NIAID is supporting clinical trials to evaluate a broad-spectrum aminoglycoside and a Phase I trial measuring IV fosfomycin in the lung as a possible treatment for hospital-acquired and ventilator-associated pneumonia.

MERS-CoV

NIAID continues to pursue research on therapeutics to treat MERS-CoV. A polyclonal antibody-based therapeutic supported by NIAID has completed a Phase I clinical trial at the NIH Clinical Center. An NIAID-supported Phase I clinical trial of a monoclonal antibody therapeutic against MERS-CoV is in protocol development and is scheduled to start in 2018.

Other Therapeutics

NIAID continues testing of approved antibiotics for additional indications under the FDA Animal Rule. Two antibiotics for prophylaxis of inhalational anthrax in special populations have been tested; NIAID will submit additional studies requested by FDA in 2018 and present data in support of a label indication to an Advisory Committee. NIAID also has data on two antibiotics for inhalational tularemia that will be submitted to FDA in 2018. NIAID continues to pursue qualification for multiple animal models.

Diagnostics

Multiplex Development

In collaboration with the Department of Defense, NIAID is supporting the development of a multiplex PCR-based diagnostic to detect biodefense and emerging pathogens that cause acute fevers, including *Bacillus anthracis*, *Yersinia pestis*, *Francisella tularensis*, Ebola virus, Marburg virus, and Zika virus.

Broad Spectrum Antimicrobials

NIAID also continued its support of research to combat antimicrobial resistance, including more than $11 million in second-year funding for nine research projects supporting

enhanced diagnostics to rapidly detect antimicrobial-resistant bacteria. NIH and BARDA continue to collaborate in sponsoring the Antimicrobial Resistance Diagnostic Challenge prize competition expected to award up to $20 million for the successful development of innovative, rapid, point-of-need diagnostic tests to combat the development and spread of antibiotic resistant bacteria.

Other Countermeasure Research

Filoviruses - Ebola/Marburg

NIAID continues to support PREVAIL III, a study to understand the long-term health consequences of Ebola virus disease (EVD)-related eye, musculoskeletal, and neurological problems among Ebola survivors.

NIAID is supporting studies that may lead to understanding immune correlates of protection for Ebola and Marburg vaccines, which are essential for vaccine licensure under the FDA Animal Rule as they serve to bridge nonclinical immunogenicity data to human immunogenicity data to predict likely clinical benefit.

NIAID has supported the development of the EBOV and SUDV oronasal ferret model of filovirus disease. The ferret is the only fully immunocompetent small animal model in which unadapted filoviruses cause a lethal disease. Lethal dose (LD50) and pathogenesis studies have been completed and proof-of concept studies for the evaluation of vaccine efficacy are in progress.

Radiation and Nuclear Countermeasures Program (RNCP)

NIAID manages the Radiation and Nuclear Countermeasures Program (RNCP), with funding from a direct appropriation to the NIH OD and engages in frequent collaborations with other NIH Institutes, HHS sister agencies, other U.S. Government and non-U.S. Government partners, and international groups to optimize research efforts. Research focuses on radiation medical countermeasure (MCM) and biodosimetry development from early stage to licensure, for use in triage and treatment of injuries resulting from a radiation incident. For example, NIAID supports preclinical and clinical testing of MCMs for FDA licensure and since FY 2005 has evaluated more than 550 MCMs and biodosimetry approaches, met with more than 340 companies, and conducted 138 preclinical studies on more than 50 MCMs, including efficacy for radiation-induced bone marrow, gut, and lung injuries, and radionuclide decorporation. Currently there are over 250 treatments for radiation injury and biodosimetry under study within the RNCP.

In FYs 2016–2017, the FDA allowed Phase 1 clinical trials to proceed for five radiation MCMs developed through NIAID's support. These MCMs included three radionuclide decorporation agents, one novel growth factor, and one cellular therapy.

Since 2005, the NIAID-funded Centers for Medical Countermeasures against Radiation Consortium (CMCRC) has evaluated >250 MCM and biodosimetry approaches, published more than 1,100 papers, initiated more than 40 patents and awarded 200 radiation pilot projects.

NIAID also supports a non-human primate cohort of 118 animals, which provides insight into effects in radiation survivors and give researchers access to samples from an animal model similar to humans.

Chemical Countermeasures Research Program (CCRP)

The medical research program directed against chemical threats, directed by the NIAID Chemical Countermeasures Research Program (CCRP), focuses on basic/mechanistic research and early product development of chemical MCMs for use in treating injuries and preventing lethality during and after a mass casualty chemical release event. Since 2006, more than 450 different potential MCMs have been evaluated, and the program currently supports the study of more than 75 potential medical countermeasures for chemically induced injuries.

The CCRP supports an overall research infrastructure network and engages in frequent collaborations with other NIH Institutes, HHS sister agencies, other U.S. Government and non-U.S. Government partners, and international groups to optimize research efforts. This research infrastructure includes contracts with research institutions, interagency agreements with the Department of Defense (DoD) and HHS, and a NIH-wide research grant program called the Countermeasures Against Chemical Threats (CounterACT) program directed by the National Institute of Neurological Disorders and Stroke (NINDS) under the oversight of NIAID.

In partnership with the DoD, NIAID RNCP, and BARDA, the CCRP began efforts to explore the potential efficacy of Neupogen to protect against the immunosuppressive effect of sulfur mustard poisoning.

NIH continues to support the multi-departmental effort to secure FDA approval for midazolam as a treatment against adult and pediatric seizures due to nerve agent poisonings.

NIH/NIAID MCM Transitions

The fundamental mission of NIH/NIAID is to conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. Candidate biomedical products and therapeutics emerge as we continually enhance and expand our research knowledge. Each of the MCM candidates that transitions to BARDA is the output of multiple years of investments in our research portfolio, typically starting with basic research on the disease fundamentals, and progressing through applied and then advanced research. Between FYs 2017 and 2021, NIH forecasts that more than 50 MCM candidates will be eligible for consideration for transition to BARDA's Advanced Research and Development (ARD) program (Table 4), in alignment with overall PHEMCE priorities. These candidates are not guaranteed to transition to BARDA. Their transition is dependent on scientific progress, threat prioritization, and availability of funding.

NIAID is promoting the development of many broad-spectrum antiviral and antibacterial candidates that were or will be eligible to transition to BARDA in FYs 2017–2021. These therapeutic candidates are designed to provide solutions for threat agents and to be responsive to emerging infectious diseases, including: Ebola, Zika, and antibiotic-resistant bacterial infections. For example, NIAID transitioned two smallpox antiviral candidates to BARDA for further development. One of these two antivirals, ST-246 (tecovirimat) was submitted as a New Drug Application (NDA) to the FDA in December 2017 and approved in 2018. In addition, monoclonal antibody candidates for smallpox have been funded by NIAID and evaluated in the various animal efficacy models and have shown activity comparable to ST-246 against multiple poxviruses. These drug candidates also have been transitioned to BARDA for further development.

To address radiation and nuclear threats, NIAID is supporting several candidates with the potential for transition to BARDA including treatments for the hematopoietic and gastrointestinal acute radiation syndrome (ARS) and delayed effects of acute radiation exposure (DEARE). An agent to treat radiation-induced thrombocytopenia recently transitioned and is being advanced for further development by BARDA.

To address chemical threats, the CCRP continues to transition products to BARDA. For example, in FY 2017, the CCRP successfully transitioned a Duke University-led / GSK-partnered antidote (TRPV4 channel blockers) to BARDA for advanced development as a treatment for lung injuries after chlorine inhalation. GSK is also developing this compound to treat respiratory diseases and if successful, the drug could become a first-in-class drug for the targeted respiratory conditions and the first approved treatment for lung injury from chlorine. Under this two-year, $17 million cost-sharing with ASPR, GSK will complete non-clinical large animal studies to demonstrate efficacy against chlorine.

In FYs 2016–2017, the CCRP (through its contracted CounterACT Efficacy Research Facility) developed and transitioned a large animal model (swine) of cyanide intoxication to BARDA and discovered that the current FDA-approved intravenous cyanide MCM therapy is also effective when administered intramuscularly, which is the preferred approach for mass casualty emergency.

Table 4: Medical Countermeasure Products Eligible For Transition from NIH to BARDA, FY 2017–2021						
Portfolio	**Project Name**	**FY**	**FY**	**FY**	**FY**	**FY**
Anthrax	Thermostable AV7909 Vaccine				X	
Anthrax	Plant produced Vaccine				X	
Anthrax	Intranasal rPA based anthrax vaccine					X
Anthrax	Antibiotic data submission to FDA		X	X		
Anthrax	Antibiotic data submission to FDA		X	X		
Botulinum Toxin	Cell based monoclonal(s) (B)			X		
Botulinum Toxin	Cell based monoclonal(s) (C, D)			X		
Botulinum Toxin	Cell based monoclonal(s) (E)				X	
Broad Spectrum Antibiotic	Broad-spectrum fluorocycline (IV)				X	
Broad Spectrum Antibiotic	Broad-spectrum fluorocycline (oral)				X	
Broad Spectrum Antibiotic	β-lactamase inhibitor (IV)				X	
Broad Spectrum Antibiotic	β -lactamase inhibitor (oral)					X
Broad Spectrum Antiviral	Viral RNA polymerase inhibitor for Ebola and Marburg viruses	X				
Chemical	Vesicant: Ocular Therapy (to mitigate sulfur mustard-induced eye injuries)					X
Chemical	Vesicant: Systemic Therapy (to mitigate sulfur mustard-induced immunosuppression)			X		
Chemical	Vesicant: Monoclonal Antibody Therapy (to mitigate sulfur mustard-induced acute airway injuries)		X			
Chemical	Pulmonary: Oral Nitrite Therapy (to mitigate chlorine-induced pulmonary injuries)			X		
Chemical	Pulmonary: TRPV4 Channel Blockers (to mitigate chlorine-induced respiratory injuries)	X				
Chemical	Pharmaceutical-Based Agents: Pseudo-irreversible Receptor Antagonist Therapy (to mitigate opioid-induced respiratory depression)			X		
Chemical	Neurological: Neuroprotectant Therapy (to mitigate nerve agents/pesticides-induced neurodegeneration)				X	
Chemical	Neurological: Anticonvulsant Therapy (to mitigate nerve agents/pesticides-induced seizure activity)		X			
Chemical	Neurological: Antidotal Therapy (MCM to rescue nerve agents/pesticides-inhibited AChE)				X	
Chemical	Cellular Respiration: Antidotal Therapy (MCM to directly detoxify cyanide in circulation)				X	X
Chemical	Cellular Respiration: Cardio and Neuroprotective Therapy (MCM to mitigate toxicity to the heart and brain after cyanide/hydrogen sulfide poisoning)					
Pandemic Influenza	Universal flu vaccine	X				
Pandemic Influenza	Universal flu vaccine		X			
MERS-CoV	Polyclonal Antiserum		X			
MERS-CoV	Monoclonal Antibody			X		
Radiation Biodosimetry	microRNA markers for evaluation of radiation exposures					X
Radiation Biodosimetry	Ultra-high-throughput proteomics					X
Radiation Biodosimetry	RABIT II cytogenetics platform				X	
Gastrointestinal Acute Radiation Syndrome	Fibroblast growth factor peptide					X
Hematopoietic Acute Radiation Syndrome	Novel pegylated growth factor to mitigate neutropenia and increase survival				X	
Hematopoietic Acute Radiation Syndrome	Drug to mitigate thrombocytopenia and increase survival		X			
Hematopoietic Acute Radiation Syndrome	PF4 inhibitor to mitigate thrombocytopenia and increase survival				X	
Hematopoietic Acute Radiation Syndrome	Repurposed TPO mimetic to mitigate thrombocytopenia and increase survival		X			
Hematopoietic Acute Radiation Syndrome	Flt-3 ligand to increase survival				X	
Hematopoietic Acute Radiation Syndrome	Thrombomodulin peptide to reduce vascular/endothelial damage and increase survival				X	
Hematopoietic Acute Radiation Syndrome	Thrombopoietin mimetic to mitigate thrombocytopenia and increase survival			X		
Hematopoietic Acute Radiation Syndrome	TLR 2/6 lipoprotein agonist to increase survival and stimulate hematopoiesis					X
Hematopoietic Acute Radiation Syndrome	Heparin binding growth factor to mitigate neutropenia and thrombocytopenia to increase survival				X	
Radiation-Induced Lung Injury	ACE inhibitor to mitigate lung fibrosis and increase survival				X	
Radiation-Induced Lung Injury	Antioxidant SDG to mitigate lung fibrosis and increase survival				X	
Radiation-Induced Lung Injury	Approved/inhaled lung surfactant to mitigate fibrosis				X	
Radionuclide Decorporation Agent	Oral absorption enhancer Diethylenetriaminepentaacetic acid (DTPA)			X		
Radionuclide Decorporation Agent	Oral hydroxypyridinone to remove internalized plutonium, uranium, and americium			X		
Ricin Toxin	Thermostable RIVAX Vaccine				X	
Tuberculosis	Thermostable (lyophilized) tuberculosis vaccine (ID93 + GLA-SE)				X	
Tularemia	Doxycycline dataset for FDA review		X		X	
Tularemia	Ciprofloxacin dataset for FDA review		x		X	
Viral Hemorrhagic Fevers (Ebola)	Ad/MVA vaccine (multivalent)			X		

Multiyear Budget: BARDA

The Pandemic and All Hazards Preparedness Act of 2006 amended the Public Health Service (PHS) Act and created BARDA, a component of ASPR, to support the advanced research and development, and acquisition of MCMs. These MCMs mitigate the medical consequences of man-made threats such as CBRN threats, and natural threats such as pandemic influenza and other emerging or re-emerging infectious diseases (e.g., Zika, Ebola, MERS-CoV, etc.). BARDA transitions MCM candidates from early development supported by other PHEMCE partners (NIH and DoD) or from private-sector industry, directly into advanced development towards FDA approval.

BARDA appropriations provide three funding sources to support advanced research and development, Project BioShield, and the pandemic influenza program (Table 5). BARDA's Advanced Research and Development program includes activities supporting Phase 2 and 3 clinical trials, and manufacturing process optimization and validation towards FDA approval, and post-marketing requirements and commitments. During emerging infectious disease epidemic responses, BARDA may look to the early phase of the MCM development pipeline to pull candidates into clinical trials. Through PBS, BARDA also acquires CBRN MCMs that are expected to qualify for FDA approval within 10 years for stockpiling in the SNS. Following FDA approval or licensure, the SNS is responsible for replenishing expiring MCMs to maintain preparedness.

Advanced Research and Development

BARDA works with public and private partners to transition candidates for vaccines, antivirals, diagnostics, and medical devices from early development into the advanced and late-stages of development and approval. In the biopharmaceutical industry, commercial medical products require 8–15 years to develop and reach licensure or approval by the U.S. Food and Drug Administration (FDA), and the same is true for MCMs. To have such MCMs with which to respond during a public health emergency, the federal government must maintain continuous development efforts over many years. BARDA's cost-efficient and innovative approach to MCM development is stimulating dormant industry sectors and revolutionizing the medical technology needed to protect communities from national health security threats and other public health emergencies.

BARDA's advanced research and development decisions are guided by the maturity of products in the early research and development pipeline of PHEMCE partner agencies. When feasible, medical products transition from early-stage research and development with PHEMCE partners into BARDA's advanced research and development portfolio. BARDA also strategically supports advanced development and acquisition of medical countermeasures that are existing products that can be repurposed to meet medical countermeasure needs or new multipurpose products with commercial indications that meet public needs. This approach increases the sustainability of these medical countermeasures, makes them less dependent on federal government support, and provides alternate mechanisms (e.g., vendor managed inventory systems) to stockpiling in the Strategic National Stockpile (SNS).

BARDA, in partnership with industry, has built a robust and formidable pipeline for advanced research and development of medical countermeasures. These efforts focus on combatting the medical consequences of 13 material threats identified by the Department of Homeland Security (DHS). These advanced development programs have supported 27 products under Project BioShield; 14 of these products have been procured for the SNS.

Table 5: Estimated BARDA Spending by Funding Source FY 2017–2021 (Dollars in Millions)

Funding Source	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	Total
Advanced Research and Development	$546	$537	$512	$995	$1,025	$3,615
PI - PHSSEF, Annual Appropriations	$10	$28	$33	$61	$174	$306
PI - PHSSEF, Annual No-Year	$55	$215	$210	$714	$775	$1,969
PI - PHSSEF, Sup Bal No-Year	$197	$0	$252	$0	$0	$449
Project BioShield SRF, No-Year	$532	$710	$510	$895	$990	$3,636
Total	**$1,339**	**$1,490**	**$1,517**	**$2,665**	**$2,964**	**$9,975**

BARDA's advanced research and development programs also have led to FDA licensure or approval of six new products since 2012 using the FDA Animal Rule. In conjunction with the FDA and industry, BARDA developed new animal models to support development of products utilizing the Animal Rule as a pathway to approval. The FDA approved the following BARDA-supported CBRN MCMs under the Animal Rule: Raxibacumab anthrax antitoxin (2012), hBAT botulinum antitoxin (2013), Anthrasil (AIG) anthrax polyclonal antitoxin (2015), Neupogen (2015) to treat hematopoiesis, BioThrax (2015) for post-exposure prophylaxis in individuals suspected of exposure to anthrax, and ANTHIM (obiltoxaximab) anthrax antitoxin (2016). In FY 2017, the FDA approved an antibiotic candidate, Vabomere, to treat severe drug resistant infections. Additional FDA approvals for novel antibiotics, a radiation MCM, a smallpox antiviral, and a smallpox vaccine for at-risk individuals are also projected for approval in FYs 2018–2019.

With these recent FDA approvals, BARDA met and exceeded the HHS goal of four CBRN medical countermeasures licensed by the FDA by the end of 2015. In FY 2017, six new projects were funded under PBS bringing the total number of candidates supported under PBS to 27. In FY 2017, BARDA supported two Ebola vaccine candidates, two Ebola therapeutic candidates, and two biodosimetry devices; one a point-of-care device and the other a lab-based, high-throughput device. These candidates have been supported under ARD and were considered mature enough to transition to PBS. The development pipeline remains poised to continue this trend, transitioning CBRN products from advanced research and development programs to acquisition under Project BioShield (for the SNS) and towards FDA approval or licensure.

Project BioShield

Over the last decade, BARDA's commitment to advanced development, enhanced partnerships with industry, and sustained investments in potential products made possible under Project BioShield (PBS), has led to the support of 27 products that are critical to prepare for, and treat the effects of these threats. Fourteen of these products have been delivered to the Strategic National Stockpile (SNS), with additional products to be delivered in FYs 2018 and 2019. The progress achieved through PBS continues to boost the nation's readiness to respond to the medical consequences of anthrax, botulism, smallpox, radiological and nuclear agents, and chemical threats. As a result, the medical countermeasure development pipeline for CBRN threats holds more promise today than ever before. BARDA, with its proven track record, is uniquely positioned to make innovative progress in the procurement of CBRN MCMs to save lives.

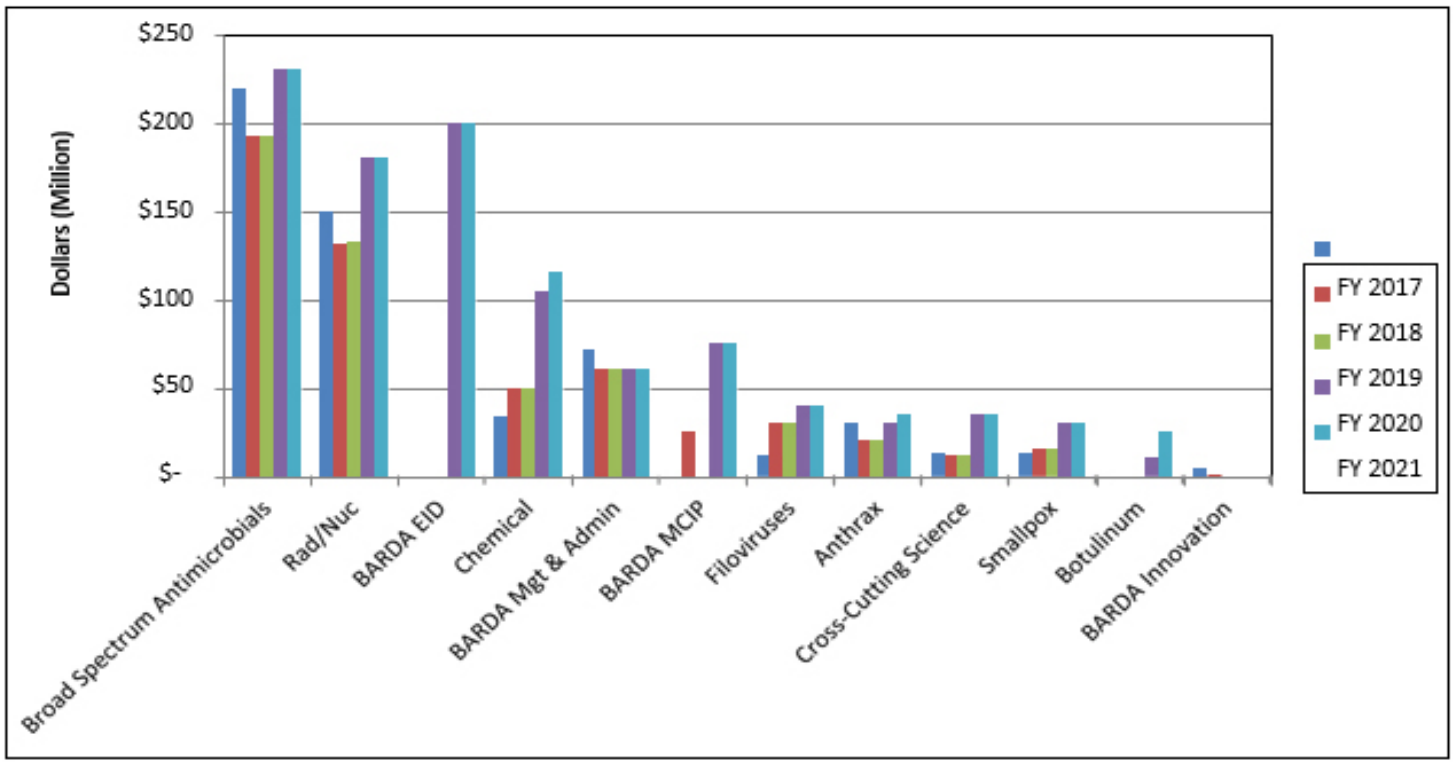


Figure 4: Estimated BARDA ARD Spending by Fiscal Year

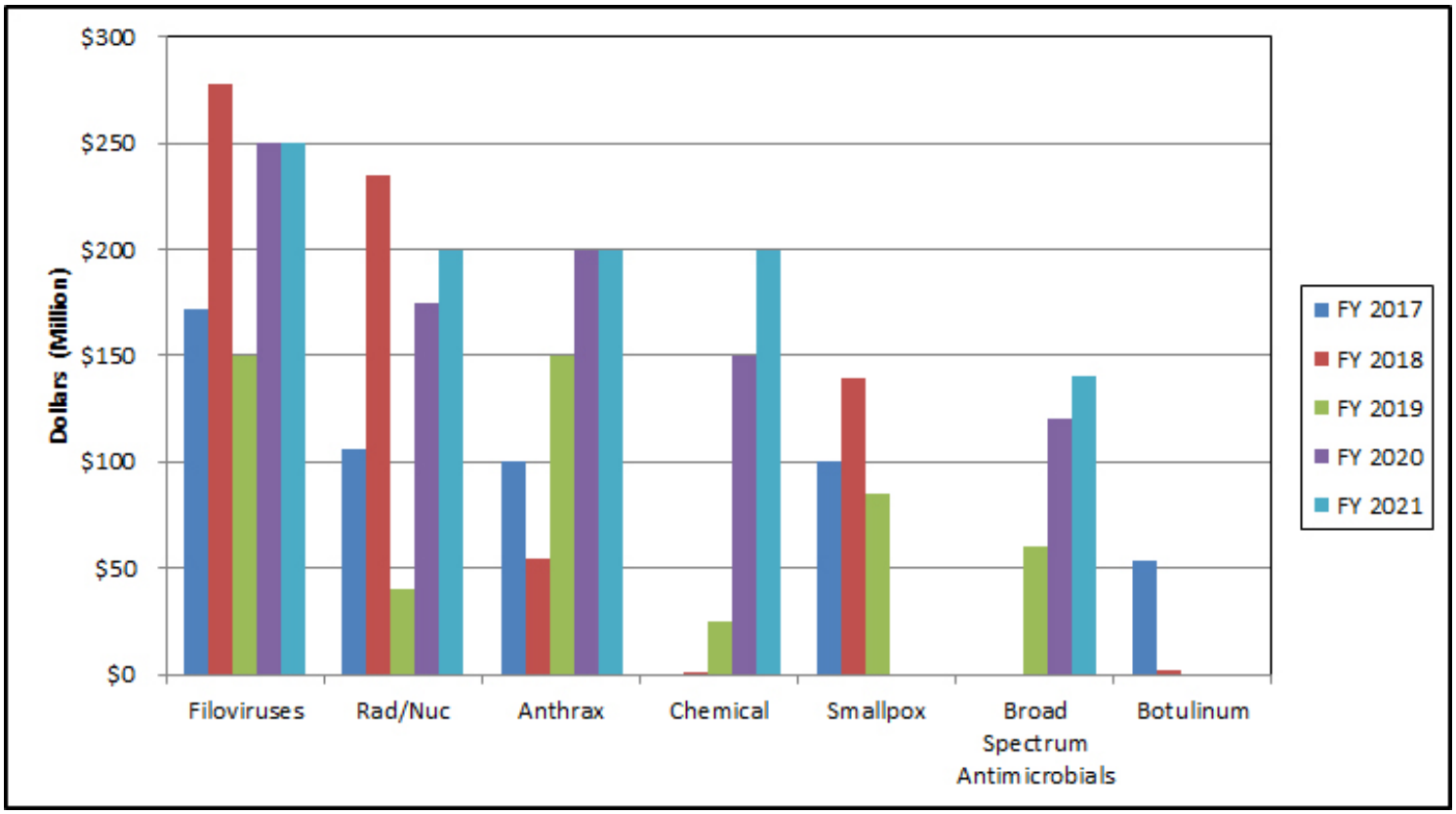


Figure 5: Estimated BARDA Project BioShield Spending by Fiscal Year

The Project BioShield Act of 2004 (P.L. 108–276) provided specific authorities and funding through FY 2013 for late-stage development and procurement of CBRN MCMs. The law also provided the FDA with the legal ability to quickly authorize the use of these experimental MCMs during public health emergencies. The Pandemic and All-Hazards Preparedness Act (PAHPA) of 2006 and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) further amended the Project BioShield authorities in the Public Health Service Act. Created by PAHPA, BARDA made unprecedented progress in developing and acquiring products necessary to protect health during CBRN incidents. To minimize lifecycle costs, BARDA pursues advanced development of product candidates, when possible, that also have commercial uses. For example, products to treat injuries resulting from radiation during a nuclear blast may also help treat cancer patients or burn victims. PBS allows BARDA to purchase promising experimental products for the SNS that are sufficiently mature for utilization under an Emergency Use Authorization (EUA) issued by the FDA. Even after procurement, BARDA continues to support companies and the late-stage development of these product candidates towards FDA approval or licensure. PBS funding is also utilized to replenish expiring CBRN MCMs in the SNS prior to FDA approval (e.g., IMVAMUNE smallpox vaccine) and post-approval in some instances (e.g., Raxibacumab anthrax antitoxin). In the latter case, the exact timing of FDA approval, which is uncertain, and budget planning, which occurs several years in advance, required BARDA to purchase anthrax antitoxin to maintain preparedness levels.

Pandemic Influenza

BARDA forecasts a significant increase in funding for pandemic influenza in FY 2019 through FY 2021. This increase is necessary to maintain domestic preparedness and pandemic response capabilities, while funding next-generation universal influenza vaccines, immunotherapeutic treatments, and advanced diagnostic devices. BARDA will also focus efforts to expand domestic manufacturing for adjuvants and needles and syringes; significant gaps in pandemic preparedness. BARDA will fund sustainment activities related to pandemic preparedness to meet domestic pandemic influenza vaccine manufacturing capacity and pre-pandemic vaccines requirements established in the National Strategy for Pandemic Influenza[7] and the Pandemic Influenza Plan: 2017 Update[8], including ongoing storage, stability, and testing of stockpiled material in the pre-pandemic vaccine and adjuvant stockpiling program.

[7] https://www.cdc.gov/flu/pandemic-resources/national-strategy/index.html

[8] https://www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf

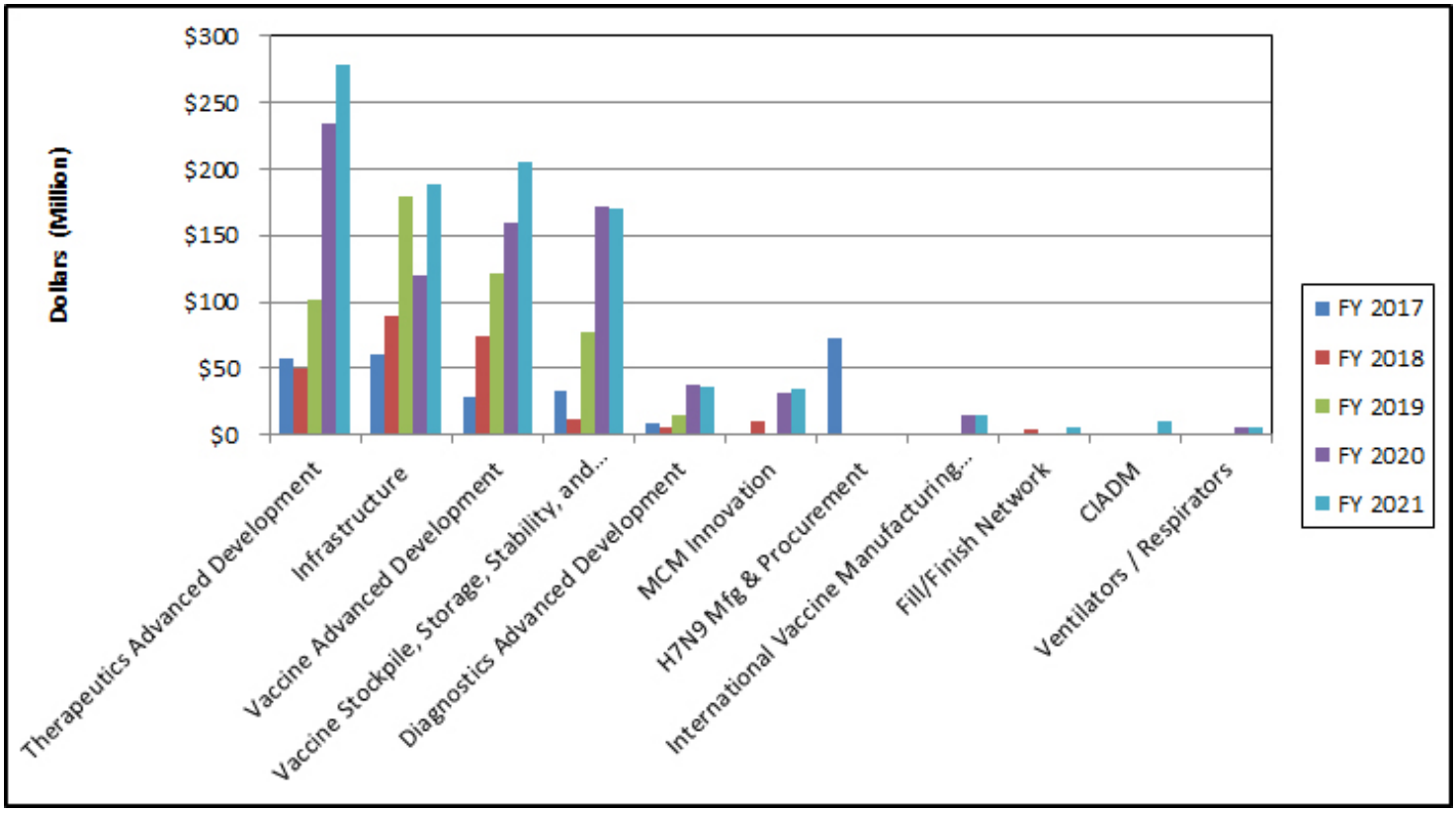


Figure 6: Estimated BARDA Pandemic Influenza Spending by Fiscal Year

BARDA will advance into late-stage clinical trials, critical MCMs in both therapeutic drugs and universal influenza vaccines, including four key therapeutic drugs targeted for patients who are severely ill, hospitalized, or elderly and for pediatric patient populations. These antiviral drugs will feature novel mechanisms of action that prevent the emergence of drug-resistant viruses, especially when co-administered with other influenza antiviral drugs, and demonstrate efficacy for longer intervals after symptom onset. BARDA will invest up to four potential next-generation universal influenza vaccine programs that could protect against all influenza strains, toward the goal of "influenza immunity for life." These vaccines would be transformational to pandemic preparedness and response but are extremely challenging to develop. BARDA will pursue a portfolio approach of multiple candidates to increase the likelihood of success. To this end, BARDA entered into two Other Transactional Authority (OTA) agreements to help bring forth novel advanced drug and vaccine candidates into the marketplace against the threat of pandemic influenza. BARDA also has supported the approval of RAPIVAB and the FDA has now extended the use of this product for pediatric patients above the age of two years with acute, uncomplicated influenza.

To enhance the long-term sustainability of the federal government's pandemic preparedness posture, BARDA will invest in new vaccine platform technologies that support rapid response to influenza and other emerging (or re-emerging) diseases and CBRN threats. Examples include scalable mRNA vaccines, recombinant expression systems, and replicon vectors. These modular platform technologies, highlighted as important in the National Biodefense Strategy working group, will be important to accelerate medical countermeasure development against emerging and reemerging biothreats against our nation.

To predict, inform, and respond to, the next influenza pandemic, BARDA will focus on home use and point-of-need medical devices and diagnostics, including wearables and other advanced innovative technologies such as in-vitro diagnostics that will empower at-risk patients to seek early treatment, prevent further disease transmission, and inform intelligent network-based interventions. To this end, devices will be integrated into a "net" of diagnostic capability augmenting current diagnostic platforms with the ability to capture, analyze and report time, geo-spatial and patient information to support a more targeted pandemic preparedness and response.

Finally, BARDA will engage the private sector to develop reusable and durable single size (i.e., one-size-fits-all) respirator/personal protective equipment for medical personnel and first responders, which is critical to maintain the emergency response workforce during times of outbreaks.

BARDA Accomplishments through FY 2017

BARDA has built a robust MCM development pipeline for CBRN, pandemic influenza, and emerging infectious disease threats that has delivered the following:

- Supported the development of 17 products for influenza, including nine vaccines, one therapeutic antiviral drug, six diagnostics, and one respiratory protective device, that have received FDA approval since 2007. This includes the first cell-based and recombinant influenza vaccines, the first pandemic vaccine with adjuvant for children, and the first intravenous influenza antiviral drug.
- Retrofitting and construction of new influenza vaccine manufacturing facilities within the continental U.S. to ensure that 600 million bulk antigen doses of pandemic influenza vaccine can be delivered for protection of the U.S. population within six months of the identification of a new pandemic virus.
- BARDA established and manages the National Pre-Pandemic Influenza Vaccine Stockpile, which contains vaccines against avian influenza H5N1 and H7N9 viruses as well as AS03 and MF59 adjuvants with an aggregate value of $1.7 billion. It also launched a program to support stockpile sustainability.
- Launched two new OTA programs to support the development of improved and potential "universal" influenza vaccines and new classes of antiviral medications, including monoclonal antibodies, for the treatment of severely-ill, hospitalized patients.
- In 2017, BARDA awarded contracts to initiate production of pre-pandemic vaccine bulk antigen for the current H7N9 strain. BARDA will manufacture 40 million doses of pre-pandemic vaccine antigen to meet the requirement of The National Strategy for Pandemic Influenza Implementation Plan. Activities to prepare master and working virus seed lots for vaccine production at various manufacturers were completed. Some bulk lots were released at the end of 2017 and clinical trials are planned for early 2018.
- Supported 21 products under PBS; 14 have already been delivered to the SNS and the remaining products will be delivered in the coming years. Six products supported under PBS have achieved FDA approval with additional approvals anticipated in FYs 2017–2019.
- In FY 2017, BARDA transitioned six products supported under ARD to PBS support for late-stage development and potential procurement. The six products included two Ebola vaccines, two Ebola therapeutics, and two biodosimetry devices to determine the level of absorbed ionizing radiation resulting from a nuclear detonation. One product is designed as a point of care, field use device and the second is a laboratory-based high-throughput device.
- With the transition of these six new products, PBS is now supporting the late-stage development of 27 different products, 14 have already been delivered to the SNS, and 6 have achieved FDA approval. This increases our preparedness posture against multiple CBRN threats.
- Neulasta (pegfilgrastim) – Supplemental approval for use to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome) (November 2015) – Amgen, Inc.
- Expanded the antimicrobial program, forming new public-private partnerships through the innovative CARB-X program, launched ahead of schedule.
- FY 2017 saw the first FDA approval of an antimicrobial product that has been supported under ARD. FDA approved Vabomere to treat complicated urinary tract infections and a kidney infection called pyelonephritis in adults. Drugs like VABOMERE that address drug-resistant, Gram-negative bacteria, including CRE, can reduce the risks posed by secondary infections that can occur in the wake of a CBRN attack due to the patient's compromised immune system.
- Flublok Influenza Vaccine – Supplemental approval to include a quadrivalent formulation (Flublok Quadrivalent) for use in persons 18 years and older (October 2016) – Protein Sciences Corporation
- Rapivab (peramivir) – Supplemental approval for an expanded Influenza antiviral drug IV in the treatment of pediatric patients 2years or older (September 2017) - BioCryst
- Cobas – Received FDA approval for an in vitro point-of-care diagnostic that can provide a 20-minute real-time PCR nucleic acid test to detect Clostridium difficile in samples (September 2017) – Roche
- Cobas Zika Molecular Diagnostic – FDA approved Zika diagnostic available for donor screening nucleic acid PCR test of Zika virus RNA in samples of human plasma (October 2017) – Roche.
- Leukine (sargramostim) was approved in March 2018 to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).

Table 6: MCM Product Transitions from ARD to PBS, FYs 2017–2021	
Medical Countermeasure	**Estimated Transition Timeframe (FY)**
Therapeutics for Ebola (continued support)	2018-2021
Vaccines for Ebola (continued support)	2018-2021
IV Smallpox Antiviral	2018
Chemical Vesicant Therapeutics	2018
New antimicrobial drugs	2019-2020
Cell-based therapeutic for hematopoietic ARS	2019-2021
Chemical nerve agent antidote	2019-2021
New product(s) to address burn injury	2020-2021
Small molecule therapeutics for skin and lung ARS	2019-2021

BARDA MCM Transitions

During FYs 2017–2021, BARDA anticipates multiple MCM product transitions from its ARD program to Project BioShield (Table 6). As an immature program transfers to BARDA from outside sources, BARDA's ARD funds are expended to help the program mature. When products are at a state of maturation where PBS funds can be used, BARDA makes an initial procurement and the product is delivered to the SNS. In recent years, BARDA transitioned candidate MCM products from ARD to PBS such as: Ebola vaccines and therapeutics, supported clinical trials for pediatric patients under PBS supported burn products biothreat, and biodosimetry devices for use in a point-of-care or high-throughput setting.

The prior list (Table 4) of NIH product transitions represents part of the realm of possible projects BARDA will accept and fund in future years. These projects are not guaranteed to transition to BARDA. BARDA will review their scientific merit and prioritize them along with projects from DoD, industry, and other sources, and determine an overall plan consistent with the goals established by the PHEMCE.

Following FDA approval or licensure, an MCM stored in the SNS will become the financial responsibility of the SNS. Replenishment of the product following expiration will be determined by the SNS's budget resources. Table 7 highlights a list of products that BARDA anticipates will need replenishment in this report's timeframe.

Table 7: MCM Product Transitions from BARDA to SNS, FYs 2017–2021	
Medical Countermeasure	**Estimated Transition Timeframe (FY)**
Anthrax Therapeutic	2019
Anthrax Therapeutic #1	2020
Anthrax Therapeutic #2	2020
Botulinum Antitoxin	2020
Smallpox Vaccine	2020
Smallpox Antiviral	2020
Chemical Anticonvulsant	2020
Anthrax Vaccine with adjuvant [1]	2020-2021
Rad/Nuc Thermal Burn Product #1 [2]	2021
Rad/Nuc Thermal Burn Product #2 [3]	2021
Rad/Nuc Thermal Burn Product #3 [4]	2021
Rad/Nuc Thermal Burn Product #4 [5]	2021

[1] BARDA estimates that this product will need replenishment and be FDA approved by the indicated fiscal year but insufficient contract information is available to include a cost estimate in the DSNS data.
[2] Ibid.
[3] Ibid.
[4] Ibid
[5] Ibid.

Multiyear Budget: SNS

As stated in the FY 2019 President's Budget, the SNS was transferred from CDC to ASPR. Putting the SNS under ASPR will increase operational effectiveness and efficiencies and strengthens integration with ASPR's existing medical countermeasures (MCM) program, which will streamline MCM development and medical response capabilities. In sum, the move is designed to improve the domestic preparedness posture by optimizing MCM development, response, and utilization, while also strengthening response capabilities to health security threats. These investments will lead to better outcomes for the National Health Security Strategy, National Biodefense Strategy, and the PHEMCE.

The Division of Strategic National Stockpile (DSNS) is responsible for the management of the SNS, including acquisition of commercially available pharmaceuticals, devices, and ancillary supplies, to meet PHEMCE requirements. DSNS also procures replacements for FDA-approved MCMs, including MCMs initially procured by BARDA through Project BioShield after those MCMs achieve FDA approval or licensure. DSNS requires accurate forecasting to make strategic procurement and investment decisions, in consultation with the PHEMCE governance body. Stockpile inventory management uses current stockpile holdings to forecast future on-hand holdings, product expiration, and product replacement timelines. The SNS budget projection model estimates funding needs to maintain and manage SNS stockpiled MCMs in out-years. The budget forecast are models produced annually in the spring and accounts for changing market conditions and product movements. It provides accurate current inventory and budget information to the multiyear budget and informs DSNS decision-making for current-year budget execution, spend plan development, and formulation for future fiscal years. DSNS's current projections assume additional efficiencies realized via the FDA and DoD Shelf Life Extension Program that were not reflected in the FY 2016–2020 Report.

For the period, FY 2017–2021, SNS estimates spending under the baseline scenario at $3.8 billion to maintain the formulary at FY 2019 levels and replenish products originally supported by Project BioShield that achieve FDA approval or licensure. This is $858 million, or 29 percent, more than the five-year total of $2.9 billion included in the FYs 2016–2020 Report. Figure 7 shows the estimated spending by portfolio.

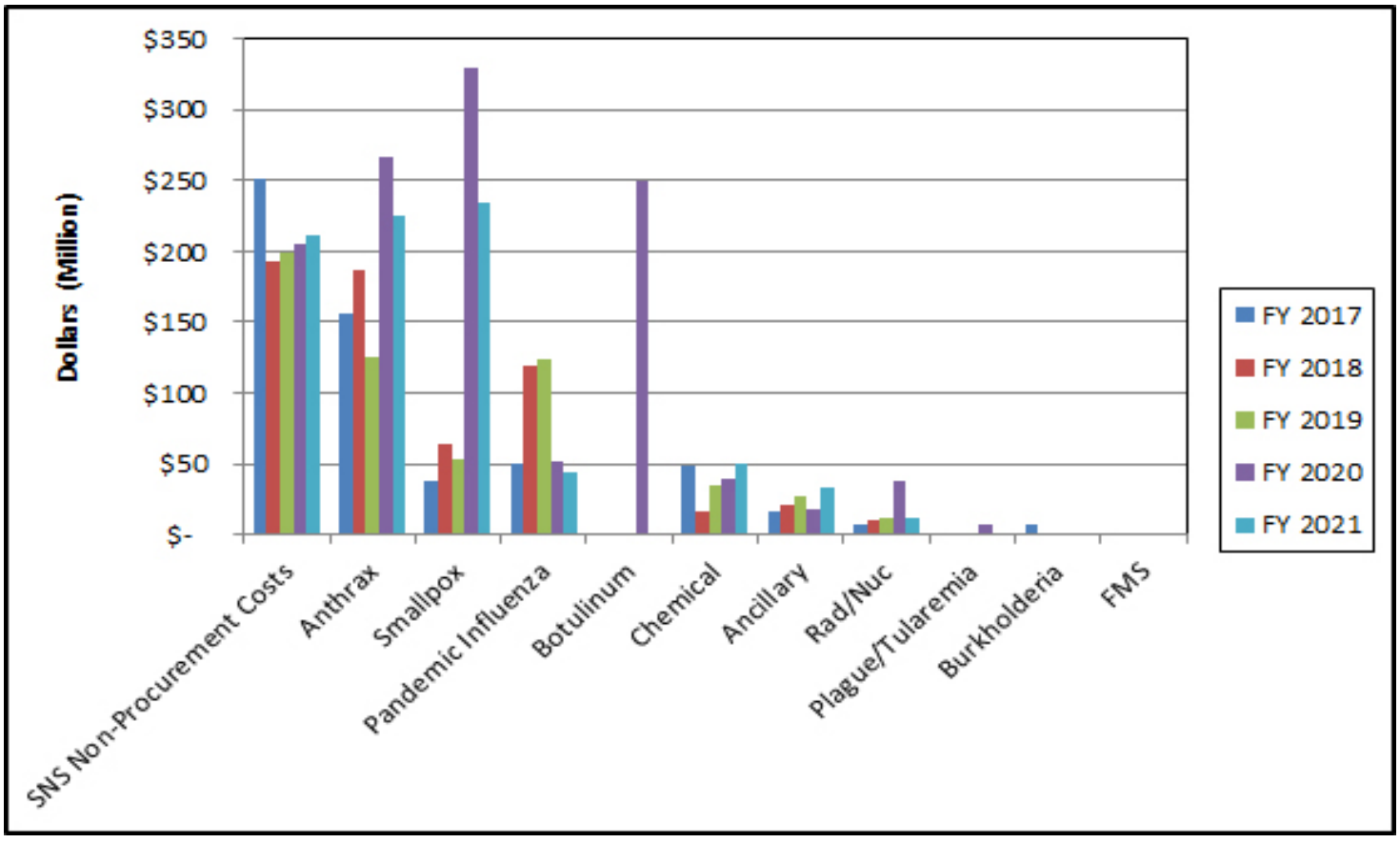


Figure 7: Estimated SNS Spending by Fiscal Year

Table 8: Estimated SNS Spending Needed for MCM Product Replenishment of Products Achieving FDA Approval or Licensure Previously Procured by BARDA, FYs 2017–2021		
Medical Countermeasure	**Estimated Transition Timeframe (FY)**	**Estimated Cost FY 2020 & FY 2021 (dollars millions)**
Anthrax Therapeutic	2019	$222.3
Anthrax Therapeutic	2020	$80.0
Anthrax Therapeutic	2020	TBD[1]
Botulinum Antitoxin	2020	$250.0
Smallpox Vaccine	2020	$144.0
Smallpox Antiviral	2020	$202.7
Chemical Anticonvulsant	2020	TBD[2]

[1]Cost estimate pending policy review of anthrax antitoxin stockpiling requirements.
[2]Cost estimate pending FDA review of product.

Of the $3.8 billion, $1.8 billion will be spent in FYs 2017–2019 consistent with FY 2017 and FY 2018 annual appropriations and the FY 2019 President's Budget. This total also includes $1.1 billion to maintain the formulary in FYs 2020–2021 and $899 million to replenish products transitioning from Project BioShield. Table 8 breaks out the products expected to transition from Project BioShield to SNS and their associated two-year replenishment costs.

Background on Establishing MCM Stockpiling Goals

To determine the appropriate stockpiling goal, the PHEMCE MCM requirements process leverages public health consequence modeling, subject matter expert evaluations, and estimates of current national response capabilities. Developed by DHS, Material Threat Assessments (MTA) informs medical consequence assessments for chemical, biological, radiological, and nuclear (CBRN) threats. MTAs project the number of individuals who may be exposed to each threat in a selection of plausible scenarios that have the potential to impact national health security. Public health response and medical consequence modeling conducted by HHS calculates the rate of morbidity and mortality because of such exposures.

The PHEMCE subject matter expert groups assess the mitigated consequence modeling and identified the number of casualties that could benefit from intervention with pharmaceutical and non-pharmaceutical MCMs (i.e., the need-based quantity). The capabilities of the medical and public health systems to effectively utilize broad categories of MCMs (e.g., oral or parenteral) are then assessed to arrive at the operational quantity. Finally, these inputs, along with the development of desired product characteristics, lead to the stockpiling goal recommended for an MCM class.

Stockpiling goals may include both centrally stockpiled and alternatively stockpiled MCMs.[9] The MCM requirement process and subsequent stockpiling goals are based upon sound scientific, medical, and epidemiological principles and result in a national stockpile of MCMs that can be effectively utilized during a public health emergency. The PHEMCE is also exploring alternatives to stockpiling as appropriate. Such alternatives include "just-in-time" manufacturing or procurement and support for surge manufacturing capabilities.

High-priority, naturally occurring threats with the potential to become public health emergencies, such as emerging infectious diseases and pandemic influenza, are also considered by the PHEMCE. MCM needs for these threats are analyzed through this standardized process and translated to stockpiling goals, as appropriate.

[9]Alternative stockpiling methods include stockpiling of bulk product, home or business caching, or other vendor- or user-managed inventory approaches.

CDC MCM Accomplishments Beyond SNS

In every fiscal year, the majority of SNS appropriated funding is directed to procurement and maintenance of the stockpiled holdings of medical countermeasures. More than 98% of the 801 product lines in the SNS are commercially available countermeasures that are purchased through federal supply schedules or simple contracting mechanisms to meet the government's requirements. In FY 2017, the strategic procurement executed by SNS in line with the prioritized recommendations made by PHEMCE in the 2014 SNS Annual Review (FY2017 Plan) resulted in replacement of expiring countermeasures to maintain priority MCM capabilities for anthrax and chemical threats, as well as the addition of new capabilities to address *Burkholderia mallei*, *Burkholderia pseudomallei* and secondary infections for patients exposed to radiation. Investments in the maintenance of stockpiled supplies to include storage, quality control, compliance, transportation, security and day to day management of the $7.0 billion inventory of MCMs resulted in an inventory accuracy rate of 98.39% on annual wall to wall inventories, and no loss of product due to compliance, security or environmental storage issues.

Acquisition and maintenance of MCM inventories only protect the population against public health threats if MCMs reach civilians in a timely manner. To enhance the nationwide capacity for effective response to public health emergencies and strengthen the last mile efforts to distribute and dispense MCMs, the non-procurement costs noted above, in part, support the scientific, clinical, regulatory, laboratory and public health work from across CDC that is critical in ensuring effective use of SNS assets. With the transfer of the SNS to ASPR, future funding support (FY 2019 and onward) for CDC activities in support of effective MCM utilization are yet to be determined.

Improving state and local health department readiness

CDC has supported public health preparedness and responses to real-world events. Over the past year, CDC worked with public health partners in the 10 highest risk urban areas of the country (as defined by the Department of Homeland Security's Urban Area Security Initiative (UASI)). SNS, in collaboration with public health and threat-specific experts throughout CDC, is working with these partners to assist each jurisdiction with identifying gaps in plans to respond to a large-scale anthrax event, improving operational readiness, and validating the amount of time needed to deliver stockpile products. In FY 2017, CDC conducted tabletop exercises with nine UASI jurisdictions. CDC also worked to better define its commitment to working with high-risk jurisdictions in the event of a public health emergency by signing five updated Memoranda of Agreement with UASI jurisdictions in FY 2017.

CDC collaborates with state and local health departments to improve MCM planning for operational readiness. CDC's Division of State and Local Readiness recently developed and implemented the national MCM operational readiness review (ORR) process to assess state and local readiness for a large MCM mission and identify areas where technical assistance is required. CDC also recently developed the Online Technical Resource and Assistance Center (On-TRAC) portal as a web-based resource and sharing center State, Tribal, Local, and Territorial (STLT) staff can access resources, engage in peer-to-peer information exchange, and request technical assistance. CDC integrates public health surveillance and investigation data at the federal level that assists in evaluation and characterization of public health emergencies. This information helps inform deployment decisions for MCMs from the SNS.

With SNS and CDC activities, in FY 2017 CDC was able to provide substantial training to prepare federal, state, and local partners. This year, CDC conducted 21 objective-based external SNS training courses tailored to specific state and local requirements. SNS also trained 3,758 federal and STLT emergency responders representing 13 different project areas using in-person trainings at STLT locations and the Federal Emergency Management Agency's Center for Domestic Preparedness facilities in Alabama, and virtually led training via web meetings.

The FY 2017 events included:

- Nine UASI Distribution Tabletop Exercises;
- Three STLT Distribution and Dispensing Full Scale Exercises;
- Three Receive, Stage, and Store (RSS) Operations courses; and
- Online and virtual courses focused on mass dispensing; Closed PODs; RealOpt; and other relevant topics.

CDC SMEs also provide technical assistance on the use of deployed SNS assets. This year CDC provided guidance to clinicians and public health departments on the use of botulism antitoxin, and anthrax vaccine In addition, as part of the hurricane response, CDC experts also provided technical assistance on the ground to Puerto Rico department of health on the management and administration of over 68,000 doses of influenza vaccine in addition to other vaccines provided to support vaccine preventable diseases.

Regulatory Science

To use certain medical countermeasure within the SNS, regulatory mechanism to allow use of products may be required. CDC manages and oversees all SNS regulatory functions associated with stockpiled MCMs and works closely with the FDA to develop regulatory packages to support emergency use of MCMs that are not yet approved, or approved for the indications, such as Emergency Use Authorizations (EUAs) and Emergency Use Instructions (EUIs). In FY 2017, CDC regulatory science activities included the development of EUAs to support procurement and emergency use of investigational atropine auto-injectors for the CHEMPACK program, pre-EUAs to allow prophylaxis and treatment of melioidosis and glanders, caused by the Tier 1 select agents, *Burkholderia pseudomallei* and *Burkholderia mallei*. CDC also developed EUIs for MCMs for Hematopoietic Acute Radiation Syndrome (H-ARS) to enable use of MCMs for radiation incidents. CDC Regulatory Science activities also include the development of post-marketing data collection required by FDA for certain MCMs. CDC works closely with manufacturers to develop protocols to capture data from health care facilities and public health officials.

Threat and Clinical Guidance development

CDC experts throughout the agency systematically review and synthesize the evidence and develop and publish threat specific guidance, clinical guidance and clinical tools for the use of MCMs within the SNS. This work also includes guidance development for MCM use with pediatric populations. CDC recently published clinical guidance for the care and management of pregnant women and infants affected by Zika infection, and it is working on improving the clinical guidance available for dealing with radiation, botulism, and plague exposures in all affected populations, including children.

Advancements in MCM Science and Research

CDC programs conduct research and assess the scientific literature and data related to MCMs. As an example, CDC's smallpox program develops diagnostics, therapeutics and vaccines for smallpox as well as the systems with which to study them. CDC developed improved testing to demonstrate exposure to chemical agents. CDC's Toxins Laboratory is the only laboratory in the world able to make advanced measurements needed to determine distribution and effectiveness of SNS antitoxins, while reporting all anthrax and botulism testing results in 24 hours or less. CDC's Radiation Laboratory maintains and applies state-of-the-art analytical methods to determine the amount of radionuclide(s) inhaled or ingested following a radiologic incident and assess the need for medical management of individuals, including use of limited medical countermeasures.

CDC also develops surveillance and diagnostic tests to allow rapid detection and patient identification that may be used in an influenza pandemic or other incidents with high consequence pathogens. Annually, CDC plays a central role in the global process for development of seasonal influenza vaccinations and decision-making and early development of pandemic vaccines. As a WHO Collaborating Center (CC), CDC's Influenza Division conducts year-round surveillance for early detection and identification of antigenically drifted seasonal influenza viruses as well as novel influenza A viruses that may have pandemic potential to inform countermeasure development. The Influenza Division collects and analyzes influenza viruses from around the world for epidemiological, antigenic, antiviral susceptibility and genetic characterizations. It is also responsible for making candidate vaccine viruses (CVVs) for vaccine manufacturers to use to mass produce flu vaccines. Together with other WHO CCs CDC's Influenza Division provides essential information for the WHO to make recommendations on appropriate viruses to be included in annual seasonal influenza vaccines as well as vaccines for pandemic preparedness. CDC's Collaborating Center also maintains a repository of influenza specimens and virus isolates from worldwide sources. These viruses are made available to WHO laboratories, vaccine manufacturers, other public health partners and research institutions.

In 2017, CDC experts also provided leadership of the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) Ebola vaccine campaign in West Africa and supported collaborative research and development on Ebola therapeutics. CDC MCM research also includes advancements in the storage and use of personal protective equipment. This year CDC has conducted studies to assess impact of long-term storage/ stockpiling of personal protective equipment (PPE), assessments of feasibility and acceptability of using elastomeric for healthcare worker protection, and studies to determine the best use of N95 respirators to improve the procurement, management and use of stockpiled PPE.

Operational Science and Response

CDC continues to work with the Department of Defense (DoD) as part of its commitment to the common defense of the country. Following a General Accounting Audit recommendation in 2007, SNS assumed responsibility for managing DoD's stockpiles of certain vaccines. SNS worked collaboratively with DoD to engage alternate sources of supply to support the shortfall in availability of nerve agent antidotes and other medical countermeasures.

CDC Quarantine Stations provide a platform for responding to small naturally occurring outbreaks in a timely fashion. For

example, CDC Quarantine stations and experts in Botulism have established an operational process for storage of botulism antitoxin at CDC quarantine stations to improve logistics for rapid distribution demonstrated to save lives.

In addition, CDC continues to lead the work in operational planning to ensure the most effective and timely delivery of public health countermeasures. This year, CDC completed the feasibility and acceptability assessments for leveraging the commercial pharmaceutical supply chain for antiviral drug distribution and dispensing. These activities included legal analysis, pharmacy throughput studies, stakeholder accessibility studies and engagements, and modeling to assure that the proposed concept may be operationalized. CDC has also begun assessments on how to leverage direct to consumer delivery (including mail order pharmacies) and using technology advancement in pharmacies to better monitor and direct patients to where to receive drug.

Multiyear Budget: FDA

The FDA is responsible for ensuring that MCMs to counter CBRN and emerging and re-emerging infectious disease threats (such as pandemic influenza, MERS-CoV, and Zika virus), as well as MCMs to address antimicrobial resistance are safe, effective, and secure. In addition to its regulatory responsibilities, the FDA works closely with interagency partners through the PHEMCE to build and sustain the MCM programs necessary to respond effectively to public health emergencies. It also works with DoD to facilitate the development and availability of MCMs to support the unique needs of the warfighter.

The FDA facilitates the development of and access to safe and effective MCMs to counter high-priority CBRN and emerging infectious disease threats, as well as MCMs to address antimicrobial resistance[10] through a variety of activities, including:

- Providing regulatory advice, guidance and technical assistance to MCM developers and U.S. government agencies that support MCM development;
- Reviewing MCM marketing applications and approving those that meet standards for safety, efficacy, and quality;
- Supporting the establishment and sustainment of an adequate supply of MCMs;
- Enabling access to available MCMs that are not yet approved through an appropriate mechanism (e.g., clinical trials, expanded access, Emergency Use Authorization (EUA));
- Ensuring that MCMs used in response to threats are monitored for safety and effectiveness;
- Rapidly responding to national and global health security threats;
- Supporting regulatory science to help translate emerging technologies into innovative, safe and effective MCMs; and
- Ensuring that FDA regulations and policies adequately support MCM development and enable preparedness and response activities.

In 2010, the FDA launched its Medical Countermeasures Initiative (MCMi), building on the substantive MCM work ongoing at the FDA and focusing increased resources on promoting the development of MCMs by establishing clear regulatory pathways for MCMs, instituting effective regulatory policies and mechanisms to facilitate timely access to available MCMs, and advancing MCM regulatory science to create the tools that support regulatory decision-making.

The multiyear budget projection includes an increase of $21 million in FY 2020 for the MCMi, in addition to the three percent across-the-board increase for FDA MCM program areas included in this report (Figure 8) for a total base MCMi program level of $45.9 million. This additional funding would enable the FDA to establish a base capacity at a program level more consistent with the level that had been supported with the $170 million no-year funding received in FY 2010. For example, from FY 2011 through FY 2015, FDA supported an approximate investment in the MCMi of $52 million per year on average through a combination of budget authority and no-year funds. This resource increase is essential to the FDA's ability to foster the establishment of clear, scientifically supported regulatory pathways for MCMs as well as to fill critical scientific gaps that inform regulatory decision making and support efforts to establish regulatory policies and mechanisms to facilitate the efficient use of available MCMs.

FDA Accomplishments through FY 2017

As detailed in the MCMi Program Updates, the FDA continues to make substantial progress in facilitating the development and availability of safe and effective MCMs. Major accomplishments in FYs 2017–2018 with respect to CBRN and emerging infectious disease threats include:

- Approval of MCMs for smallpox, radiological/nuclear threats, chemical threats, and pandemic influenza;
- Working proactively with U.S. government partners, international partners, medical product developers, and others to help accelerate the development and availability of MCMs to respond to the Zika virus outbreak in the Americas. This includes issuing Emergency Use Authorizations (EUAs) to enable emergency access to eight diagnostic tests for Zika virus (in addition to 12 Zika diagnostic tests authorized for emergency use in FY 2016), granting 16 amendments to address clarifications

[10] In addition to advancing product development to address antimicrobial resistance, FDA's responsibilities with respect to addressing antimicrobial resistance include: (1) promoting the appropriate and responsible use of antibiotics in the food supply and medical settings; (2) conducting surveillance for antimicrobial resistance among foodborne bacteria and disseminating timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria; and (3) strengthening supply chains to protect consumers from substandard and counterfeit medical products (as well as from deliberate and unintended product adulteration), which helps reduce the emergence and spread of drug-resistance.

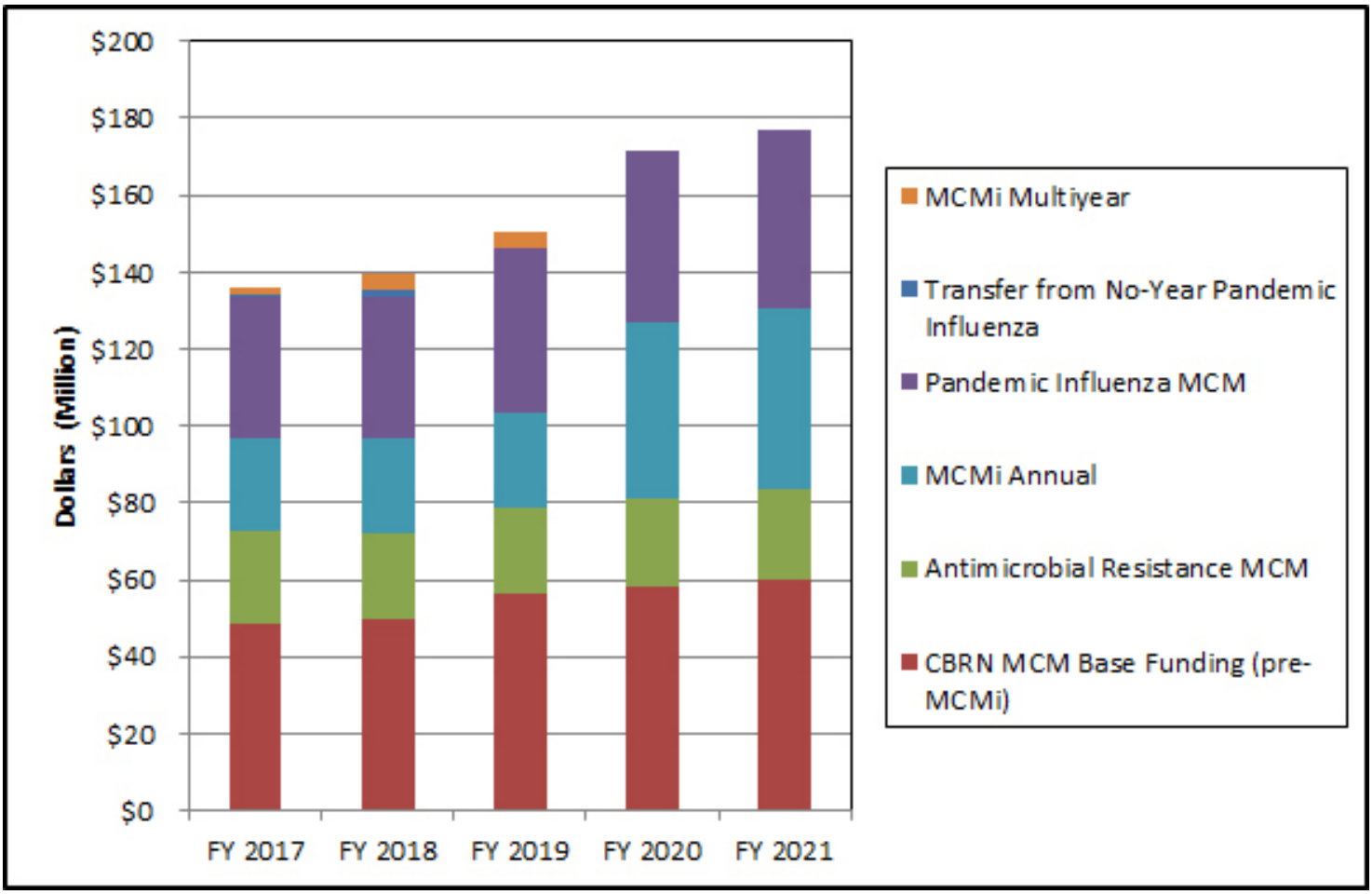


Figure 8 Estimated FDA Spending by Funding Source and Fiscal Year

or updates to the authorized diagnostic tests' labeling or Fact Sheets, approving of the first test for screening for Zika virus in blood donations, and holding eight pre-Investigational New Drug (IND) meetings for Zika vaccines and reviewing six Zika vaccine INDs from 13 different sponsors;

- Issuing an EUA enabling the emergency use of an auto-injector for an MCM to address a gap in preparedness for chemical threats;
- Testing MCM drugs submitted for shelf-life extension under the Shelf-Life Extension Program to support the sustainment of an adequate supply of MCMs in federal stockpiles and granting shelf-life extensions for 2,020 lots of MCM drugs maintained in the SNS;
- Issuing draft guidance to government public health and emergency response stakeholders on testing to extend the shelf life of doxycycline tablets or capsules to support stakeholders' efforts to sustain adequate supplies for anthrax preparedness;
- Issuing draft guidance for industry explaining how the FDA is implementing the material threat medical countermeasure priority review voucher (PRV) program;
- Issuing final guidance for industry on EUA of medical products and other related authorities;
- Issuing guidance on enforcement of FDA's regulations governing informed consent requirements for clinical investigations that involve no more minimal risk to human subjects, which helped to address DoD challenges related to development of field diagnostic devices and decision support tools
- Establishing a formal fellowship program between FDA and the DoD to support the training of DoD scientific and medical personnel in medical product development and FDA's regulatory processes; and
- Sustaining a robust MCMi Regulatory Science Program to help accelerate the FDA's ability to perform science-based review of MCMs.

With respect to efforts to address antimicrobial resistance, FDA has employed a variety of mechanisms to help speed the development and availability of medical products to address antimicrobial resistance such as accelerated

approval, fast-track designation, priority review, and breakthrough therapy designation. In addition, FDA issued a guidance that explains FDA's current thinking about possible streamlined development programs and clinical trial designs for antibacterial drugs to treat serious bacterial diseases in patients with an unmet medical need, including antibacterial drugs that are pathogen-focused and a guidance that provides information on the implementation of Title VIII of the FDA Safety and Innovation Act titled Generating Antibiotic Incentives Now (GAIN).

The FDA also continues to provide regulatory advice and guidance to MCM sponsors and applicants and U.S. government agencies funding MCM development as well as preparing for potential use of MCMs under EUA and other appropriate authorities. Additionally, the FDA continues to implement new authorities included in the 21st Century Cures Act (Public Law 114-255) to facilitate the development and availability of MCMs as well as to work closely with state and local public health authorities and responders to support preparedness and response capabilities at the state and community levels, including responding to numerous EUA- and other emergency use-related inquiries, and participating in multiple national-level workshops and meetings on legal preparedness, and FDA's roles in MCM distribution and dispensing.

FDA MCM Transitions

Regulatory responsibility for MCMs does not transition to FDA from another federal agency. The FDA's regulatory role overlaps the respective roles of NIAID, BARDA, and CDC. Generally, FDA engagement with a medical product begins when a product sponsor approaches the agency seeking guidance relating to the development and review of its investigational product. Frequently, for drugs and biologics, this relationship is initiated via a pre-investigational new drug (pre-IND) meeting (21 CFR 312.82(a)),[11] which occurs prior to the submission of an investigational new drug (IND) application.[12] If a product sponsor does not request a pre-IND meeting, then FDA's engagement on a medical product will generally begin when the sponsor submits an IND application, which is required to conduct clinical trials with the investigational product (21 CFR Part 312). The FDA's regulatory oversight of medical products continues throughout its lifecycle, even after the product is approved. The FDA will continue to work with product developers and PHEMCE partners to support MCM development and availability and to help facilitate smooth product transitions from NIAID and DoD to BARDA, and from BARDA to SNS.

[11]The text describes the process for drugs or biologics. If the investigational product is a medical device, the process would be similar, but an investigational device exemption (IDE) would be submitted instead of an IND.

[12]The primary purpose of pre-IND meetings is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of Phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND. For sponsors developing MCMs, the appropriateness of the use of the Animal Rule as a regulatory pathway (see 21 CFR 314.600-650 for drugs and 21 CFR 601.90-95 for biological products) and details of the proposed animal efficacy models may also be discussed. While pre-IND meetings are not required for submitting an IND application, FDA strongly encourages product sponsors to request pre-IND meetings.

Case Study: The 2014 Ebola Outbreak in West Africa

The response to the Ebola virus outbreak in West Africa provided a valuable case study of the PHEMCE's ability to convene its members and rapidly move products across program boundaries efficiently and effectively during a crisis. The 2015 report included a case study examining the PHEMCE's response and gave an initial description of the efforts to develop MCMs against the Ebola virus. This section updates that case study.

Viral Hemorrhagic Fevers (VHF) caused by Ebola Virus and Marburg Virus are biological threat agents posing a threat to national security as well as global public health threats. The outbreak of the Ebola virus in West African countries, which began in December 2013, highlighted the severity of the disease as well as the extreme challenges the world faces in providing adequate medical care, preventing disease transmission, and the developmental status of the MCM pipeline. With historic mortality rates for viral hemorrhagic fevers observed in natural outbreaks between 40-90 percent, the consequences would be catastrophic if Ebola or Marburg viruses were used in a terrorist incident. To save lives, the U.S. government launched an immediate, large-scale response with a substantial number of MCMs.

For more than a decade, NIH and DoD supported the early development of Ebola MCMs. Since the early 1990s, the DoD funded a long-standing program in filovirus MCM's and has had a rich portfolio of basic and pre-clinical studies and candidate products to draw upon. Following the 2001 terrorist attacks on the United States, NIAID markedly enhanced its biodefense research portfolio and supported the development and testing of candidate products to prevent or treat emerging viral hemorrhagic fevers, including those caused by Ebola. NIAID and DoD research on Ebola focuses on understanding how the Ebola virus causes illness and on developing and testing new diagnostics, vaccines, and therapeutics. As such, NIAID and DoD were well-positioned to respond rapidly to the crisis in West Africa because of these longstanding investments in biodefense and emerging infections research. Critical to these efforts are NIAID's and DoD's collaborations with PHEMCE partners as well as with academia, industry, and international organizations. Because of these longstanding investments in Ebola research and development, the PHEMCE responded rapidly to the epidemic in West Africa. BARDA is now supporting development of three immunotherapeutic and antiviral drug candidates, one that may have broad spectrum activity, and three vaccine candidates. BARDA transitioned two vaccine candidates and two therapeutic candidates to Project BioShield in FY 2017.

CDC scientists have had a long history in the development of diagnostic approaches for Ebola and Marburg, and this expertise was utilized in public private partnerships coordinated with BARDA to facilitate the use of PCR-based as well as lateral flow-based assays for Ebola in the West African response. These assays were important for the timely segregation of cases from non-cases, to prevent forward disease transmission during the response.

Therapeutics

At the beginning of the epidemic, the existing candidate therapeutic drugs that were considered potentially applicable to Ebola virus treatment were in the very early stages of development, with limited production capability. Mapp Biopharmaceutical's antibody cocktail, ZMapp, was the first therapeutic identified for immediate PHEMCE investment in response to the events of 2014. This experimental drug was in early stage development in the DoD and was first administered under "compassionate use" to several people infected with the Ebola virus during the 2014 Ebola outbreak in West Africa. The product had not been used in direct patient care prior to this compassionate use application. There was a great deal of work required to ramp up production and testing of the product for larger scale use in clinical trials. NIAID worked closely with partners at DoD, BARDA, and FDA to advance the development and testing of ZMapp. These efforts led to the launch of a clinical trial under the auspices of the Partnership for Research on Ebola Virus in Liberia (PREVAIL), a U.S. Government (via NIAID) partnership with the government of Liberia. The trial, named PREVAIL II, was testing the safety and efficacy of ZMapp in infected people at sites in West Africa and the United States. This ongoing trial, comparing treatment with ZMapp plus optimized standard of care versus optimized standard of care alone, was designed so that results can be assessed rapidly, and the protocol adjusted as needed to enable the most rapid assessment of ZMapp's safety and efficacy. While the trial results showed a potential benefit of administration of ZMapp, the trial was terminated due to the diminishing number of cases and missed the primary endpoints.

BARDA invested in ZMapp to support all necessary steps allowing for enhanced pilot-scale production of this product. The initial production method for this product required the use of tobacco plants to express the

three different monoclonal antibodies in the mixture. To mitigate the limited scale of production under this method, BARDA began to invest in other means to improve production scale, described below. Efforts are focused on optimizing the manufacturing process, analytical product lot release, clinical sample assays, and manufacturing clinical investigational lots of ZMapp for Phase III safety and efficacy clinical studies. Through the Phase 3 studies in February 2015, BARDA continued to support the development and manufacture of ZMapp using BARDA's Fill Finish Manufacturing Network for ongoing clinical studies in support of FDA approval. In addition, BARDA partnered with two manufacturers of tobacco-based products to determine whether other tobacco expression systems could produce higher yields of ZMapp in their proprietary tobacco plants. These efforts were initiated as a risk mitigation strategy to potentially expand manufacturing capacity but are no longer being pursued.

BARDA also has formed partnerships with two large pharmaceutical companies (Genentech and Regeneron) to produce monoclonal antibody therapeutics using methods that can be manufactured in larger quantities faster than tobacco-based technology. Both companies' antibody therapeutics showed promise in non-human primate studies undertaken in June 2015 with support from BARDA's Non-Clinical Studies Network. Genentech developed and produced humanized-cell versions of ZMapp monoclonal antibodies under a research agreement with Mapp Biopharmaceuticals. Genentech is expressing the antibodies in their specialized Chinese hamster ovary (CHO) mammalian cell line, a proven manufacturing platform for licensed monoclonal antibodies. In July 2015, BARDA issued a task order to Emergent, as one of BARDA's Centers for Innovation and Advanced Development and Manufacturing (CIADM), to manufacture the Genentech Ebola monoclonal antibodies for further evaluation. This effort was paused with the cessation of the outbreak. Regeneron's monoclonal antibody therapeutic also showed efficacy equivalent to ZMapp. The drug was developed with ZMapp-like and novel Ebola monoclonal antibodies that are fully humanized and expressed at high levels. Regeneron's product is currently under. Both the Mapp Bio and Regeneron products were transitioned to late-stage development and potential procurement under Project BioShield in FY 2017.

Additional candidate Ebola therapies supported by NIAID and BARDA include BioCryst's BCX4430. Further, BARDA partnered with BioCryst to support development of this small molecule antiviral drug candidate that has potential for broad spectrum activity against viral hemorrhagic fever viruses. BARDA supported manufacturing efforts and non-clinical studies to support NIAID's Phase 1 clinical studies of this molecule and supported additional Phase 1 and 2 studies in 2016. BARDA continues to work with NIAID and BioCryst on this candidate.

In FYs 2018–2019, BARDA is planning on initiating programs to develop MCMs, particularly therapeutics, to address Marburg virus and Ebola-Sudan. These programs will help BARDA develop MCMs for threat agents for which BARDA currently has no MCMs.

Lastly, a first-in-human trial evaluating an experimental treatment for Ebola virus disease began at the NIH Clinical Center in May 2018. The Phase 1 clinical trial examines the safety and tolerability of a single monoclonal antibody called mAb114, which was developed by scientists at NIAID and their collaborators. MAb114 is a monoclonal antibody—a protein that binds to a single target on a pathogen—isolated from a human survivor of the 1995 Ebola outbreak in the Democratic Republic of the Congo (DRC). NIAID VRC, in collaboration with the National Institute of Biomedical Research in the DRC and the Institute for Biomedical Research in Switzerland, discovered that the survivor retained antibodies against Ebola 11 years after infection. They isolated the antibodies and tested the most favorable ones in laboratory and non-human primate studies, and selected mAb114 as the most promising. In collaboration with the VRC, scientists at the Geisel School of Medicine at Dartmouth College illustrated that the monoclonal antibody binds to the hard-to-reach core of the Ebola virus surface protein and blocks the protein's interaction with its receptor on human cells. A single dose of mAb114 protected non-human primates for days after lethal Ebola virus infection. The antibody was developed in partnership with the U.S. Army Medical Research Institute of Infectious Diseases and the Defense Advanced Research Projects Agency and manufactured for clinical studies by the company MedImmune based in Gaithersburg, Maryland. The Phase 1 trial is currently open to accrual with enrollment expected to be completed in 2018.

Vaccines

Since 1999, the NIAID VRC has pursued multiple early-generation Ebola vaccine candidates, culminating in a vaccine candidate currently in large-scale clinical trials. VRC scientists, in collaboration with GlaxoSmithKline, developed an experimental vaccine that uses the chimpanzee adenovirus type 3 (cAd3) as a carrier, or vector, to express an Ebola virus protein designed to stimulate protective immune responses.

An NIAID-sponsored Phase II clinical trial of cAd3-EBOZ in Liberia, the PREVAIL I study. The study also evaluated an additional vaccine candidate, rVSV-EBOV, developed with support from the DoD, BARDA, and NIAID. Interim findings in more than 600 people enrolled in the PREVAIL I study, began in February 2015, indicate that the two experimental Ebola vaccines appear to be safe. The PREVAIL I trial was terminated due to the low prevalence of Ebola cases in Liberia but did show that both vaccines appeared to be safe.

NIAID also has collaborated with the biopharmaceutical industry, academia, and other federal agencies to develop additional Ebola vaccine candidates. NIAID is supporting a Phase 1 clinical trial of a prime-boost vaccine strategy composed of an adenovirus-vectored vaccine developed by Johnson & Johnson and a modified vaccinia virus Ankara-vectored vaccine developed by Bavarian Nordic. In addition, NIAID scientists are collaborating with investigators at Philadelphia's Thomas Jefferson University to produce a vaccine candidate based on an existing rabies vaccine that could generate immunity to Ebola, Marburg, and rabies viruses. The investigators plan to pursue a version of the vaccine for human and veterinary use, as well as a version for use in African wildlife that could help prevent transmission of Ebola virus from animals to humans. NIAID also is partnering with the University of Texas Medical Branch at Galveston to advance a human parainfluenza virus-vectored Ebola vaccine developed by NIAID scientists. An intranasal vaccine candidate using a second-generation version of this vector system began Phase 1 clinical trials in early 2018.

In FY 2015, BARDA awarded contracts for advanced development and manufacturing of four monovalent Ebola Zaire vaccine candidates: ChAd3 (GSK), rVSVΔG (Newlink/Merck), rVSVN4CT1 (Profectus), and Ad26/MVA (Janssen/Bavarian Nordic). These projects specifically funded manufacturing of clinical trial material, process improvements and scale-up of the manufacturing processes to commercial scale in support of an international effort by product sponsors, governments, and non-government organizations to accelerate vaccine development activities to address the 2014 West African Ebola outbreak. As a result, three of the four vaccine candidates have completed Phase 2 and/or Phase 3 clinical trials with one vaccine candidate, Newlink/Merck's rVSVΔG, demonstrating potential clinical efficacy during a ring vaccination trial conducted by the WHO and other partners in Guinea. BARDA also supported the CDC-sponsored STRIVE clinical trial. BARDA transitioned the Merck and Janssen/Bavarian Nordic candidates for late-stage development and potential procurement under Project BioShield in FY 2017. Unfortunately, the licensing and stockpiling of a monovalent vaccine against Ebola-Zaire addresses only part of the federal government's filovirus requirement. For FY 2018 and beyond, there will be a need for continued development of vaccines for Ebola-Sudan and Marburg viruses. Several of the vaccine platforms supported by NIAID, DoD, and BARDA during the 2014 Ebola outbreak can be leveraged to support the development of vaccines for Ebola-Sudan and Marburg.

BARDA also supported development of a point of care lateral flow diagnostic developed by OraSure. This product received emergency use authorization from the FDA.

The Ebola response has highlighted the importance of the core services of the National Medical Countermeasures Infrastructure Response Network established by BARDA established by BARDA. Based on experience gained in this response, BARDA is poised to respond to future emerging and infectious diseases.

The response to the Ebola virus outbreak also highlighted the desire to access investigational MCMs in the face of an emerging infectious disease with high mortality for which there are no proven treatments or vaccines. From early in the outbreak, there was significant interest in exploring the possibilities to provide access to unproven MCMs to prevent, treat and diagnose Ebola. FDA worked throughout the epidemic to facilitate access to investigational MCMs as necessary and appropriate through the most appropriate mechanism. For example, FDA enabled access to investigational drugs and vaccines outside of clinical trials prior to the establishment of clinical trials through its expanded access mechanism when such access had been granted by the product sponsor and the clinical circumstances warranted. In addition, FDA authorized the use of 10 investigational diagnostic tests for Ebola under its Emergency Use Authorization authority.

Conclusion

This report represents HHS's current estimates for the basic research, advanced research and development, regulatory review and approval, procurement, stockpiling, and replenishment of the United States government's civilian medical countermeasure enterprise. This budget forecast is provided without regard to the competing priorities that the Secretary, other HHS officials, and the President must consider as the President's Budget is developed.

The PHEMCE successfully delivered medical products to the SNS that mitigate the risk presented by the most important threats to the nation. It did so with a continuous focus on being effective stewards of the resources that have been provided by Congress. Since its inception, the PHEMCE targeted resources to the high-priority threats and as a result has a ready stockpile of MCMs against anthrax, smallpox, and botulinum. In recent years, the PHEMCE expanded its capabilities by procuring MCMs against chemical, radiological, and nuclear threats. Additionally, PHEMCE prioritizes the needs of special or vulnerable populations, such as children, pregnant women, the immunocompromised, in the development of products and technologies.

The PHEMCE also is implementing the provisions in the 21st Century Cures Act. This includes integrating acquisitions management directly into BARDA and initiating the new Division of Research Innovation and Ventures (DRIVe). DRIVe's goals include creating universal treatment options for broad classes of pathogens, ensuring access to life-saving medical countermeasures for all Americans, transforming the process by which medical countermeasures are developed (non-animal testing). Inaugural areas of impact for DRIVe include solving sepsis, and Early Notification to Act, Control and Treat (ENACT) infectious diseases.[13] The PHEMCE maintains its commitment to progress also by improving MCM response capabilities and identifying the need for a 20 percent increase in total forecasted funding relative to the FYs 2016–2020 Report. The increase in estimated funding is a result of a more comprehensive assessment of the cost to develop and maintain the SNS formulary, especially products initially procured by BARDA under Project BioShield, that are anticipated to achieve FDA approval or licensure and require replacement during this report's timeframe. The FY 2019 President's Budget signaled the transfer of the SNS to ASPR. Putting the SNS under ASPR will consolidate strategic decision-making around the development and procurement of medical countermeasures and streamlines leadership to enable nimble responses to public health emergencies. Efficiencies across the medical countermeasure enterprise are expected. In coordination with the PHEMCE, the SNS will develop strategies to meet the national priorities for federal stockpiling, to maintain and improve SNS capabilities, and to address inventory gaps. Through these strategies, the enterprise will be more sustainable, productive, and effective at developing, stockpiling, and deploying the medical countermeasures needed to save lives and protect America from 21st Century health security threats.

For several years, the PHEMCE has faced difficult decisions regarding the SNS formulary due to existing MCM requirements and successful Project BioShield products successfully achieving licensing or approval, while the SNS' purchasing power has remained essentially unchanged. Plans for completing the 2017 SNS Annual Review (Fiscal Year 2020 Plan) are under review.

The PHEMCE faces the challenge of maintaining a stockpile of MCMs against a plethora of low-probability, high-consequence threats, while maintaining the capacity to rapidly respond to novel threats like emerging or re-emerging infectious diseases. To stretch the taxpayer dollar further, the PHEMCE is examining new mechanisms for reducing development and stockpiling costs. These include new public-private partnerships to reduce development costs, vendor-managed inventory of commercially available drugs to reduce replenishment costs, and the development of next-generation MCMs.

[13] https://drive.hhs.gov/about.html

Appendix A – Spend Plan Tables

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2017 - FY 2021 Total
ASPR	BARDA	Direct Appropriation, Multiyear	Anthrax	Therapeutics	$5.5	$0.0	$0.0	$0.0	$0.0	$5.5
ASPR	BARDA	Direct Appropriation, Multiyear	Anthrax	Vaccine	$24.2	$20.0	$20.0	$30.0	$35.0	$129.2
ASPR	BARDA	Direct Appropriation, Multiyear	Botulinum	Next generation candidates	$0.0	$0.0	$0.0	$10.0	$25.0	$35.0
ASPR	BARDA	Direct Appropriation, Multiyear	BARDA EID		$0.0	$0.0	$0.0	$200.0	$200.0	$400.0
ASPR	BARDA	Direct Appropriation, Multiyear	BARDA Innovation		$5.0	$1.0	$0.0	$0.0	$0.0	$6.0
ASPR	BARDA	Direct Appropriation, Multiyear	BARDA MCIP	Medical Countermeasures Innovation	$0.0	$25.0	$0.0	$75.0	$75.0	$175.0
ASPR	BARDA	Direct Appropriation, Multiyear	BARDA Mgt & Admin		$71.6	$60.0	$60.0	$60.0	$60.0	$311.6
ASPR	BARDA	Direct Appropriation, Multiyear	Broad Spectrum Antimicrobials	BARDA CARB	$107.0	$107.0	$107.0	$107.0	$107.0	$535.0
ASPR	BARDA	Direct Appropriation, Multiyear	Broad Spectrum Antimicrobials		$112.3	$85.0	$85.0	$123.0	$123.0	$528.3
ASPR	BARDA	Direct Appropriation, Multiyear	Chemical		$34.2	$50.0	$50.0	$105.0	$115.0	$354.2
ASPR	BARDA	Direct Appropriation, Multiyear	Cross-Cutting Science	Animal Models	$11.6	$11.0	$11.0	$30.0	$30.0	$93.6
ASPR	BARDA	Direct Appropriation, Multiyear	Cross-Cutting Science	Clinical Services Network	$1.0	$1.0	$1.0	$5.0	$5.0	$13.0
ASPR	BARDA	Direct Appropriation, Multiyear	Filoviruses		$11.3	$30.0	$30.0	$40.0	$40.0	$151.3
ASPR	BARDA	Direct Appropriation, Multiyear	Rad/Nuc	ARS - Neutropenia/ Skin/ Lung/GI	$84.5	$57.0	$60.0	$100.0	$100.0	$401.5
ASPR	BARDA	Direct Appropriation, Multiyear	Rad/Nuc	Biodosimetry and Biodiagnostics	$41.0	$50.0	$48.0	$30.0	$30.0	$199.0
ASPR	BARDA	Direct Appropriation, Multiyear	Rad/Nuc	Thermal Burn Products	$24.4	$25.0	$25.0	$50.0	$50.0	$174.4
ASPR	BARDA	Direct Appropriation, Multiyear	Smallpox	Vaccine/Antivirals	$12.4	$15.0	$15.0	$30.0	$30.0	$102.4

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2017 - FY 2021 Total
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	Diagnostics Advanced Development	$0.6	$0.0	$0.0	$6.0	$5.8	$12.4
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	Fill/Finish Network	$0.0	$0.0	$0.0	$0.0	$3.0	$3.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	International Vaccine Manufacturing Initiative	$0.0	$0.0	$0.0	$15.0	$15.0	$30.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	Vaccine Stockpile, Storage, Stability, and Testing	$9.4	$2.1	$33.0	$40.0	$150.0	$234.5
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	Vaccine Advanced Development	$0.0	$25.9	$0.0	$0.0	$0.0	$25.9
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Antigen Sparing Vx AD	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	CIADM	$0.0	$0.0	$0.0	$0.0	$10.0	$10.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Diagnostics Advanced Development	$8.2	$5.5	$15.0	$31.0	$30.0	$89.7
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Fill/Finish Network	$1.5	$2.7	$0.0	$0.0	$3.0	$7.2
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Infrastructure	$0.0	$88.8	$123.0	$119.2	$188.2	$519.2
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Therapeutics Advanced Development	$27.3	$49.3	$42.0	$234.5	$278.9	$632.1
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Vaccine Advanced Development	$5.0	$48.7	$30.0	$160.2	$205.2	$449.1

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2017 - FY 2021 Total
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Vaccine Stockpile, Storage, Stability, and Testing	$12.9	$10.0	$0.0	$132.0	$20.0	$174.9
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Ventilators / Respirators	$0.0	$0.0	$0.0	$5.0	$5.0	$10.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	MCM Innovation	$0.0	$10.0	$0.0	$32.0	$35.0	$77.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Diagnostics Advanced Development	$0.1	$0.0	$0.0	$0.0	$0.0	$0.1
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	H7N9 Mfg & Procurement	$72.0	$0.0	$0.0	$0.0	$0.0	$72.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Infrastructure	$60.1	$0.0	$55.9	$0.0	$0.0	$116.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Therapeutics Advanced Development	$30.5	$0.0	$60.0	$0.0	$0.0	$90.5
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Vaccine Advanced Development	$23.6	$0.0	$91.5	$0.0	$0.0	$115.1
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Vaccine Stockpile, Storage, Stability, and Testing	$10.3	$0.0	$45.0	$0.0	$0.0	$55.3
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Fill/Finish Network	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ASPR	BARDA	Project BioShield SRF, No-Year	Anthrax	Therapeutics	$0.0	$24.0	$0.0	$0.0	$0.0	$24.0
ASPR	BARDA	Project BioShield SRF, No-Year	Anthrax	Vaccine	$100.5	$30.0	$150.0	$200.0	$200.0	$680.5
ASPR	BARDA	Project BioShield SRF, No-Year	Botulinum	Botulinum Antitoxin	$53.3	$2.4	$0.0	$0.0	$0.0	$55.7
ASPR	BARDA	Project BioShield SRF, No-Year	Broad Spectrum Antimicrobials		$0.0	$0.0	$60.0	$120.0	$140.0	$320.0

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2017 - FY 2021 Total
ASPR	BARDA	Project BioShield SRF, No-Year	Chemical	Chemical Countermeasures	$0.0	$0.7	$25.0	$150.0	$200.0	$375.7
ASPR	BARDA	Project BioShield SRF, No-Year	Filoviruses	Ebola	$171.9	$277.5	$150.0	$250.0	$250.0	$1,099.4
ASPR	BARDA	Project BioShield SRF, No-Year	Rad/Nuc	ARS - Skin/Lung/GI	$0.0	$205.0	$35.0	$100.0	$100.0	$440.0
ASPR	BARDA	Project BioShield SRF, No-Year	Rad/Nuc	Biodosimetry	$50.0	$0.3	$0.0	$25.0	$25.0	$100.3
ASPR	BARDA	Project BioShield SRF, No-Year	Rad/Nuc	Thermal Burns	$56.0	$30.0	$5.0	$50.0	$75.0	$216.0
ASPR	BARDA	Project BioShield SRF, No-Year	Smallpox	Antivirals	$0.0	$102.7	$35.0	$0.0	$0.0	$137.7
ASPR	BARDA	Project BioShield SRF, No-Year	Smallpox	Vaccine	$100.0	$37.0	$50.0	$0.0	$0.0	$187.0
NIH	NIAID	Direct Appropriation, Annual	Anthrax	Basic/Other Research	$7.7	$8.3	$7.5	$7.7	$7.9	$39.2
NIH	NIAID	Direct Appropriation, Annual	Anthrax	Vaccine	$27.2	$29.4	$26.6	$27.3	$28.1	$138.6
NIH	NIAID	Direct Appropriation, Annual	Botulinum	Antitoxins	$5.2	$5.6	$5.1	$5.2	$5.4	$26.5
NIH	NIAID	Direct Appropriation, Annual	Botulinum	Basic/Other Research	$2.3	$2.4	$2.2	$2.3	$2.3	$11.5
NIH	NIAID	Direct Appropriation, Annual	Botulinum	Vaccine	$0.7	$0.7	$0.6	$0.7	$0.7	$3.4
NIH	NIAID	Direct Appropriation, Annual	Broad Spectrum Antimicrobials	Antibiotics	$282.1	$332.1	$300.6	$309.0	$317.7	$1,541.5
NIH	NIAID	Direct Appropriation, Annual	Broad Spectrum Antimicrobials	Antivirals	$112.2	$121.0	$109.5	$112.6	$115.8	$571.1
NIH	NIAID	Direct Appropriation, Annual	Cross-Cutting Science	Animal Models/Regulatory Science	$25.1	$27.1	$24.5	$25.2	$25.9	$127.8
NIH	NIAID	Direct Appropriation, Annual	Cross-Cutting Science	Basic/Other Research	$264.4	$285.3	$258.2	$265.4	$272.9	$1,346.3
NIH	NIAID	Direct Appropriation, Annual	Cross-Cutting Science	Product Development	$187.7	$202.6	$183.3	$188.4	$193.7	$955.7
NIH	NIAID	Direct Appropriation, Annual	Cross-Cutting Science	Translational	$98.1	$105.9	$95.8	$98.5	$101.3	$499.5

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2017 - FY 2021 Total
NIH	NIAID	Direct Appropriation, Annual	Filoviruses	Basic/Other Research	$45.6	$49.2	$44.5	$45.7	$47.0	$232.0
NIH	NIAID	Direct Appropriation, Annual	Filoviruses	Vaccine	$23.9	$25.8	$23.4	$24.0	$24.7	$121.8
NIH	NIAID	Direct Appropriation, Annual	Multiplex Diagnostics	Diagnostics	$60.0	$64.8	$58.6	$60.2	$61.9	$305.6
NIH	NIAID	Direct Appropriation, Annual	Pandemic Influenza	Basic/Other Research	$101.3	$109.3	$98.9	$101.7	$104.5	$515.8
NIH	NIAID	Direct Appropriation, Annual	Pandemic Influenza	Vaccine	$87.4	$127.4	$115.3	$118.5	$121.8	$570.4
NIH	NIAID	Direct Appropriation, Annual	Other Threats	Basic/Other Research	$381.4	$411.5	$372.4	$382.8	$393.6	$1,941.8
NIH	NIAID	Direct Appropriation, Annual	Other Threats	Vaccine	$101.7	$109.8	$99.3	$102.1	$105.0	$518.0
NIH	NIAID	Direct Appropriation, Annual	Plague/Tularemia	Basic/Other Research	$11.0	$11.8	$10.7	$11.0	$11.3	$55.8
NIH	NIAID	Direct Appropriation, Annual	Plague/Tularemia	Vaccine	$4.4	$4.8	$4.3	$4.4	$4.6	$22.5
NIH	NIAID	Direct Appropriation, Annual	Smallpox	Basic/Other Research	$11.6	$12.5	$11.3	$11.6	$11.9	$58.9
NIH	NIAID	Direct Appropriation, Annual	Smallpox	Vaccine	$1.1	$1.2	$1.1	$1.1	$1.2	$5.8
NIH	NIAID	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Vaccine Advanced Development	$0.0	$15.0	$0.0	$0.0	$0.0	$15.0
NIH	Non-NIAID	Direct Appropriation, Annual	Broad Spectrum Antimicrobials	Antibiotics/Antiviral	$2.0	$2.1	$2.0	$2.0	$2.1	$10.2
NIH	Non-NIAID	Direct Appropriation, Annual	Multiplex Diagnostics	Diagnostics	$1.6	$1.6	$1.5	$1.6	$1.6	$7.9
NIH	Non-NIAID	Direct Appropriation, Annual	Other Threats	Basic/Other Research	$24.1	$25.4	$23.7	$24.3	$25.0	$122.5
NIH	Non-NIAID	Direct Appropriation, Annual	Other Threats	Vaccine	$0.5	$0.5	$0.5	$0.5	$0.5	$2.3
NIH	Non-NIAID	Transfer from No-Year PI Funding	Pandemic Influenza	Vaccine	$43.6	$22.4	$0.0	$0.0	$0.0	$66.0
NIH	OD	Direct Appropriation, Annual	Chemical	Chemical Countermeasures Research	$47.5	$49.2	$45.8	$47.1	$48.4	$238.0

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2017 - FY 2021 Total
NIH	OD	Direct Appropriation, Annual	Rad/Nuc	Nuclear/Radiological Countermeasures	$45.9	$47.9	$44.7	$45.9	$47.2	$231.6
NIH	OD	Ebola Emergency Funding, Multiyear, Direct	Broad Spectrum Antimicrobials	Antivirals	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
NIH	OD	Ebola Emergency Funding, Multiyear, Direct	Filoviruses	Basic/Other Research	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
NIH	OD	Ebola Emergency Funding, Multiyear, Direct	Filoviruses	Vaccine	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
NIH	OD	Ebola Emergency Funding, Multiyear, Direct	Multiplex Diagnostics	Diagnostics	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
NIH	OD	Zika Emergency Funding, Multiyear, Direct	Multiplex Diagnostics	Diagnostics	$11.9	$0.0	$0.0	$0.0	$0.0	$11.9
NIH	OD	Zika Emergency Funding, Multiyear, Direct	Other Threats	Basic/Other Research	$9.4	$0.0	$0.0	$0.0	$0.0	$9.4
NIH	OD	Zika Emergency Funding, Multiyear, Direct	Other Threats	Vaccine	$130.7	$0.0	$0.0	$0.0	$0.0	$130.7
ASPR	DSNS	Direct Appropriation, No-Year	Ancillary	Other supportive (incl. antimicrobials)	$16.9	$21.0	$27.2	$18.1	$32.4	$115.5
ASPR	DSNS	Direct Appropriation, No-Year	Anthrax	Antibiotic	$12.8	$130.6	$89.9	$114.4	$74.6	$422.4
ASPR	DSNS	Direct Appropriation, No-Year	Anthrax	Therapeutic	$0.0	$0.0	$36.0	$152.2	$150.1	$338.3
ASPR	DSNS	Direct Appropriation, No-Year	Anthrax	Vaccine	$143.4	$55.5	$0.0	$0.0	$0.0	$198.9
ASPR	DSNS	Direct Appropriation, No-Year	Botulinum	Therapeutic	$0.0	$0.0	$0.0	$250.0	$0.0	$250.0
ASPR	DSNS	Direct Appropriation, No-Year	Burkholderia	Antibiotic	$6.2	$0.7	$0.6	$0.3	$0.6	$8.5
ASPR	DSNS	Direct Appropriation, No-Year	Chemical	Anticonvulsant	$0.0	$0.0	$0.6	$1.2	$3.2	$4.9

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2017 - FY 2021 Total
ASPR	DSNS	Direct Appropriation, No-Year	Chemical	Nerve agent antidote	$48.7	$15.5	$33.4	$38.1	$46.7	$182.4
ASPR	DSNS	Direct Appropriation, No-Year	FMS	Antibiotic	$0.1	$0.3	$1.1	$0.3	$1.1	$2.7
ASPR	DSNS	Direct Appropriation, No-Year	Pandemic Influenza	Antiviral	$50.0	$104.1	$108.5	$35.9	$28.3	$326.8
ASPR	DSNS	Direct Appropriation, No-Year	Pandemic Influenza	Other supportive (incl. antimicrobials)	$0.0	$15.0	$15.0	$15.0	$15.0	$60.0
ASPR	DSNS	Direct Appropriation, No-Year	Plague/Tularemia	Antibiotic	$0.0	$0.0	$0.0	$7.6	$1.3	$8.9
ASPR	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Antibiotic	$0.3	$0.0	$0.3	$0.0	$0.3	$0.9
ASPR	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Antineutropenic	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ASPR	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Antiviral	$0.2	$0.5	$0.3	$0.5	$0.3	$1.7
ASPR	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Decorporation	$3.0	$0.0	$0.0	$0.0	$0.4	$3.4
ASPR	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Other	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ASPR	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Other supportive (incl. antimicrobials)	$3.5	$9.0	$10.3	$37.1	$10.1	$70.1
ASPR	DSNS	Direct Appropriation, No-Year	Smallpox	Antiviral	$0.9	$0.7	$0.9	$120.1	$84.2	$206.7
ASPR	DSNS	Direct Appropriation, No-Year	Smallpox	Therapeutic	$0.0	$12.9	$12.9	$46.7	$36.9	$109.4
ASPR	DSNS	Direct Appropriation, No-Year	Smallpox	Uricosuric	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ASPR	DSNS	Direct Appropriation, No-Year	Smallpox	Vaccine	$37.3	$50.5	$38.6	$162.8	$112.8	$401.9
ASPR	DSNS	Direct Appropriation, No-Year	SNS Non-Procurement Costs		$251.7	$193.7	$199.5	$205.5	$211.6	$1,062.0
FDA	MCM Initiative	Direct Appropriation, Annual	FDA Regulatory Science	Antimicrobial Resistance MCM	$24.2	$22.4	$22.3	$23.0	$23.7	$115.5
FDA	MCM Initiative	Direct Appropriation, Annual	FDA Regulatory Science	CBRN MCM Base Funding (pre-MCMi)	$48.3	$49.8	$56.4	$58.1	$59.8	$272.4

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2017 - FY 2021 Total
FDA	MCM Initiative	Direct Appropriation, Annual	FDA Regulatory Science	MCMi Annual	$24.6	$24.6	$24.6	$45.9	$47.3	$166.9
FDA	MCM Initiative	Direct Appropriation, Annual	FDA Regulatory Science	Pandemic Influenza MCM	$36.3	$36.7	$43.3	$44.5	$45.9	$206.7
FDA	MCM Initiative	Ebola Emergency Funding, Multiyear, Direct	FDA Regulatory Science	Ebola Emergency	$2.9	$0.0	$0.0	$0.0	$0.0	$2.9
FDA	MCM Initiative	Transfer from No-Year PI Funding	FDA Regulatory Science	Transfer from No-Year Pandemic Influenza	$1.0	$2.1	$0.0	$0.0	$0.0	$3.1
FDA	MCM Initiative	Direct Appropriation, Multiyear	FDA Regulatory Science	MCMi Multiyear	$1.8	$4.1	$4.1	$0.0	$0.0	$10.0

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