U.S. Department of Health and Human Services

Public Health Emergency Medical Countermeasures Enterprise Multiyear Budget

Fiscal Years 2016-2020

PUBLIC HEALTH EMERGENCY
PHEMCE
MEDICAL COUNTERMEASURES ENTERPRISE

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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 third submission in response to that requirement. The 21st Century Cures Act further amended the PHS Act to require the MYB to be submitted to Congress and be made publicly available no later than March 15 each year and in a manner that does not compromise national security. Completion of the FY 2018 President's Budget as well as passage of the Consolidated Appropriations Act, 2017, delayed the transmission of this report.

For the five-year period FYs 2016–2020, the PHEMCE estimates total spending will total $20.4 billion, a $271 million, or 1 percent, decrease compared with the projections in the 2015 PHEMCE MYB Report, which had a five-year total of $20.7 billion. The report includes enacted levels for FY 2017 and the President's Budget request for FY 2018. The five-year funding total includes aggregated MCM-related spending estimates for the National Institutes of Health (NIH), $8.2 billion, a $1.2 billion, or a 13 percent decrease; ASPR, $8.6 billion, a $1.1 billion, or a 15 percent increase; the Centers for Disease Control and Prevention (CDC), $2.9 billion, a $258 million, or 8 percent decrease; and the Food and Drug Administration (FDA), $751 million, a $49 million, or a 7 percent increase; compared to the 2015 Report. Within individual threat areas or portfolios across the PHEMCE, this total reflects budget increases in filoviruses, smallpox, chemical threats, cross-cutting science, and botulinum. Portfolios with net decreases include NIH's other threats, pandemic influenza, broad spectrum antimicrobials, anthrax, and radiological and nuclear threats. The out-year funding levels (FY 2019 and FY 2020) 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.

The following summary describes estimated spending by threat for the cumulative five-year period and the change relative to the last year's report:

Broad Spectrum Antimicrobials: $3.3 billion, which represents a decrease of $67 million (-2 percent), for new products to address gaps in antimicrobial needs for threats caused by gram negative bacteria (broad-spectrum antimicrobials). These investments are consistent with objectives in the *National Strategy for Combating Antibiotic Resistant Bacteria*.

Pandemic Influenza: $3.1 billion, which represents a decrease of $251 million (-8 percent), across NIH, ASPR, FDA and CDC, 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).

NIH Cross-Cutting Science Portfolio: $2.3 billion, which represents an increase of $45 million (+2 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: $1.9 billion, which represents a decrease of $774 million (-28 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: $1.8 billion, which represents a decrease of $92 million (-5 percent). This portfolio supports the development, procurement and licensure of the next-generation anthrax vaccine, NuThrax, as well as anthrax therapeutics.

Radiological and Nuclear Threats: $1.5 billion, which represents a decrease of $138 million (-8 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): $1.1 billion, which represents an increase of $240 million (+29 percent), to support activities associated with the transition of MCM candidates from early development supported by the NIH and the Department of Defense into advanced development at the Biomedical Advanced Research and Development Authority (BARDA), an office within ASPR. 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, attaining the ability to manufacture these MCMs at commercial scale, and ultimately procurement of vaccine and therapeutic MCMs. BARDA anticipates transition of vaccine and therapeutic candidates to Project BioShield (PBS) in FY 2017 which accounts for a portion of the increase.

Smallpox: $844 million, which represents an increase of $167 million (+25 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 stockpiles.

Chemical Threats: $821 million, which represents an increase of $120 million (+17 percent), including research at NIAID, the National Institute of Neurological Disorders and Stroke, and other NIH institutes, for the development of safe and more effective therapeutics to treat exposure to nerve agents, vesicating chemicals, pulmonary agents, and toxic industrial chemicals.

The remaining funds ($3.8 billion) for the five-year period are allocated to other threats, portfolios, associated, and administrative costs. More information is available in the section on PHEMCE-Wide Findings.

This 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 facilitate the organization's success. The PHEMCE built an Advanced Research and Development pipeline with more than 200 products, stockpiling 14 countermeasures in the Strategic National Stockpile (SNS), managed by CDC, that are available during a public health emergency and achieving FDA approval of 23 products since 2007. In 2016, the PHEMCE quickly increased attention in response to the Zika virus epidemic in the Western Hemisphere, and rapidly moved to develop diagnostic assays to

identify Zika virus infections and assays to screen the blood supply, develop novel vaccines, and establish other research efforts to evaluate potential therapeutics aimed at infected individuals. Zika presented very unique issues due to its impact on developing fetuses, and the potential to be spread by sexual contact, in addition to its mosquito-borne transmission. Other work in Zika was aimed at vector control including the development of novel mosquito repellents and toxicants.

Cost estimates for the HHS PHEMCE agencies are equal to actual appropriations in FY 2016 and FY 2017, the FY 2018 President's Budget, and use a professional judgment budget to estimate potential investments for two future years (FYs 2019–2020). For FY 2016, the data are consistent with the Consolidated Appropriations Act, 2016. For FY 2017, the data are consistent with the Consolidated Appropriations Act, 2017. The FY 2018 funding estimates are equal to those contained in the FY 2018 President's Budget. The out-year funding levels (FYs 2019–2020) were developed without regard to the competing priorities considered in the budget development process. These priorities must be considered as future President's Budgets are developed. The spending estimates included herein are subject to change in the future.

In addition to detailing estimated spending, this report describes major improvements and advances in other activities that contribute to PHEMCE outcomes. The PHEMCE is realizing greater efficiency by developing a portfolio tracking tool that examines the advanced development of MCMs in the U.S., Canada, the United Kingdom, and Australia. An additional tool—the portfolio cost tool— is under development that will model the costs associated with advanced development across the MCM portfolios within the United States government programs. To reduce costs throughout a product's lifespan, decisions about formulation and use often need to be made early in the development process. BARDA developed the Total Life Cycle Cost Containment Model and is working with industry partners to examine how a product's characteristics affect procurement and replenishment costs. Finally, ASPR's contracting office, the Office of Acquisitions Management, Contracts, and Grants, reduced the average number of days to award a solicitation from 315 days to 68 days in the last five years.

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 for products stored at the SNS. These costs include: storage, security, overhead, etc. 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.

All told, the PHEMCE has greatly expanded the readiness posture of the United States against a range of potential threats. The agencies of the PHEMCE have also followed one of the PHEMCE core principals to be good stewards of the federal funds that have been provided, in order to return value to the U.S. taxpayer.

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 in order 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 agency partners: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and 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 *2016 Public Health Emergency Medical Countermeasures Enterprise Multiyear Budget, FY 2016–2020,* 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.[1] The report consolidates PHEMCE budget planning 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 FYs 2016–2020 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-consuming, risky, and expensive endeavor, requiring substantial coordination among federal agencies, and the concerted efforts of commercial partners. Prioritizing agency 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

[1] 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.

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 at the CDC's 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 31 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 at the SNS by 2020. These MCMs will not yet have achieved FDA approval at the time of stockpiling, 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.[2] For the reporting period covered in this report, these MCMs procured under PBS would remain the financial responsibility of BARDA. CDC will be responsible for the replenishment costs of those MCMs procured by BARDA under PBS after those products achieve FDA approval. CDC procures all other commercially available, FDA-approved materials for the SNS. As such, a primary budgetary issue facing the PHEMCE is the relative financial resource requirements for PBS and SNS.

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 PHS Act added by section 102 of the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013. Cost estimates for the HHS PHEMCE agencies reflect actual appropriations in FY 2016 and FY 2017, the amounts requested in the FY 2018 President's Budget, and potential investments for two future years (FYs 2019–2020). For FY 2016, the data are consistent with the Consolidated Appropriations Act, 2016, and exclude emergency supplemental appropriations and transfers for Zika. For FY 2017, the data

[2] 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 authorize the "emergency use" of MCMs 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.

are consistent with the Consolidated Appropriations Act, 2017.[3] For 2018, the amounts are identical to those requested by the four HHS PHEMCE agencies in the FY 2018 President's budget.

For FYs 2019 and 2020, funding estimates are to support MCM-related activities, including research, development, and/or procurement of MCMs. (Estimates for procurement costs are point-in-time estimates, and they may change in future reports to reflect current market prices.) NIH's inflationary increase in the out-years is 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. CDC assumed funding levels necessary to maintain the current SNS inventory and FDA assumed a three percent increase for each of FY 2019 and 2020. The out-year funding levels (FY 2019 and FY 2020) 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.

The 21st Century Cures Act further amended the PHS Act to require the MYB to be submitted to Congress and be made publicly available no later than March 15 each year and in a manner that does not compromise national security. This report complies with that requirement.

[3] The FY 2017 Omnibus (H.R.244) recently provided the FDA with $10 million in no-year funding to "to prevent, prepare for, and respond to emerging health threats, including the Ebola and Zika viruses, domestically and internationally and to develop necessary medical countermeasures and vaccines, including the review, regulation, and post market surveillance of vaccines and therapies, and for related administrative activities." The FDA is developing a spend plan for this funding and it is not included in FDA's total.

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, CDC, ASPR, and FDA. This section presents PHEMCE-level information in two different approaches: first as an aggregated approach, and second, as a more granular, agency level to highlight accomplishments and projections over the course of the five-year period. The PHEMCE does not itself expend any appropriations, but helps to coordinate those appropriations to achieve the Department's overall objectives.

In total, the four HHS agencies spent $3.7 billion on MCMs and MCM-related activities in FY 2016 (Table 1). Spending across the agencies is broken down as follows: NIH, $1.9 billion; ASPR, $1.1 billion; CDC, $575 million; and FDA, $137 million. (Additional details for spending estimates are presented in Appendix A – Spend Plan Tables.) PHEMCE investments for the five-year period total $20.4 billion, a $271 million, or 1 percent, decrease compared with the projections in the 2015 Report. This five-year total includes aggregated MCM-related funding estimates for NIH, $8.2 billion, a $1.2 billion or a 13 percent decrease; ASPR, $8.6 billion, a $1.1 billion or a 15 percent increase; CDC, $2.9 billion, a $258 million or an 8 percent decrease; and FDA $751 million, a $49 million or a 7 percent increase, as compared to the 2015 Report.

Agency	FY '16	FY '17	FY '18	FY '19	FY '20	Total
ASPR	$1,068	$1,330	$1,222	$2,206	$2,738	$8,563
CDC	$575	$575	$575	$590	$602	$2,917
FDA	$137	$140	$142	$165	$166	$751
NIH	$1,878	$2,039	$1,374	$1,415	$1,460	$8,167
Total	$3,658	$4,085	$3,313	$4,376	$4,966	$20,398

Table 1: Estimated Total PHEMCE Spending by Agency and Fiscal Year (Dollars in Millions)

Threat-Based Approaches

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

Figure 1 depicts estimated PHEMCE spending by portfolio for FYs 2016–2020. As ranked by cumulative estimated spending, PHEMCE's investments reflect the priorities established in the 2016 PHEMCE SIP. Consistent with the *National Strategy for Combating Antibiotic Resistant Bacteria*, one of the largest estimates is for new products to address gaps in antimicrobial needs for threats caused by gram-negative bacteria (broad-spectrum antimicrobials), totaling $3.3 billion over five years, which represents a decrease of $67 million (-2 percent). (Decreases noted here and below are decreases from the estimates contained in the 2015 MYB Report).

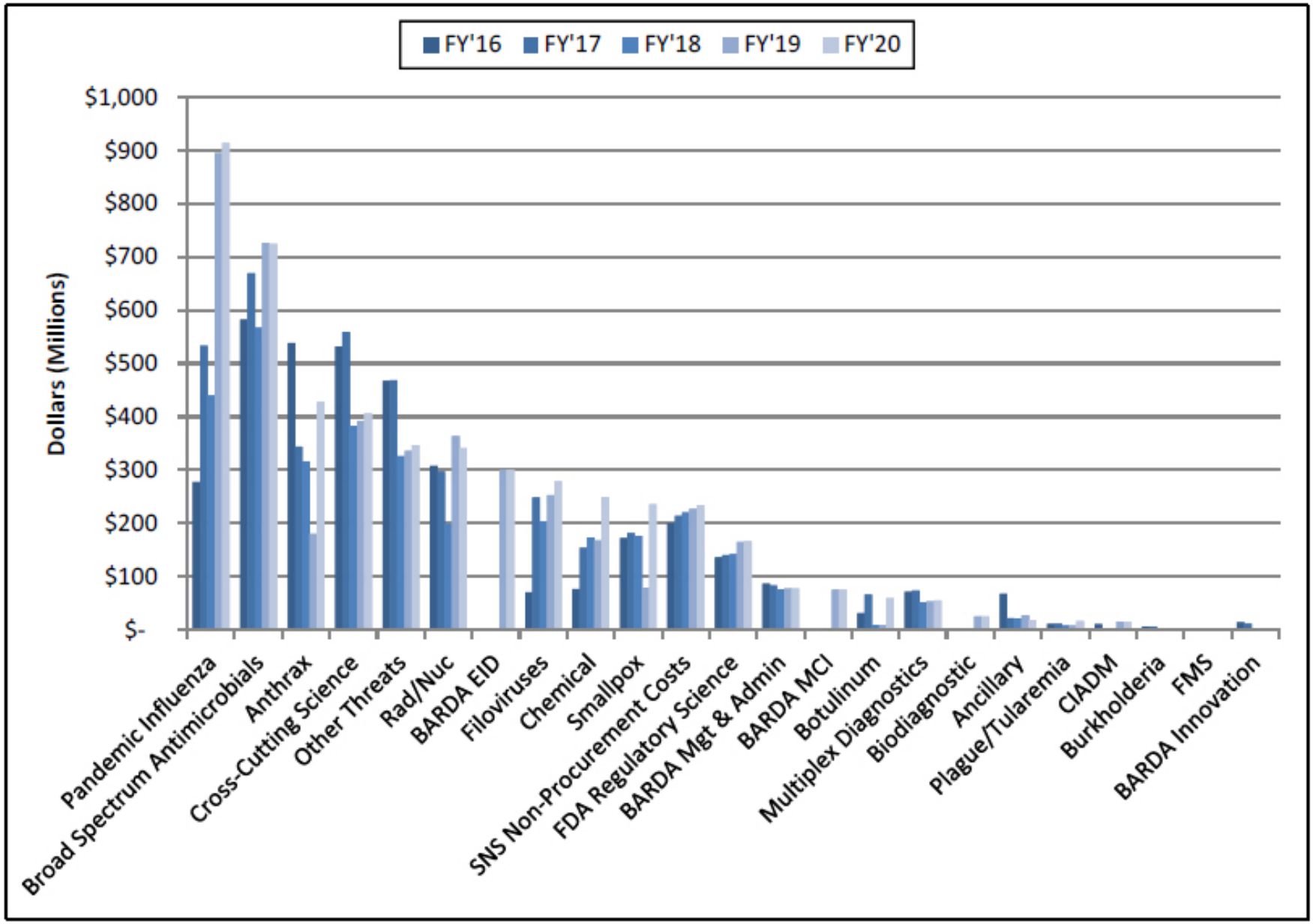


Figure 1: Estimated PHEMCE Spending by Portfolio and Fiscal Year

Across NIH, BARDA, CDC, and FDA, estimated spending on pandemic influenza is $3.1 billion over the five-year period, which represents a decrease of $251 million (-8 percent). Despite the decrease relative to the 2015 Report, the spending forecast for FY 2019 and FY 2020 increases significantly at BARDA. This increase is critical to support achievement and sustainment of pandemic preparedness. The 2017 National Pandemic Influenza Plan establishes a goal 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."[4] To attain this goal, 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, universal influenza vaccines, home-use diagnostics, as well as reusable respirators, and universal portable ventilators.

Cross-Cutting Science includes 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 $2.3 billion, which represents an increase of $45 million (+2 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, water-borne 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 $1.9 billion, which represents a decrease of $774 million (-28 percent).

The next largest threat-specific investment is the anthrax portfolio, with total estimated spending of $1.8 billion over the five-year period, which represents a decrease of $92 million (-5 percent). This portfolio supports the development, procurement and approval of the next-generation anthrax vaccine, NuThrax, as well as anthrax therapeutics. Relative to last year's report, CDC's replenishment costs decrease due to the forecasted procurement of NuThrax, a new anthrax vaccine adsorbed (AVA) that includes adjuvant, by BARDA. This new procurement would meet anthrax vaccine requirements starting in FY 2019. These reductions may allow for increased PHEMCE prioritization and recommendations for procurement of MCMs to address existing gaps with respect to other products in anthrax or other threat portfolios.

Spending on MCMs against radiological and nuclear threats, the next largest investment for this five-year period, totals $1.5 billion, which represents a decrease of $138 million (-8 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.

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

In the filovirus portfolio, the PHEMCE estimates it will spend $1.1 billion, which represents an increase of $240 million (+29 percent). This increase supports the late-stage development and procurement of MCMs against the Ebola virus. The PHEMCE will continue to support activities associated with the transition of MCM candidates from early development supported by the NIH and the DoD into advanced development at BARDA and towards FDA approval. 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.

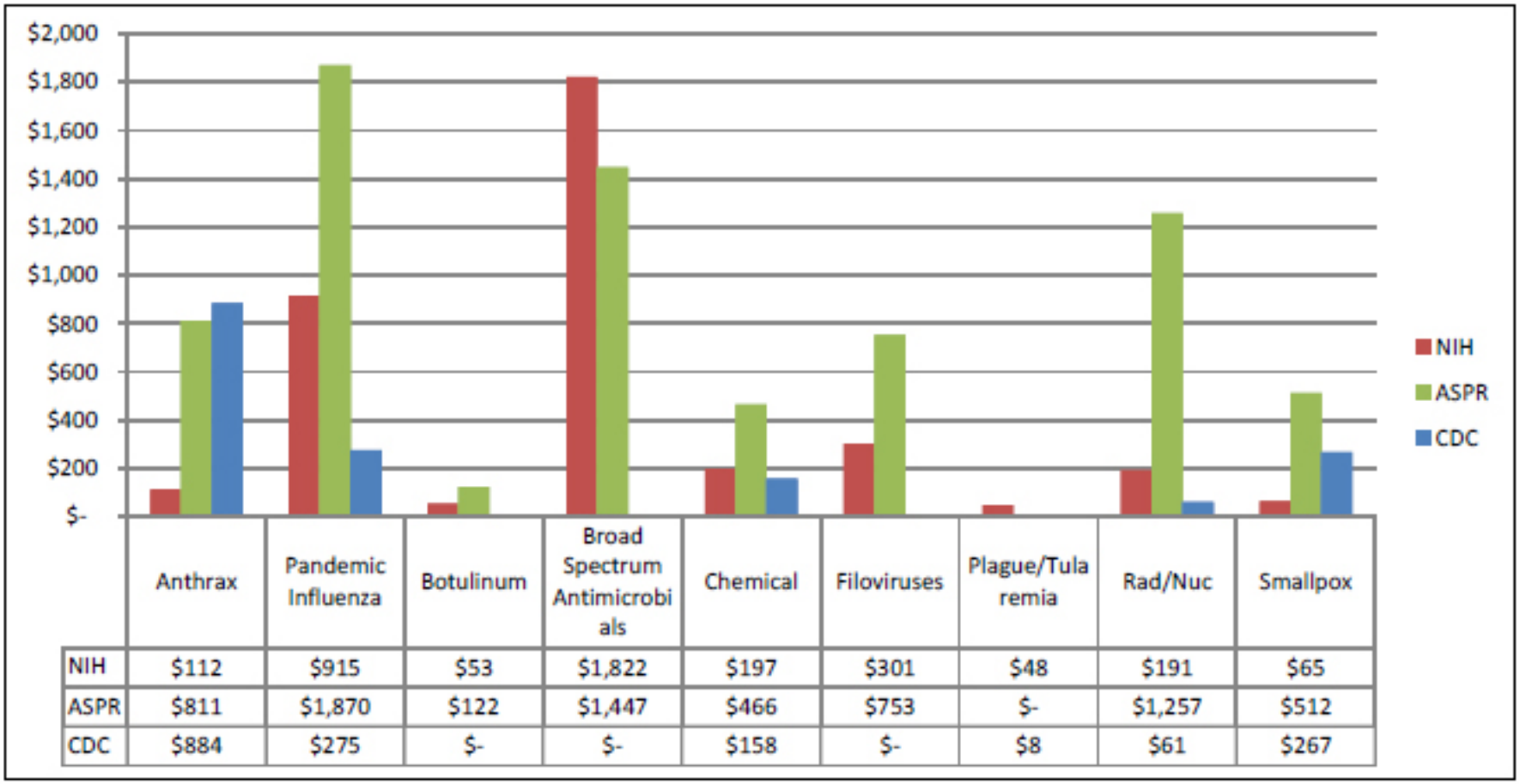
Investment in MCMs to mitigate smallpox is forecasted to have a five-year total of $844 million, which represents an increase of $167 million (+25 percent). This increase reflects the investment in a lyophilized formulation of IMVAMUNE, a non-replicating smallpox vaccine being developed for individuals 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 sustainment costs.

Spending on MCMs to mitigate chemical threats is forecasted to have a five-year total of $821 million, which represents an increase of $120 million (+17 percent). The chemical threats program 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

MCM development necessitates varied levels of funding 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 particular 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, will 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 (i.e., vaccine, therapeutic, diagnostic, etc.). Relatively more mature portfolios require sustained investment by CDC (or BARDA) in replenishment costs (e.g., anthrax, pandemic influenza, chemical, nerve agent, and smallpox). Relatively less mature portfolios will show an absence of CDC spending (e.g., broad spectrum antimicrobials, filoviruses, and radiological or nuclear threats). Significant investment by BARDA often signals that novel MCMs are going to be procured and stockpiled in the SNS during this report's timeframe.



	Anthrax	Pandemic Influenza	Botulinum	Broad Spectrum Antimicrobials	Chemical	Filoviruses	Plague/Tularemia	Rad/Nuc	Smallpox
NIH	$112	$915	$53	$1,822	$197	$301	$48	$191	$65
ASPR	$811	$1,870	$122	$1,447	$466	$753	$-	$1,257	$512
CDC	$884	$275	$-	$-	$158	$-	$8	$61	$267

Figure 2: MCM Spending by High-Priority Portfolio and Agency for FY 2016 - 2020

Product Transitions

Transition of candidate or approved products across the partner agencies is a key indicator of success of PHEMCE. Coordination among the agencies 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 signifying the next stage of development) for development or procurement. It may also inform decision-making around PHEMCE activities such as the SNS Annual Review.

Cost-Saving Methods and Other Efficiencies Adopted by the PHEMCE

BARDA Total Lifecycle Costs

Total Life Cycle Costs (TLCC) containment is a major component of BARDA's MCM sustainability strategy. The PHEMCE's current MCM portfolio faces sustainability challenges. The financial burden could limit resources to respond to new threats and our ability to maintain existing capabilities, and threatens to erode financial investments already made. Opportunities exist to impact TLCC throughout the development life cycle. Launched in 2013, BARDA utilizes an internal "TLCC tool" to estimate and evaluate the TLCC of a product in BARDA's portfolio. The tool has helped BARDA understand the cost of drug development while improving financial planning and portfolio management. In FY 2016, BARDA implemented a TLCC Cost Avoidance Register to track savings throughout a product's lifecycle. BARDA's staff now regularly includes these assessments in advance of making a contract award and during contract In-Process Reviews. It is currently executing a pilot program where manufacturers provide TLCC assessment and cost-avoidance strategies during pre-award communications. A sponsor's TLCC assessment offers many benefits including: requiring the sponsor to communicate its technical approach to controlling lifecycle costs; allowing BARDA to evaluate the sponsor's technical approach; providing information on commercial and biodefense markets; and identifying projects where sustainability presents a significant challenge and provides the opportunity to propose cost-avoidance mitigation strategies.

Tools for Portfolio Tracking and Projection of Future Development Costs

The PHEMCE developed a set of tools to identify contract level costs for advanced development of specific products across the various U.S. federal programs in the PHEMCE as well as for products for these same threats in other international programs overseen by defense and public health agencies in Canada, the United Kingdom, and Australia. The development of the portfolio tracking tool has been jointly funded to meet the needs of HHS and the DOD. Additionally, a cost-model tool is in joint development by these same departments to provide PHEMCE partners with the ability to estimate future costs for the full spectrum of advanced development costs for products as they relate specifically to government-based investments. This model is being evaluated against commercial databases to validate the approach and to account for differences in cost that result from governmental versus commercial investments.

Office of Acquisitions Management, Contracts and Grants

Working closely with BARDA on all contract awards, the Office of Acquisitions Management, Contracts, and Grants (AMCG) is a multifaceted organization within ASPR that is wholly dedicated to service and support. AMCG provides the entire ASPR community with holistic, flexible, consistent, and innovative acquisition and grants solutions. As an ASPR-wide

contracting office, AMCG oversees procurement integrity issues within the organization. In FY 2016, AMCG achieved the following: awarded multiple Zika cooperative agreements supporting the World Health Organization and NIH; awarded CARB initiative for CARB-X and Antimicrobial Resistance; awarded vaccine development, blood screening, pathogen reduction studies, and diagnostics contracts; facilitated 20 BARDA Decision Gate In-Process Reviews; and facilitated the successful approval by the HHS Senior Procurement Executive of the major BARDA Acquisition Strategies.

For the period FYs 2012–2016, AMCG issued 19 Requests for Proposals. The average days to award a contract following a public solicitation decreased significantly over this five-year period from 315 days to 68 days. The award period is based on the Procurement Action Lead Time, which includes the posting of the solicitation notice, the receipt of an acceptable proposal, and the evaluation and negotiation to actual award of the contract. AMCG personnel addressed various inquiries throughout the process. To ensure that programmatic requirements were met, each proposal received a vigorous Technical Panel Review comprised of Subject Matter Experts and highly qualified acquisition personnel. Once a proposal was given a satisfactory rating, negotiations followed.

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 under the relatively flat line budgets that have been seen or are estimated over the period of the five-year budget. Successful procurement of an MCM obligates CDC to expend more funding on sustainment of the SNS. First, CDC faces replacement 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 they receive FDA approval. 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 translate to increasing levels of risk across the threat portfolios and jeopardize the nation's ability to realize the full benefits of prior research and development investments. In prior years, the SNS Annual Review proposed reducing anthrax vaccine holdings and the 2015 SNS Annual Review proposed reducing both anthrax vaccine and antibiotics to prevent anthrax disease to meet budget constraints. Beyond these immediate stockpiling challenges, the PHEMCE must address the entire range of capabilities required to effectively use stockpiled MCMs in an emergency response. The ability of state and local partners to receive, distribute, and dispense MCMs is as important as establishing and maintaining a complete inventory of the appropriate pharmaceuticals and medical supplies.

Multiyear Budget by Agency: NIH/NIAID

NIH leads basic research towards a comprehensive understanding of the scientific and medical aspects of potential CBRN threat agents and emerging threats, such as the Zika virus and the Middle East Respiratory Syndrome coronavirus (MERS-CoV). Research supported by NIH also includes genomic centers and animal models that can inform the development of countermeasures for CBRN and emerging infectious disease threats. NIH also supports translational and product development efforts—through Phase 1 and into Phase 2 clinical trials—to exploit scientific discoveries and novel concepts that could lead to innovative interventions in response to specific threat agents and public health concerns.

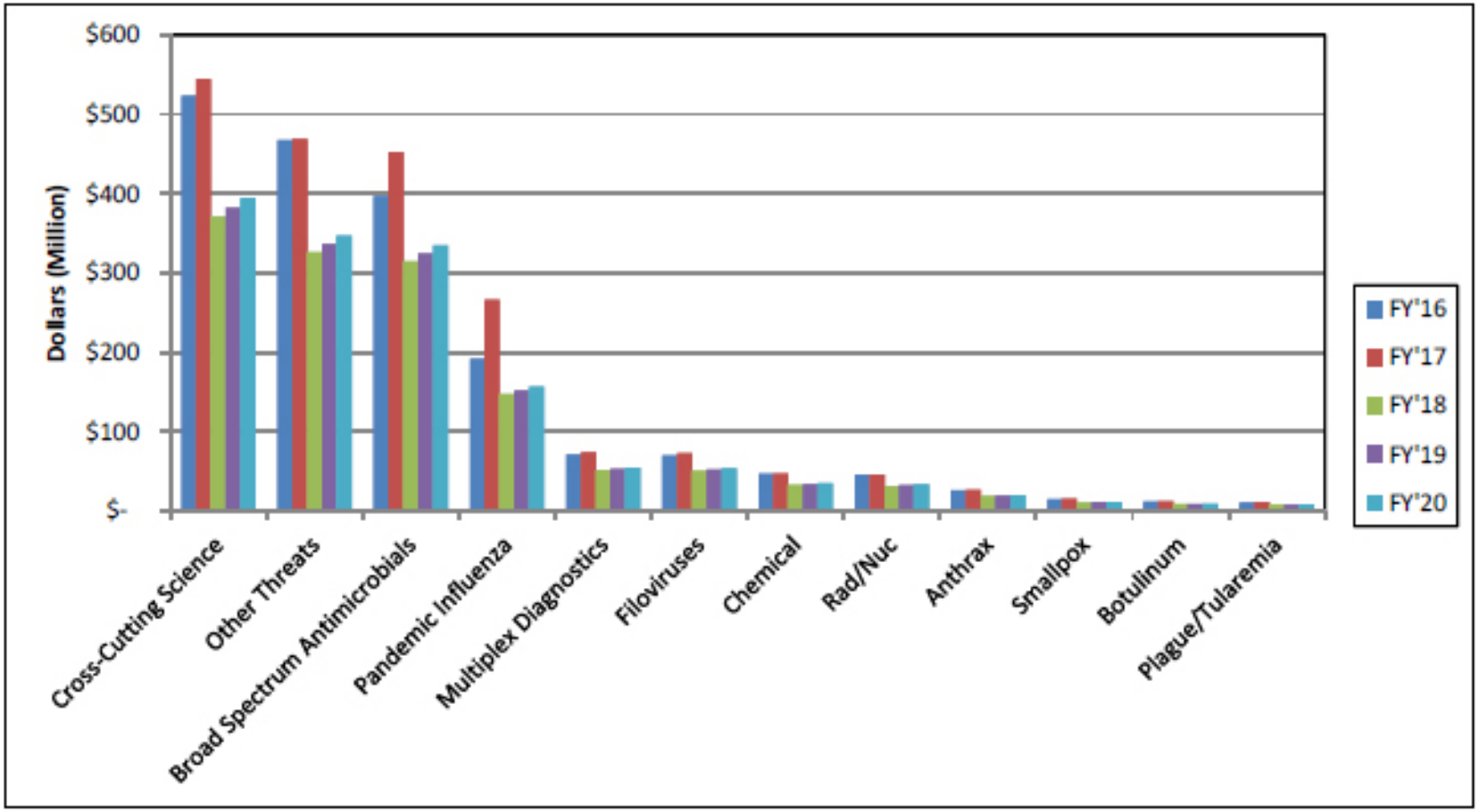


Figure 3: Estimated NIH MCM Spending by Fiscal Year

NIH/NIAID Accomplishments

In FY 2016, NIAID made significant progress in advancing MCMs to protect against emerging infectious diseases, biodefense pathogens, and chemical, radiological, and nuclear threats.

NIAID is responding to the public health threat posed by Zika virus through a multifaceted approach to the development of countermeasures. Most of these activities are focused on vaccine development: NIAID's Vaccine Research Center (VRC) is developing a DNA vaccine candidate that entered Phase 1 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. In addition, NIAID is working with Walter Reed Army Institute of Research, BARDA, and Sanofi Pasteur, to develop a Zika Purified Inactivated Virus Vaccine candidate. This candidate vaccine entered Phase 1 trials in late 2016. Several additional candidates are also in preclinical development. NIAID is also investigating promising therapeutics, screening small-molecules for activity *in vitro* and *in vivo* against the virus and supporting isolation and evaluation of monoclonal antibodies. Finally, NIAID is supporting efforts to improve diagnostics for the virus.

NIAID responded both domestically and internationally with a portfolio of research activities to address the Ebola virus disease (EVD) outbreak in West Africa through the accelerated development of vaccines, therapeutics, and diagnostics. This research included product development, preclinical studies, screening and testing of candidates, animal model development, and pilot-lot manufacturing. NIAID started two Phase 1 clinical trials in the U.S. using the Janssen MVA/Ad heterologous prime boost platform. Enrollees in the first trial with the monovalent Ebola vaccine have completed the primary vaccination series and are awaiting the one-year boost vaccination. The second Phase 1 trial using the multivalent filovirus vaccine began in September 2016. NIAID's efforts were the basis for, and continue to support, other clinical efforts in Europe, the U.K. and Africa, that use the Janssen vaccine. 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; PREVAIL II, a randomized controlled study comparing ZMapp to optimized standard of care in Liberia, Sierra Leone, Guinea, and the United States; and PREVAIL III, a study to understand the long-term health consequences of EVD among survivors.

NIAID published two peer-reviewed manuscripts for two studies that provide data and justification for a dose sparing strategy for a licensed anthrax vaccine.[5] This strategy could potentially double the amount of vaccine available for use in an emergency in the event of inadequate vaccine supply. Antibiotic requirements may also be reduced and potential cost reductions for the SNS could be considerable.

Non-clinical research, funded by NIAID, was instrumental in achieving supplemental FDA-approvals for filgrastim (Neupogen, Amgen) in March 2015 and peg-filgrastim (Neulasta,

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[5] Vaccine. 2016 Dec 12; 34(51):6518-6528. Evaluation of early immune response-survival relationship in cynomolgus macaques after Anthrax Vaccine Adsorbed vaccination and Bacillus anthracis spore challenge. Sivko GS, Stark GV, Tordoff KP, Taylor KL, Glaze E, VanRaden M, Schiffer JM, Hewitt JA, Quinn CP, Nuzum EO.

Vaccine. 2016 Dec 12; 34(51):6512-6517. Cross-species prediction of human survival probabilities for accelerated anthrax vaccine absorbed (AVA) regimens and the potential for vaccine and antibiotic dose sparing. Stark GV, Sivko GS, VanRaden M, Schiffer J, Taylor KL, Hewitt JA, Quinn CP, Nuzum EO.

Amgen) in November 2015 to increase the survival of adult and pediatric patients acutely exposed to myelosuppressive doses of radiation. In FY 2016, NIH/NIAID-funded efficacy studies on a mesenchymal stromal cell therapy for radiation injury that furthered initiation of a clinical trial to treat incomplete bone marrow recovery following hematopoietic cell transplantation.

NIAID also continued its support of research to combat antimicrobial resistance, including more than $11 million in first-year funding for nine research projects supporting enhanced diagnostics to rapidly detect antimicrobial-resistant bacteria. NIH and BARDA collaborated to launch a prize competition that may result in the awarding of 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. NIH 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. CARB-X was created to help address the threat of antibiotic resistance. It is one of the world's largest public-private partnerships focused on preclinical discovery and development of new antimicrobial products.

NIAID supports the development of new influenza therapeutics and vaccines, including universal influenza vaccines and those against influenza viruses with pandemic potential. Several NIAID supported candidates are advancing toward clinical evaluation, including a hemagglutinin (HA) stem-only ferritin nanoparticle candidate developed by the NIAID VRC, a novel replication deficient-live virus vaccine and a chimeric HA vaccine candidate designed to focus the immune response against the conserved HA stem domain. NIAID's virus-like particles (VLP)-based influenza vaccine candidate was shown to provide significant protection in mice following challenge with influenza viruses. In 2016, NIAID initiated 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.

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 polyclonal antibody-based therapeutic supported by NIAID has moved into a Phase 1 clinical trial at the NIH clinical center. An NIAID supported Phase 1 clinical trial of a monoclonal antibody therapeutic against MERS-CoV is in protocol development and is scheduled to start in 2017.

Ongoing NIH efforts address specific high-priority PHEMCE needs and requirements. NIH programmatic accomplishments have included transitioning a next-generation smallpox vaccine to BARDA for further development. This vaccine candidate is being developed for use in immunocompromised populations and in those with atopic dermatitis. NIH also transitioned two smallpox antiviral candidates to BARDA for further development.

NIH continues testing of approved antibiotics for additional indications under the FDA Animal Rule. Two additional antibiotics have received supplemental approvals to treat as well as prevent pneumonic plague. Ciprofloxacin was approved in February 2015 with support by NIAID and Avelox (moxifloxacin) was approved in May 2015 using an NIAID-developed animal model. Additional antibiotics for prophylaxis of inhalational anthrax in special populations have been tested and are under review at FDA. In addition, NIH continues to pursue qualification for multiple animal models.

The NIH CounterACT program overseen by NIAID and led by NINDS in partnership with other institutes and centers, such as the National Institute of Environmental Health Sciences, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Eye Institute continues to support high-quality research on next-generation MCMs for chemical threats. The program includes interagency agreements with DoD laboratories, contracts with other laboratories that conduct preclinical studies essential for therapeutic development, and a network of Research Centers of Excellence and research project grants at some of the most prestigious universities in the nation. In FY 2016, the program renewed some of its Centers of Excellence and many other cooperative agreements. In partnership with the DoD and BARDA, the NIH continues to support the multi-departmental effort to secure FDA approval for midazolam as a treatment against seizures due to nerve agent poisonings. NIH CounterACT researchers have also discovered and advanced several promising new therapeutics along the research and development pipeline, and many manufacturers have had tech watch meetings with BARDA to discuss transition towards advanced development, including a promising MCM for pulmonary chlorine exposure that was successfully transitioned to BARDA in FY 2016 (see Table 2).

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—starting with basic research on the disease fundamentals, and progressing through applied and then advanced research. Between FYs 2016 and 2020, NIH forecasts that more than 48 MCM candidates will be eligible for consideration for transition to BARDA's Advanced Research and Development (ARD) program (Table 2), 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 will be eligible to transition to BARDA in FYs 2016–2020. 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.

To address radiation and nuclear threats, NIAID is supporting several candidates for the hematopoietic and gastrointestinal ARS and DEARE. A Phase 1 clinical trial is being planned for a novel, oral, radionuclide decorporation agent that was initially developed with NIH funding. Although no new radiation candidates transitioned to BARDA in FY 2016, five drugs and three biodosimetry approaches that received earlier funding from NIAID continue to be pursued under BARDA research contracts.

There are close to 50 different potential MCM candidates in various stages of research and development within the current NIH CounterACT portfolio. In FY 2016, the NIH CounterACT program transitioned the chlorine antidote known as R-107 (Radikal Therapeutics Inc.) to BARDA, after more than $2.6 million in funding over four years from the NIH (see Chlorine MCM). Under the agreement with ASPR, the company will develop a more efficient way to produce large quantities of R-107 and conduct non-clinical studies to establish the drug’s safety and effectiveness as a lifesaving treatment for acute lung injury resulting from inhaled chlorine.

If the non-clinical studies are successful, R-107 could begin clinical studies to establish safety and efficacy in humans. The initial two-year $15.9 million contract with BARDA could be extended up to a total of $84.9 million over seven years.

Portfolio	Project Name	FY16	FY17	FY18	FY19	FY20
Anthrax	Vaccine				X	
Anthrax	Vaccine					X
Anthrax	Antibiotic data submission to FDA			X		
Anthrax	Antibiotic data submission to FDA			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 Marburg virus		X			
Chemical	Doxycycline treatment for the ocular effects of Sulfur Mustard			X		
Chemical	Novel BBB-penetrating oxime for nerve agents					X
Chemical	Neuroprotectant for nerve agents				X	
Chemical	Anticonvulsant and neuroprotective therapy			X		
Chemical	Neurosteroid treatment for organophosphate intoxication			X		

Portfolio	Project Name	FY16	FY17	FY18	FY19	FY20
Chemical	Transient Receptor Potential (TRP) Channel Antagonist for Chlorine		X			
Chemical	Antidote for cyanide (dimethyl trisulfide)				X	
Chemical	Antidote for cyanide (sodium tetrathionate)					X
Chemical	R107 antidote for chlorine	X				
Pandemic Influenza	Universal flu vaccine		X			
Pandemic Influenza	Universal flu vaccine			X		
MERS-CoV	Polyclonal Antiserum			X		
MERS-CoV	Monoclonal Antibody			X		
Biodosimetry	microRNA markers for evaluation of radiation exposures					X
Biodosimetry	Ultra high-throughput proteomics					X
Biodosimetry	RABIT II cytogenetics platform					X
Gastrointestinal Acute Radiation Syndrome	LPA analog to increase survival				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	peg-TPOm to mitigate thrombocytopenia and increase survival	X				

Portfolio	Project Name	FY16	FY17	FY18	FY19	FY20
Hematopoietic Acute Radiation Syndrome	PF4 inhibitor to mitigate thrombocytopenia d increase survival				X	
Hematopoietic Acute Radiation Syndrome	Pleotrophin to mitigate neutropenia & thrombocytopenia/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	Proteoliposome medical countermeasures to increase survival				X	
Hematopoietic Acute Radiation Syndrome	Placenta-derived cell therapy			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	Small molecule 512 to mitigate fibrosis and increase survival					X
Radiation-Induced Lung Injury	Approved/inhaled lung surfactant				X	
Radionuclide Decorporation Agent	Oral absorption enhancer Diethylenetriaminepentaacetic acid			X		

Portfolio	Project Name	FY16	FY17	FY18	FY19	FY20
Radionuclide Decorporation Agent	Oral hydroxypyridinone			X		
Tularemia	Doxycycline dataset for FDA review			X		
Viral Hemorrhagic Fevers (Ebola)	Ad/MVA vaccine (multivalent)				X	

Table 2: Medical countermeasure products ready for transition from NIH to BARDA, FY 2016–2020

Multiyear Budget by Agency: ASPR/BARDA

The Pandemic and All Hazards Preparedness Act of 2006 amended the 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.

Advanced research and development 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, the SNS is responsible for further replenishment of these MCMs.

BARDA forecasts a significant increase in funding for pandemic influenza in FY 2019 and FY 2020. This increase is necessary to maintain domestic preparedness, while funding next-generation universal influenza vaccines, immunotherapeutic treatments, and advanced diagnostic devices. 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,[6] including ongoing storage, stability, and testing of stockpiled material in the pre-pandemic vaccine and adjuvant stockpiling program.

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 in 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 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.

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

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

technologies 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.

ASPR/BARDA Accomplishments

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 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.

- ASPR/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 new 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.

- 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.

- Issued RFPs for Ebola vaccines and therapeutics under Project BioShield in FY 2017, as well as both point-of-care and high-throughput biodosimetry devices.

- 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.

More recent FDA approvals include the following:

- Biothrax (Anthrax Vaccine Adsorbed) – Supplemental approval for post-exposure prophylaxis when administered in conjunction with recommended antibacterial drugs (November 2015) – Emergent BioSolutions;

- Anthim (obiltoxaximab) – Monoclonal antibody approved for the treatment of inhalational anthrax in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or not appropriate (March 2016) – Elusys;

- Biothrax (Anthrax Vaccine Adsorbed) – Approval of large-scale manufacturing of BioThrax at Building 55 (August 2016) – Emergent BioSolutions;

- Flucelvax Quadrivalent Influenza Virus Vaccine – Supplemental approval to extend the age range for use to include persons 4 years to <18 year of age (May, 2016) - Seqirus, Inc.;

- Q-Pan (Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted - Supplemental approval to extend the age range for use to include persons 6 months through 17 years (September 2016) – GlaxoSmithKline; and

- 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.

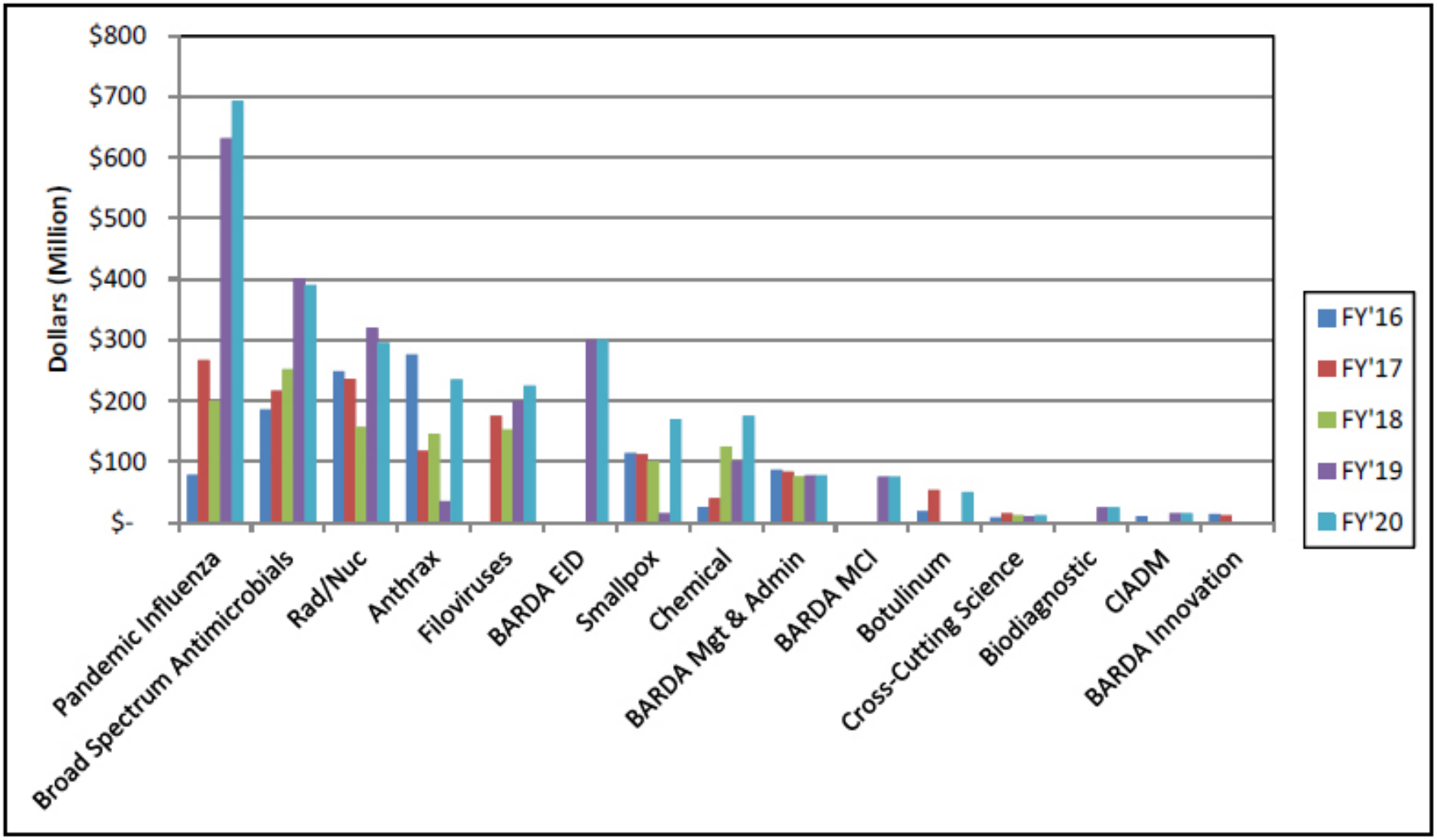

Figure 4: Estimated BARDA MCM Spending, by Portfolio

BARDA expanded its "capabilities-based" approach by establishing the National MCM Response Infrastructure. These core service assistance programs routinely provide aid to product developers, and include the following:

- In 2011, established the Nonclinical Studies Network including 17 laboratories to develop animal models and conduct animal challenge studies to evaluate MCMs;

- In 2012, established three Centers for Innovation in Advanced Development and Manufacturing (CIADMs) in Texas, Maryland, and North Carolina, to expand domestic pandemic influenza vaccine manufacturing capacity and enable production of vaccines and biological products (e.g., monoclonal antibodies) for use against CBRN threats and emerging infectious diseases. BARDA has used the CIADMs to accelerate development of therapeutics for Ebola, develop a second-generation anthrax vaccine, and manufacture experimental vaccines to protect against influenza viruses with pandemic potential. More recently, the CIADMs have been used to conduct a variety of studies to move vaccine candidates quickly through early stages of Zika vaccine development;

- In 2013, established the Fill Finish Manufacturing Network (FFMN) including four contract manufacturing organizations to assist MCM developers, supplement BARDA's national pandemic influenza vaccine manufacturing capacity, and address aseptic drug shortages. The FFMN was critical to the production of Ebola monoclonal antibodies in 2014–2015 for clinical studies in West Africa. In 2016, two new partners were added to the FFMN to expand capabilities to include live vectored virus. In addition, these partners will assist in fill finish needs, such as: small molecule sterile injectable drugs, large molecule sterile drugs, monoclonal antibodies, pre-clinical, clinical and FDA approved MCMs;

- In 2014, established the Clinical Studies Network (CSN), which is composed of five clinical research organizations with full clinical study capabilities worldwide. In 2015, BARDA's CSN helped CDC conduct the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE), a clinical study of an Ebola vaccine candidate.

ASPR/BARDA MCM Transitions

During FYs 2016–2020, BARDA anticipates multiple MCM product transitions from NIH and DoD to BARDA (Table 3). 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: biothreat diagnostics, antimicrobials and artificial skin for use with thermal burn patients, and biodosimetry devices for use in a point-of-care or high-throughput setting.

The prior list 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.

Medical Countermeasure	Estimated Transition Timeframe (FY)	Provider	Recipient
Therapeutics for Ebola	2017	BARDA ARD	PBS
Vaccines for Ebola	2017	BARDA ARD	PBS
IV Smallpox Antiviral	2017	BARDA ARD	PBS
Chemical Vesicant Therapeutics	2018	BARDA ARD	PBS
New antimicrobial drugs	2018	BARDA ARD	PBS
Cell-based therapeutic for hematopoietic ARS illness	Beyond 2018	BARDA ARD	PBS
Chemical nerve agent antidote	Beyond 2018	BARDA ARD	PBS
Small molecule therapeutics for skin and lung ARS trauma	Beyond 2018	BARDA ARD	PBS

Table 3: Medical countermeasure product transitions within BARDA from FYs 2016–2020

Multiyear Budget by Agency: CDC/DSNS

The Centers for Disease Control and Prevention (CDC) has the lead role within the federal government for public health surveillance, epidemiologic and laboratory investigations, public health communications, and delivery of MCMs for public health emergencies. MCM delivery is managed under CDC's Office of Public Health Preparedness and Response (OPHPR). OPHPR's Division of the 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 SNS-held, FDA-approved MCMs, as well as MCMs initially procured by BARDA through PBS once those MCMs achieve FDA approval. Through OPHPR's Division of State and Local Readiness (DSLR), CDC supports the public health infrastructure at state, local, tribal and territorial (SLTT) levels and builds the capacity to detect and respond effectively to public health emergencies, including effective utilization of critical MCMs. CDC is responsible for providing MCM training and guidance to SLTT partners on how to receive MCMs from the SNS, and on developing and exercising their preparedness plans to support MCM mass distribution and dispensing. Input from SLTT partners, representing the end-users of MCMs, is imperative throughout the PHEMCE decision-making processes.

CDC is the lead agency in exploring alternative methods of MCM forward deployment and dispensing, and developing clinical guidance on the use of MCMs. CDC performs practical research that helps guide the use of MCMs, such as dose-sparing studies of the anthrax vaccine and research on the smallpox vaccine. CDC also develops diagnostic tests that may be used in an influenza pandemic and other biological events. Additionally, the CDC works with the FDA to develop investigational new drug protocols to enable the clinical testing of investigational MCMs and pre-Emergency Use Authorization (EUA) packages that will form the basis of an EUA request and issuance when circumstances indicate that MCMs not yet approved, or approved for the particular indication, would need to be used under an EUA. Furthermore, the CDC develops Emergency Use Instructions for MCMs used for their approved indications. 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.

CDC requires accurate forecasting to make strategic procurement and investment decisions, in consultation with the PHEMCE governance body, for SNS capabilities. To project these budget requirements, DSNS relies on a model grounded in two main components: lifecycle cost analysis and stockpile inventory projection. Lifecycle cost analysis is a tool to estimate the total product cost over the shelf-life of each product, and the stockpile inventory projection is a mathematical system based on current stockpile holdings used to forecast future on-hand balances, expiration and replacement timelines. Combining the outputs of both models, the SNS budget projection model estimates requirements to maintain and manage SNS stockpiled MCMs in out-years. These budget estimates are produced biannually to update the variable inputs including changing market conditions and product movements. They provide accurate current inventory and budget information to the multiyear budget and inform DSNS decision-making for current year budget execution, spend plan development, and formulation for future fiscal years. CDC's current projections for FY 2019 and FY 2020 reflect lower amounts compared to the 2015 PHEMCE Multiyear Budget Report, based on additional efficiencies realized via the FDA/DoD Shelf Life Extension Program and the transition to Nuthrax vaccine procurement by BARDA. However, CDC anticipates potential increases to these projections

due to several contracts for smallpox-related medical countermeasures that will need to be renegotiated during this time frame. These projections will be updated to reflect new information when it becomes available.

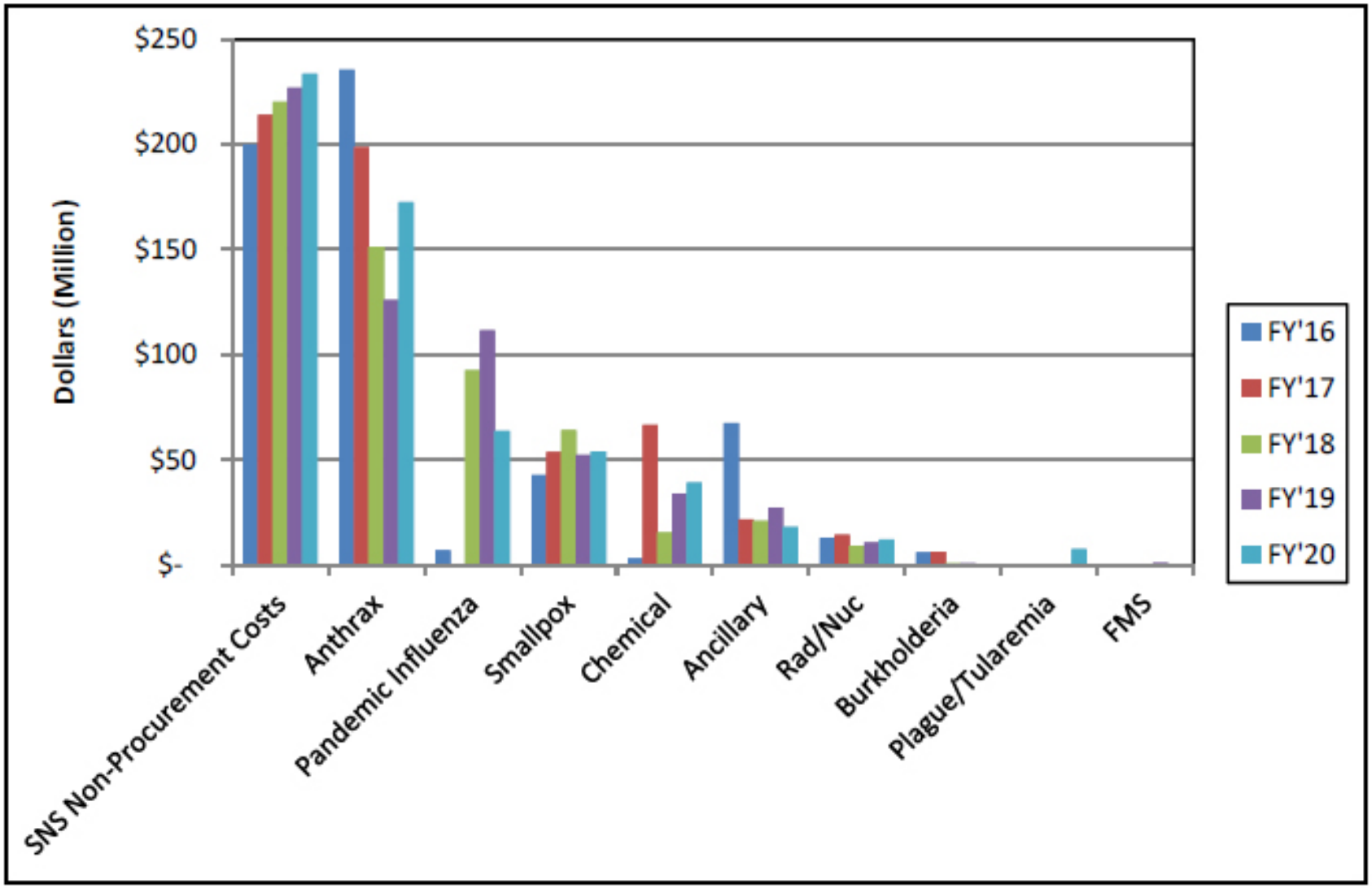

Figure 5: Estimated DSNS Spending, by Portfolio

CDC/DSNS Accomplishments

CDC's management of the SNS has been critical for both public health preparedness and responses to real-world events. Over the past 10 years, CDC increased by 500 percent the percentage of the U.S. population who can be provided antibiotic prophylactic regimens for anthrax. CDC also continues to improve nationwide access to MCMs as necessary for the management of disease threats through improving managed inventory delivery times, sustaining distribution velocity, and incorporating lessons learned. In FY 2016, CDC piloted a new cost-saving method through the CHEMPACK program to deliver MCMs to CDC's partners. This business enhancement provides an additional method to be used in the delivery of MCMs. The drop shipment method, that moves product from a CDC facility directly to a partner's facility without going through the historical CHEMPACK transportation and delivery process, reduces the travel requirements for state and local partners as well as cost and staff time for SNS personnel. In addition, it reduces CHEMPACK's transportation requirements compared to the traditional sustainment method, which uses a contracted transportation vendor and requires a team to travel to each cache site to rotate product and prepare expiring product for return shipment to an SNS warehouse. Full rollout of the drop shipment process will be initiated following socialization with all CHEMPACK participants.

CDC has Memorandums of Understanding (MOUs) with four Urban Area Security Initiative (UASI) cities to improve delivery times and continues work with New York City in the forward placement of oral prophylaxis. For the four UASIs, CDC improved delivery time from 24 hours for full delivery (guaranteed delivery time to any project area) to 5.75 hours (average) for first arrival and 10.5 hours (average) for final arrival, resulting in a decrease of 56 percent in product delivery time.

Acquisition and maintenance of MCM inventories do not protect the population against public health threats if MCMs do not reach civilians in a timely manner. Consequently, CDC provides substantial training to prepare federal, state, and local partners for effective response to public health emergencies. In FY 2016, CDC conducted 39 objective-based external SNS training courses tailored to specific state and local requirements. CDC also trained 1,893 federal and SLTT emergency responders representing 15 different project areas using in-person trainings at SLTT locations and the FEMA Center for Domestic Preparedness (CDP) facilities in Alabama, and virtually led training via web meetings. The FY 2016 events included:

- Nine Mass Antibiotic Dispensing (MAD) trainings for 267 participants;
- Three MAD Train-the-Trainer (MADT) courses for 40 participants conducted at the FEMA CDP;
- Six Receive, Stage, and Store (RSS) Operations courses for 154 participants;
- Five RealOpt courses for 64 participants;
- Eight RealOpt distance learning courses for 36 participants;
- One (special) Mobile Preparedness Course (MPC) for 19 participants in Guam;
- Two additional MPC courses for 70 participants in Florida; and
- Two SNS Preparedness courses for 81 participants conducted at the FEMA CDP.

To maximize available resources, CDC collaborated with FEMA to host two SNS Preparedness courses and two MADT courses at the CDP facility, thereby enabling CDC to reach more participants per course, while saving approximately a quarter of a million dollars in operational and travel costs.

CDC hosted a collaborative workshop with the Healthcare Industry Distributors Association (HIDA), convening more than 30 industry partners. The workshop provided a conversational forum to discuss anticipated challenges and potential opportunities for improved communication and coordination amid a possible public health emergency response or during a period of product shortage. The discussion helped identify gaps in the medical supply chain and potential solutions, including capabilities that SNS and HIDA can provide when there is a shortage of medical supplies impacting the supply chain. The facilitated discussion also focused on options and methods for improved communication, coordination, and continuity between CDC and the supply chain partners prior to and during an emergency.

Mechanical ventilators are stockpiled in the SNS and available for deployment to health care facilities, through state and local governments, to supplement local shortages of supplies during a large-scale public health emergency. CDC partnered with the American Association for Respiratory Care (AARC) to provide state respiratory therapists and other health care professionals with the information necessary to utilize SNS ventilators during a large-scale pandemic influenza emergency as well as an opportunity for hands-on experience with all three stockpiled ventilator models. Since 2014, multiple live training sessions have been held across the U.S. The live trainings offer specific information on the SNS ventilator request process, ventilator kitting, storage and maintenance processes, how SNS ventilators will be allocated during an influenza pandemic or other public health emergency, and critical hands-on training. Because of the positive feedback for the live training, DSNS and AARC will conduct four to five live training sessions throughout the U.S. on an annual basis. In addition to the live training sessions, DSNS and AARC have developed on-line trainings through the AARC website.

In FY 2016, CDC continued to interface with numerous international, federal, state, tribal, and local partners, including participating in six ASPR State summits that addressed distribution and dispensing operations. At the summits, CDC shared best practices with the participants and discussed forward deployment of medical countermeasures, advance shipping notices, and agreed-upon timelines for delivery.

Since 2011, CDC has convened three separate work groups to address clinical use of anthrax medical countermeasures. The outcomes of the work groups have provided updated guidelines for use of antimicrobials for anthrax post exposure prophylaxis and treatment, anthrax antitoxins, and patient management in an anthrax mass casualty incident. In 2017, CDC engaged Advisory Committee on Immunization Practices to revise recommendations for use of anthrax vaccine

To support the shortfall in availability of atropine auto-injectors and other medical countermeasures, CDC developed a DoD Mutual Support MOU to more effectively share resources. This effort improves federal readiness and the visibility of stockpiled resources.

CDC MCM Transitions

During FYs 2016–2020, CDC anticipates two MCM product transitions from BARDA to CDC for procurement and replacement of expiring product (Table 4). CDC is responsible for the replenishment costs of those MCMs procured by BARDA under PBS after those products achieve FDA approval. Transition dates for such products are established by agreement between BARDA and CDC, to allow for effective planning and projection of funding and contracting requirements in future fiscal years. Transitioning products may not result in actual costs for that product line in the identified fiscal year, depending on the requirement quantities

and expiration dating of actual product in inventory at the time of transition. For the reporting period covered in this report, these MCMs procured under PBS would remain the financial responsibility of BARDA.

Medical Countermeasure	Estimated Transition Timeframe (FY)	Provider	Recipient
Smallpox antiviral	2019	BARDA/PBS	CDC/SNS
Anthrax antitoxin	2019	BARDA/PBS	CDC/SNS

Table 4: Medical Countermeasure Product Transition to CDC, FYs 2016-2020

Multiyear Budget by Agency: 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 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, 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.[7]

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

[7] 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.

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 2019 for the MCMi, in addition to the 3 percent across the board increase for FDA MCM program areas included in this report (Figure 6) for a total base MCMi program level of $45.9 million. This additional funding would enable the FDA to establish a MCMi 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 $52.1 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.

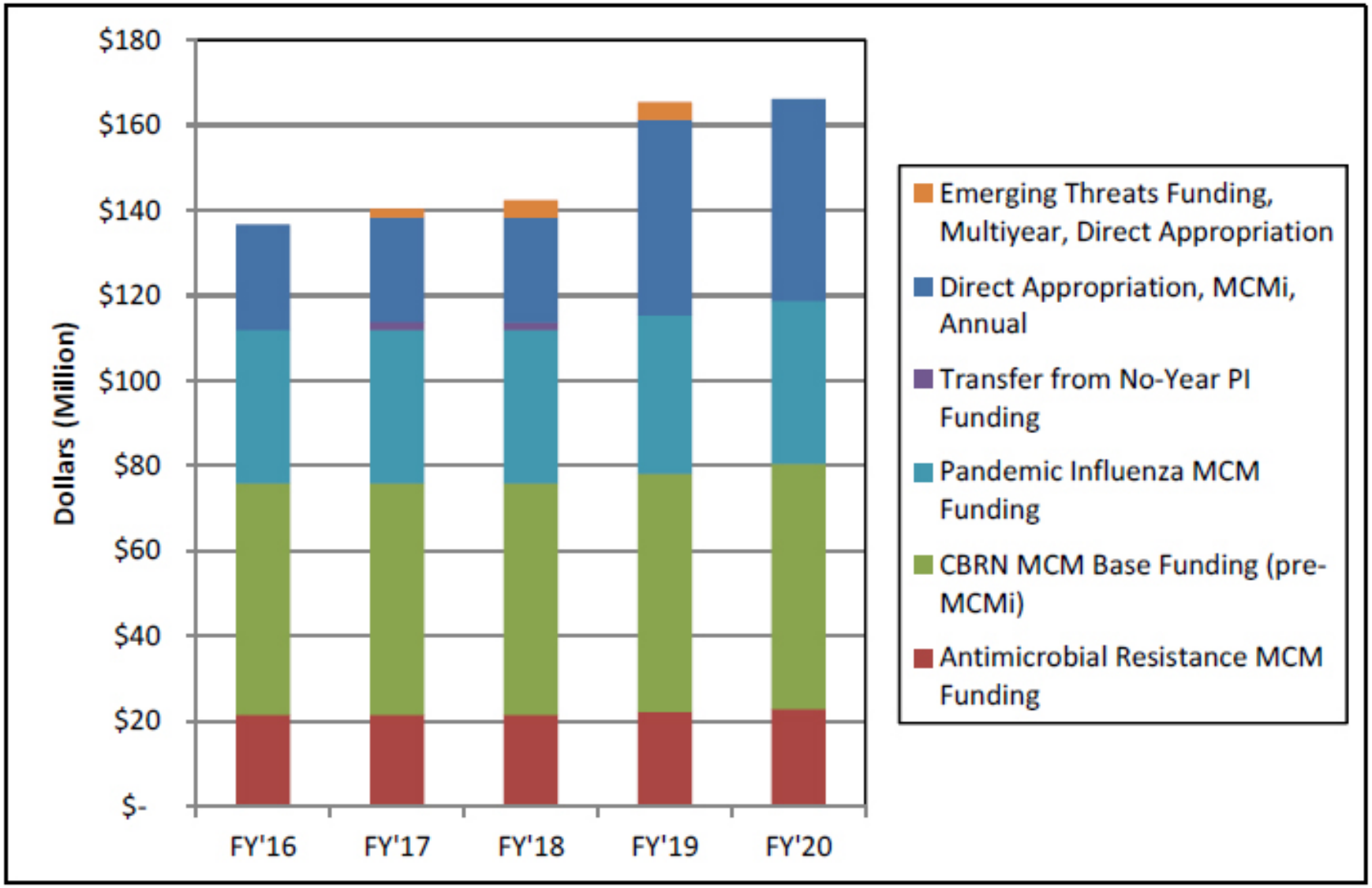

Figure 6: Estimated FDA Spending, by Funding Source and Fiscal Year

FDA Accomplishments

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 FY 2016–2017 with respect to CBRN and emerging infectious disease threats include:

(1) Approval of MCMs for anthrax, the hematopoietic syndrome of ARS, and pandemic/epidemic influenza;

(2) 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 Ebola virus outbreak in West Africa, the Zika virus outbreak in the Americas, and other emerging infectious disease outbreaks. This includes enabling emergency access to 18 diagnostic tests for Zika virus, and working with blood collection establishments to facilitate the implementation of universal screening of donated blood for Zika virus;

(3) Issuing an Emergency Use Authorization (EUA) enabling the emergency use of an auto-injector for an MCM to address a gap in preparedness for chemical threats;

(4) Testing MCM drugs submitted for shelf-life extension under the Shelf-Life Extension Program to support the sustainment of an adequate supply of MCMs and granting shelf-life extensions for 2,020 lots of MCM drugs maintained in the SNS;

(5) 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 their efforts to sustain adequate supplies for anthrax preparedness;

(6) Issuing final guidance for industry on developing products under the Animal Rule when human efficacy trials are not ethical or feasible;

(7) Issuing final guidance for industry on Emergency Use Authorization of medical products and other related authorities;

(8) Drafting and issuing emergency dispensing orders for doxycycline and ciprofloxacin for anthrax preparedness; and

(9) Sustaining a robust MCMi Regulatory Science Program to help accelerate the FDA's ability to perform science-based review of MCMs.

With respect to advancing product development to address antimicrobial resistance, major accomplishments include employing 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. Another accomplishment was creating a centralized repository of antimicrobial-resistant bacterial strains and panels to support the development of diagnostics and antimicrobial drugs.

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)),[8] which occurs prior to the submission of an investigational new drug (IND) application.[9] 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 even after the product is approved throughout its lifecycle. 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 CDC/SNS.

[8] 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.

[9] 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.

Facilitating MCM Development and Availability for Zika Virus

Since May 2015, when the first local transmission of Zika virus in the Americas was confirmed in Brazil, 61 countries and territories—including the United States, the Commonwealth of Puerto Rico, the U.S. Virgin Islands, and American Samoa—have had ongoing transmission following a new introduction of Zika virus or with a reintroduction into an area where transmission had been interrupted.[10] In the continental United States, there have been 5,326 Zika virus disease cases reported in the states [5,053 cases in travelers returning from affected areas, 224 cases acquired through presumed local mosquito-borne transmission in Florida (218 cases) and Texas (6 cases), and 49 cases acquired through other routes, including sexual transmission] and 36,610 Zika virus disease cases reported in the U.S. territories [143 cases in travelers returning from affected areas and 36,467 cases acquired through presumed local mosquito-borne transmission] as of July 12, 2017.[11] As of August 8, 2017, there are 2,112 pregnant women in the states and District of Columbia and 4,418pregnant women in the U.S. territories with laboratory-reported evidence of possible Zika virus infection.[12] From these pregnant women, 93 infants have been born with birth defects in the states and the District of Columbia, 128 infants have been born with birth defects in the U.S. territories.

While infections caused by Zika virus are usually asymptomatic, about 20 percent of infected individuals experience symptoms or mild clinical symptoms. The most common signs and symptoms are fever, rash, muscle and joint pain, and conjunctivitis (red eyes). Increases in cases of Guillain-Barré Syndrome—a rare, acute, immune-mediated peripheral nerve disease that leads to weakness, sometimes paralysis, and infrequently, respiratory failure and death—also have been noted in association with Zika outbreaks in Brazil and elsewhere. Of most concern, the recent outbreaks of Zika virus disease have coincided with a marked increase in the number of infants born with microcephaly, a birth defect characterized by an abnormally small head resulting from an underdeveloped and/or damaged brain. Recent studies have conclusively shown that Zika virus causes microcephaly and brain abnormalities in infants, as well as an array of congenital abnormalities such as eye defects, hearing loss, impaired growth, seizures, difficulty moving limbs, and other complications. At this point, the most severe outcome, congenital Zika syndrome has been described, but the full spectrum of outcomes, including less severe phenotypes is unknown. Surveillance systems that capture the longitudinal evaluation and monitoring of infants exposed in utero are critical to generate better understanding. Although it has been established that Zika infection during pregnancy can cause congenital abnormalities in the infant, ongoing surveillance and research are needed to better understand the disease and how to prevent it.

The U.S. Government response to the Zika virus outbreak spans a broad range of activities—from tracking the spread of the disease, to studying the links between Zika virus infection and infant health as well as other rare health outcomes, to accelerating research to better understand the biology of the virus, to facilitating the rapid development of medical products

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[10] WHO Zika Virus Situation Report, 10 March 2017; WHO Zika Virus Situation Report, March 10, 2017

[11] CDC 2017 Case Counts in the U.S., 2016 Case Counts in the U.S., and 2015 Case Counts in the U.S..

[12] CDC Pregnant Women with Any Laboratory Evidence of Possible Zika Virus Infection in the United States and Territories; CDC Pregnant Women with Any Laboratory Evidence of Possible Zika Virus Infection in the United States and Territories

needed to respond, to supporting public health response including vector control, and protecting pregnant women, infants and the public through education and advice. This case study will focus only on the US Government's efforts to facilitate medical product development.

Medical Countermeasure Research and Development

Prior to the recent outbreak of Zika virus, very little research had been directed at products to specifically diagnose, prevent, or treat Zika virus infection. Currently, no FDA-approved vaccines, therapeutics, or diagnostics are available to prevent, treat, or diagnose Zika virus disease and there are no FDA-approved assays to screen donated blood for the presence of Zika virus. The U.S. federal government identified and prioritized the need for products—such as blood screening assays—to ensure a safe blood supply, sensitive and specific diagnostics to aid in identifying infected individuals (especially pregnant females), and vaccines and therapeutics for the prevention and treatment of Zika virus infection respectively.

Blood Supply Safety

Early in the response to the Zika virus outbreak, the PHEMCE acted to help protect the safety of the blood supply. The FDA issued guidance in February 2016 that recommended the deferral of individuals from donating blood if they had been to areas with active Zika virus transmission, were potentially exposed to the virus, or had a confirmed infection. The guidance also recommended that areas with active Zika virus transmission, like Puerto Rico, obtain whole blood and blood components from areas of the United States without active virus transmission until a blood donor screening test for Zika virus became available to ensure the safety of its blood supply. Until blood donor screening tests for Zika virus became available, BARDA worked with CDC, FDA, and the Office of the Assistant Secretary of Health (OASH) to define requirements, conduct market research, obtain legal advice, and award a contract to transport blood products from the U.S. mainland to Puerto Rico to avoid a blood product shortage until a blood donor screening test became available. Concomitantly, FDA worked closely with the test kit developers in a highly accelerated time frame to make available the first investigational test for blood screening in March 2016. The availability of this investigational test, which has been in use in Puerto Rico since early April 2016, enabled blood establishments to resume safe blood collection in areas with active Zika virus transmission. A second investigational blood screening test was made available in June 2016. Together, these tests enabled blood donor screening to be put in place across the United States where active Zika virus transmission was established as well as in areas where local virus transmission was anticipated, helping to maintain an adequate and safe blood supply.

In August 2016, after careful consideration of the evolving scientific and epidemiologic data (including the significant number of travel-associated cases of Zika across the continental US), consultation with other public health agencies, and taking into consideration the potential serious health consequences of Zika virus infection to pregnant women and children born to women exposed to Zika virus during pregnancy, FDA issued updated guidance recommending that all states and U.S. territories screen blood with an investigational blood screening test. FDA worked with blood collection establishments to facilitate implementation of the revised guidance across the U.S. and its territories. As of July 12, 2017, 370 presumptive viremic blood

donations have been prevented from entering the blood supply in the United States and its territories.[13]

In addition to supporting the development and availability of blood screening assays to protect the blood supply, PHEMCE partners are supporting the development of pathogen reduction technologies that will inactivate Zika virus and other pathogens in donated blood.

Diagnostics

At the start of the Zika virus outbreak in the Americas, there were no diagnostic tests for the detection of Zika virus approved or authorized for use in the United States. FDA worked with CDC, which was developing diagnostic tests, to make Zika diagnostic tests rapidly available. FDA authorized the use of two CDC tests under FDA's Emergency Use Authorization (EUA) authority in February and March of 2016. FDA reached out to diagnostic manufacturers to encourage them to develop needed diagnostic tests for Zika virus. FDA immediately began working interactively with manufacturers interested in developing diagnostic tests for Zika virus to help accelerate development programs—including clarifying EUA data requirements for the Zika diagnostic tests—and to ensure that its tests are properly validated before they are used to inform patient care. FDA granted an EUA for the first commercial test in April 2016.

Once FDA authorized the emergency use of these tests, CDC rapidly distributed them to state laboratories and ensured state laboratories were proficient in their use, while also sharing information about test performance with manufacturers that were developing their own tests and released clinical guidelines for the evaluation and management of pregnant women and infants. Comparison of test performance allowed others to benchmark their tests against the first FDA-authorized Zika tests. As of this writing, there are 14 Zika nucleic acid tests available under EUA and 49 state public health laboratories have Zika nucleic acid testing capacity. There are also 3 serological tests available under EUA to assess whether individuals who may have recently been exposed to Zika had actually been infected. Forty-six states have the capacity to conduct CDC's serological test, known as MAC-ELISA. Together with CDC's Laboratory Response Network, CDC has conducted over 160,000 Zika tests. The FDA continues to work with diagnostic manufacturers once their tests are authorized under EUA to further product development, improve product performance, and make sure that authorized tests continue to meet EUA standards and public health needs. For example, FDA has issued 23 amendments to EUAs for the authorized Zika diagnostic tests—upon request from the product manufacturers—to add additional instruments or specimen types for testing.

To spur diagnostic development in the private sector, BARDA awarded four contracts during the summer of 2016 for the development of Zika diagnostics that would determine whether people have had recent exposure to Zika. Industry partners currently supported by BARDA include InBios and DiaSorin to develop a laboratory-based serological test to detect IgM antibodies (indicating recent infection), and OraSure and Chembio to develop a point-of-care diagnostic test that would allow for rapid results for the clinician and patient. Two of these companies have received Emergency Use Authorizations from the FDA for their Zika test: InBios for its ZIKV Detect IgM Capture ELISA and DiaSorin for its LIAISON XL Zika Capture IgM Assay. In

[13] CDC Zika Virus Case Counts in the U.S.

addition, BARDA, in close coordination with CDC, addressed a critical barrier for diagnostic developers by collecting blood specimens that contained Zika virus to create well-characterized panels for use in assessing how well the tests perform. The FDA has also taken several proactive steps to help advance the development of diagnostic tests for Zika virus. For example, FDA developed and made available EUA review templates delineating data requirements for a Zika virus diagnostic EUA. FDA has fulfilled more than 100 requests for the EUA templates. In addition, to help Zika diagnostic manufacturers develop nucleic acid testing-based diagnostic devices, FDA created Zika virus reference materials that are available to Zika diagnostic manufacturers that have a pre-EUA submission with FDA and have established the analytical performance of their assay. FDA has fulfilled 17 requests for the reference materials.

NIAID is facilitating the development of improved Zika virus diagnostic tests through support for NIAID investigators and grantees working to generate antibodies and recombinant protein antigens that can be used to distinguish between Zika virus and dengue virus. Studies also are underway to create new diagnostic methods that simultaneously measure antibody responses to several flaviviruses to clearly distinguish which virus caused a recent infection. In addition, NIAID grantees are working to identify unique biosignatures for Zika infection that could form the basis of other rapid diagnostic tests.

Vaccines

A safe and effective Zika vaccine would be an invaluable tool to help stop the spread of infection and prevent future outbreaks. NIAID and BARDA are developing and investigating multiple Zika vaccine candidates, including vaccines based on technologies that have shown promise against other flaviviruses. The FDA is actively engaged with NIAID and BARDA (as well as the international community and product developers) to move products forward in development as quickly as possible by providing technical support and clarifying regulatory and data requirements. The NIAID Vaccine Research Center (VRC) is developing a candidate DNA-based Zika vaccine akin to a VRC West Nile virus vaccine candidate. The DNA-based Zika vaccine candidate entered a Phase 1 clinical trial in 2016, and initial study results indicate that the vaccine is safe and induces an immune response in the range that would predict protection against Zika virus. NIAID launched a multi-site Phase 2/2b clinical trial of this vaccine in March 2017 that aims to enroll at least 2,490 healthy participants in various sites in the Americas, possibly including the continental United States and Puerto Rico, Brazil, Peru, Costa Rica, Panama, and Mexico. The trial will further evaluate whether the experimental vaccine is safe and able to stimulate an adequate immune response, and importantly whether it can prevent disease in areas with ongoing mosquito-borne Zika transmission.

BARDA invested in the vaccine development efforts by reaching out to industry partners who had proven track records in bringing vaccines to market, as well as initiating contracts with commercial partners that had more novel approaches to vaccine platforms. NIAID, BARDA, and the Walter Reed Army Institute of Research (WRAIR) are collaborating to evaluate a Zika purified inactivated vaccine (ZPIV) candidate. Multiple Phase 1 clinical trials of ZPIV began in November 2016 in several U.S. sites. BARDA contracted with Sanofi Pasteur to use its well-established manufacturing capability. Sanofi's approach is aligned with that initially developed by the U.S. Army, but incorporates other capabilities identified by Sanofi for construction of an inactivated vaccine.

BARDA also partnered with Takeda for a similar inactivated whole virus vaccine, but using a different production method. Supporting multiple vaccine candidates guards against the high

failure rate of MCM development and, in the case both succeed, would provide a competitive market. This vaccine is slated for clinical trial evaluations starting in October 2017.

Finally, BARDA has contracted with Moderna, to develop a novel mRNA (messenger RNA) delivered vaccine that would demonstrate the applicability of a rapid development approach for vaccines in general. Moderna has been enrolling study participants in several Phase 1 clinical safety trials of their mRNA vaccine candidate with a plan to begin Phase 2 trials in the U.S. and Puerto Rico in November 2017.

Slightly further back in the pipeline, NIAID scientists also are developing live-attenuated Zika vaccine candidates using an approach similar to that taken with an experimental vaccine against the closely related dengue virus. This vaccine candidate will enter an NIAID Phase 1 trial in late 2017. Another version of this approach, an experimental vaccine designed to protect against Zika and all four circulating strains of dengue virus, is scheduled to enter clinical testing by 2018. NIAID is working with academic partners in Brazil to plan later-stage trials of this combination vaccine referred to as a chimeric vaccine.

NIAID researchers also are evaluating other investigational mRNA vaccines, which are like DNA vaccines. The NIAID VRC is working with academic and industry partners to evaluate various mRNA vaccine technologies to identify potential candidates for further development. These include an investigational vaccine under development by the NIAID VRC and a pharmaceutical company that may enter clinical trials in late 2017.

NIAID grantees also are in the early stages of developing a Zika virus vaccine candidate based on a recombinant vesicular stomatitis virus – the same animal virus used to create Merck's investigational Ebola vaccine. This Zika vaccine construct will be evaluated in tissue culture and animal models. NIAID is supporting diverse early-stage Zika vaccine strategies to maximize our chances of success in rapidly reaching the goal of a licensed vaccine.

It is important to realize that the development of investigational vaccines and the subsequent clinical testing that is required to demonstrate their safety and effectiveness takes time. The pace of these trials in reaching a conclusion will depend on both the inherent effectiveness of the vaccine and the amount of Zika virus transmission near clinical trial sites. If a Zika outbreak occurs during the VRC's phase 2/2b vaccine trial, it is conceivable that we will have an indication of whether the vaccine works within one to one and one-half years. However, with the recent decline in Zika cases across the Americas, Zika vaccine clinical trials may require more time to discern whether the vaccine candidates are successful in preventing Zika virus infection. While we have begun clinical testing of several Zika vaccine candidates, a safe, effective, and licensed Zika vaccine likely will not be available for several years.

Therapeutics

Although therapeutic development was not initially a major focus, efforts by the federal government to evaluate currently available drugs as well as to develop therapeutic monoclonal antibodies have been recent additions to the MCM portfolio of efforts. Products that could reduce viral load in infected populations (including pregnant women) or that could clear persistent infection would be most desirable. NIAID has accelerated its program originally designed to screen for antiviral drugs with activity against viruses in the flavivirus family, including dengue, West Nile, yellow fever, and Japanese encephalitis viruses, as well as the closely related hepatitis C virus. NIAID has enhanced these efforts by developing an assay to

test compounds for antiviral activity against the Zika virus, and has made this test readily available to the broader research community. As of September 5, 2017, NIAID has run 831 antiviral tests. Of those, 47 yielded high or moderate activity against the Zika virus. Promising drug candidates identified by this assay are being further tested in animal models of Zika virus infection developed with NIAID support. For example, NIAID evaluated BCX4430—a broad-spectrum antiviral drug originally developed by a pharmaceutical company, with NIH and BARDA funding, as a candidate therapeutic for Ebola. NIAID-supported researchers also have identified a human antibody, ZIKV-117, that neutralizes multiple strains of the Zika virus. ZIKV-117 reduces levels of the virus in mouse reproductive tissues and decreases fetal disease in a pregnant mouse model of Zika infection, suggesting that such neutralizing Zika antibodies could be used to treat or prevent Zika virus infection in humans.

Conclusion

This report represents HHS's current estimates for the PHEMCE's MCM program. This budget plan 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 has successfully delivered medical products that address 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 has targeted resources to the high-priority threats and 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. In future years, this report forecasts the procurement of MCMs against filoviruses and additional capabilities against pandemic influenza. 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 maintains its commitment to these goals while recognizing a 1 percent decrease in total forecasted funding relative to the 2015 report. This decrease is a result of the FY 2018 President's Budget funding levels being less than what was reported in last year's report.

In the near term, the PHEMCE has continued to make critical investments along the life cycle development path for a variety of products and against a range of key health security threats due to CBRN and naturally occurring pandemic pathogens. This report forecasts that BARDA will procure MCMs against filoviruses for the SNS as early as FY 2017. Once these MCMs are stockpiled and available for use in a public health emergency, the PHEMCE will have developed and/or acquired critical MCMs against each high priority threat. Other near-term acquisitions will complement existing MCMs. For example, BARDA awarded two contracts for high-throughput biodosimetry devices. By diagnosing patients and quantifying the amount of radiation exposure patients have experienced, these diagnostics possess the potential to enable more accurate treatment and reduce any unnecessary use of therapeutics, thereby lowering costs. BARDA anticipates awarding a PBS contract for point-of-care diagnostics with similar capabilities within this report's five-year period.

In the longer term, 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. In the case of anthrax, the PHEMCE can realize lower stockpiling costs by reducing the stockpiled quantity of an MCM, lengthening the MCM's shelf-life, or shortening the course of treatment, which subsequently reduces the number of courses of antibiotic taken in combination with the MCM.

The risks to successful MCM development have evolved and the PHEMCE has responded with innovative strategies, partnerships and initiatives. In response to the limitations of the "one bug, one drug" approach, the PHEMCE expanded the MCM candidate pipeline and prioritized multiuse products. To assist small start-up manufacturers, the PHEMCE built flexible manufacturing facilities and established new capacities in the National Medical Countermeasures Infrastructure Response Network. Coordination and collaboration on

regulatory activities across the PHEMCE and with external partners is better than ever. Finally, the PHEMCE is improving MCM requirements by looking more accurately at the needs of responders in the face of a public health emergency.

Appendix A – Spend Plan Tables

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY'16	FY'17	FY'18	FY'19	FY'20	FY'16-'20 Total
ASPR	BARDA	Direct Appropriation, Multiyear	Anthrax	Therapeutics	$4.7	$2.4	$0.0	$0.0	$0.0	$7.1
ASPR	BARDA	Direct Appropriation, Multiyear	Anthrax	Vaccine	$18.3	$15.3	$18.0	$10.0	$10.0	$71.6
ASPR	BARDA	Direct Appropriation, Multiyear	BARDA EID		$0.0	$0.0	$0.0	$300.0	$300.0	$600.0
ASPR	BARDA	Direct Appropriation, Multiyear	BARDA Innovation		$14.3	$12.0	$0.0	$0.0	$0.0	$26.3
ASPR	BARDA	Direct Appropriation, Multiyear	BARDA MCI	Medical Countermeasures Innovation	$0.0	$0.0	$0.0	$75.0	$75.0	$150.0
ASPR	BARDA	Direct Appropriation, Multiyear	BARDA Mgt & Admin		$86.8	$83.3	$75.7	$77.4	$77.4	$400.6
ASPR	BARDA	Direct Appropriation, Multiyear	Broad Spectrum Antimicrobials	BARDA CARB	$107.0	$132.0	$107.0	$107.0	$140.0	$593.0
ASPR	BARDA	Direct Appropriation, Multiyear	Broad Spectrum Antimicrobials		$78.8	$85.0	$85.0	$100.0	$125.0	$473.8
ASPR	BARDA	Direct Appropriation, Multiyear	Chemical		$25.8	$40.0	$50.0	$50.0	$75.0	$240.8
ASPR	BARDA	Direct Appropriation, Multiyear	CIADM	Operations	$10.5	$0.0	$0.0	$15.0	$15.0	$40.5
ASPR	BARDA	Direct Appropriation, Multiyear	Cross-Cutting Science	Animal Models	$7.6	$14.0	$10.0	$10.0	$10.0	$51.6
ASPR	BARDA	Direct Appropriation, Multiyear	Cross-Cutting Science	Clinical Services Network	$1.0	$1.0	$2.0	$0.0	$2.0	$6.0
ASPR	BARDA	Direct Appropriation, Multiyear	Filoviruses		$0.0	$10.0	$26.0	$75.0	$75.0	$186.0
ASPR	BARDA	Direct Appropriation, Multiyear	Rad/Nuc	ARS - Neutropenia/Skin/Lung/GI	$60.7	$56.6	$57.0	$60.0	$60.0	$294.3
ASPR	BARDA	Direct Appropriation, Multiyear	Rad/Nuc	Biodosimetry and Biodiagnostics	$46.5	$50.0	$45.0	$30.0	$30.0	$201.5

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY'16	FY'17	FY'18	FY'19	FY'20	FY'16-'20 Total
ASPR	BARDA	Direct Appropriation, Multiyear	Rad/Nuc	Thermal Burn Products	$22.1	$23.0	$25.0	$30.0	$40.0	$140.1
ASPR	BARDA	Direct Appropriation, Multiyear	Smallpox	Vaccine/Antivirals	$14.0	$12.3	$11.0	$15.0	$20.0	$72.3
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	Diagnostics AD	$10.0	$0.6	$5.9	$0.0	$0.0	$16.5
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	Fill/Finish Network	$2.5	$0.0	$0.0	$0.0	$0.0	$2.5
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	International Vaccine Manufacturing Initiative	$0.0	$0.0	$0.0	$10.0	$15.0	$25.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	Vaccine Stockpile, Storage, Stability, and Testing	$12.5	$9.4	$19.0	$20.0	$20.0	$80.9
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual Appropriations	Pandemic Influenza	Vx AD (Universal, Cell and Recomb)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
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	$13.0	$13.0	$26.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Diagnostics AD	$0.0	$13.6	$0.0	$30.0	$30.0	$73.6
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Egg Supply	$0.0	$0.0	$47.0	$0.0	$0.0	$47.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Fill/Finish Network	$0.0	$1.5	$0.0	$0.5	$0.5	$2.5
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Infrastructure	$0.0	$0.0	$61.8	$78.7	$75.6	$216.1
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Therapeutics Advanced Development	$18.3	$27.3	$30.0	$215.0	$275.0	$565.7
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Universal Cell Recombinant-Vx	$12.8	$5.0	$36.1	$215.0	$215.0	$483.9
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Vaccine Stockpiles	$1.8	$12.9	$0.0	$44.0	$44.0	$102.7

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY'16	FY'17	FY'18	FY'19	FY'20	FY'16-'20 Total
ASPR	BARDA	Pandemic Influenza - PHSSEF, Annual No-Year	Pandemic Influenza	Ventilators / Respirators	$1.6	$0.0	$0.0	$5.0	$5.0	$11.6
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Diagnostics AD	$0.0	$0.1	$0.0	$0.0	$0.0	$0.1
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	H7N9 Mfg & Procurement	$0.0	$72.0	$0.0	$0.0	$0.0	$72.0
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Infrastructure	$0.0	$60.1	$0.0	$0.0	$0.0	$60.1
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Therapeutics Advanced Development	$7.7	$30.5	$0.0	$0.0	$0.0	$38.2
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Universal Cell Recombinant-Vx	$3.3	$23.6	$0.0	$0.0	$0.0	$26.9
ASPR	BARDA	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Vaccine Stockpiles	$8.2	$10.3	$0.0	$0.0	$0.0	$18.6
ASPR	BARDA	Project BioShield SRF, No-Year	Anthrax	Therapeutics	$54.7	$0.0	$0.0	$0.0	$75.0	$129.7
ASPR	BARDA	Project BioShield SRF, No-Year	Anthrax	Vaccine	$198.7	$100.5	$128.0	$25.0	$150.0	$602.2
ASPR	BARDA	Project BioShield SRF, No-Year	Biodiagnostic		$0.0	$0.0	$0.0	$25.0	$25.0	$50.0
ASPR	BARDA	Project BioShield SRF, No-Year	Botulinum	Botulinum Antitoxin	$18.5	$53.3	$0.0	$0.0	$50.0	$121.8
ASPR	BARDA	Project BioShield SRF, No-Year	Broad Spectrum Antimicrobials		$0.0	$0.0	$60.0	$195.0	$125.0	$380.0
ASPR	BARDA	Project BioShield SRF, No-Year	Chemical	Chemical Countermeasures	$0.0	$0.0	$75.0	$50.0	$100.0	$225.0
ASPR	BARDA	Project BioShield SRF, No-Year	Filoviruses	Ebola	$0.0	$165.5	$127.0	$125.0	$150.0	$567.5
ASPR	BARDA	Project BioShield SRF, No-Year	Rad/Nuc	ARS - Skin/Lung/GI	$75.3	$0.0	$5.0	$125.0	$75.0	$280.3
ASPR	BARDA	Project BioShield SRF, No-Year	Rad/Nuc	Biodosimetry	$43.8	$50.0	$0.0	$50.0	$50.0	$193.8

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY'16	FY'17	FY'18	FY'19	FY'20	FY'16-'20 Total
ASPR	BARDA	Project BioShield SRF, No-Year	Rad/Nuc	Thermal Burns	$0.0	$57.0	$25.0	$25.0	$40.0	$147.0
ASPR	BARDA	Project BioShield SRF, No-Year	Smallpox	Antivirals	$0.0	$0.0	$90.0	$0.0	$50.0	$140.0
ASPR	BARDA	Project BioShield SRF, No-Year	Smallpox	Vaccine	$100.0	$100.0	$0.0	$0.0	$100.0	$300.0
CDC	DSNS	Direct Appropriation, No-Year	Ancillary	Other supportive (incl. antimicrobials)	$67.4	$21.6	$21.0	$27.2	$18.1	$155.3
CDC	DSNS	Direct Appropriation, No-Year	Anthrax	Antibiotic	$20.8	$86.2	$95.6	$89.9	$121.1	$413.7
CDC	DSNS	Direct Appropriation, No-Year	Anthrax	Therapeutic	$0.0	$0.0	$0.0	$36.0	$51.4	$87.4
CDC	DSNS	Direct Appropriation, No-Year	Anthrax	Vaccine	$214.7	$112.3	$55.5	$0.0	$0.0	$382.6
CDC	DSNS	Direct Appropriation, No-Year	Botulinum	Therapeutic	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
CDC	DSNS	Direct Appropriation, No-Year	Burkholderia	Antibiotic	$5.9	$6.2	$0.7	$0.6	$0.3	$13.8
CDC	DSNS	Direct Appropriation, No-Year	Chemical	Anticonvulsant	$3.1	$8.6	$0.0	$0.6	$1.2	$13.4
CDC	DSNS	Direct Appropriation, No-Year	Chemical	Nerve agent antidote	$0.0	$57.9	$15.5	$33.4	$38.1	$144.9
CDC	DSNS	Direct Appropriation, No-Year	Chemical	Other	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
CDC	DSNS	Direct Appropriation, No-Year	FMS	Antibiotic	$0.2	$0.0	$0.3	$1.1	$0.3	$1.8
CDC	DSNS	Direct Appropriation, No-Year	Pandemic Influenza	Antibiotic	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
CDC	DSNS	Direct Appropriation, No-Year	Pandemic Influenza	Antiviral	$7.0	$0.0	$77.6	$96.5	$48.7	$229.8
CDC	DSNS	Direct Appropriation, No-Year	Pandemic Influenza	Ventilators / Respirators	$0.0	$0.0	$15.0	$15.0	$15.0	$45.0

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY'16	FY'17	FY'18	FY'19	FY'20	FY'16-'20 Total
CDC	DSNS	Direct Appropriation, No-Year	Plague/Tularemia	Antibiotic	$0.0	$0.0	$0.0	$0.0	$7.6	$7.6
CDC	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Antibiotic	$0.0	$0.3	$0.0	$0.3	$0.0	$0.6
CDC	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Antineutropenic	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
CDC	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Antiviral	$0.8	$0.2	$0.5	$0.3	$0.5	$2.2
CDC	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Decorporation	$10.7	$3.0	$0.0	$0.0	$0.0	$13.7
CDC	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Other	$0.0	$0.0	$0.0	$0.0	$0.0	$0.1
CDC	DSNS	Direct Appropriation, No-Year	Rad/Nuc	Other supportive (incl. antimicrobials)	$2.2	$11.1	$9.0	$10.3	$12.1	$44.8
CDC	DSNS	Direct Appropriation, No-Year	Smallpox	Antiviral	$0.7	$0.0	$0.7	$0.9	$0.7	$2.9
CDC	DSNS	Direct Appropriation, No-Year	Smallpox	Therapeutic	$3.9	$12.9	$12.9	$12.9	$12.9	$55.4
CDC	DSNS	Direct Appropriation, No-Year	Smallpox	Uricosuric	$0.0	$0.0	$0.0	$0.0	$0.0	$0.1
CDC	DSNS	Direct Appropriation, No-Year	Smallpox	Vaccine	$38.1	$40.8	$50.5	$38.6	$40.4	$208.3
CDC	DSNS	Direct Appropriation, No-Year	SNS Non-Procurement Costs		$199.6	$213.8	$220.2	$226.9	$233.7	$1,094.2
FDA	MCM Initiative	Direct Appropriation, Annual	FDA Regulatory Science	Antimicrobial Resistance MCM Funding	$21.6	$21.6	$21.6	$22.2	$22.9	$109.9
FDA	MCM Initiative	Direct Appropriation, Annual	FDA Regulatory Science	CBRN MCM Base Funding (pre-MCMi)	$54.4	$54.4	$54.4	$56.0	$57.7	$276.9
FDA	MCM Initiative	Direct Appropriation, Annual	FDA Regulatory Science	Direct Appropriation, MCMi, Annual	$24.6	$24.6	$24.6	$45.9	$47.3	$166.9
FDA	MCM Initiative	Direct Appropriation, Multiyear	FDA Regulatory Science	Emerging Threats Funding, Multiyear, Direct Appropriation	$0.0	$1.9	$4.1	$4.1	$0.0	$10.0

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY'16	FY'17	FY'18	FY'19	FY'20	FY'16-'20 Total
FDA	MCM Initiative	Direct Appropriation, No-Year	FDA Regulatory Science	Pandemic Influenza MCM Funding	$36.0	$36.0	$36.0	$37.1	$38.2	$183.2
FDA	MCM Initiative	Ebola Emergency Funding, Multiyear, Direct	FDA Regulatory Science	Ebola Emergency Funding	$13.7	$0.0	$0.0	$0.0	$0.0	$13.7
FDA	MCM Initiative	Transfer from No-Year PI Funding	FDA Regulatory Science	Transfer from No-Year PI Funding	$0.0	$1.8	$1.7	$0.0	$0.0	$3.6
NIH	NIAID	Direct Appropriation, Annual	Anthrax	Basic/Other Research	$9.2	$9.6	$6.7	$6.9	$7.1	$39.5
NIH	NIAID	Direct Appropriation, Annual	Anthrax	Vaccine	$17.0	$17.7	$12.3	$12.7	$13.1	$72.8
NIH	NIAID	Direct Appropriation, Annual	Botulinum	Antitoxins	$8.8	$9.1	$6.3	$6.5	$6.7	$37.5
NIH	NIAID	Direct Appropriation, Annual	Botulinum	Basic/Other Research	$2.9	$3.0	$2.1	$2.2	$2.2	$12.5
NIH	NIAID	Direct Appropriation, Annual	Botulinum	Vaccine	$0.7	$0.7	$0.5	$0.5	$0.5	$2.9
NIH	NIAID	Direct Appropriation, Annual	Broad Spectrum Antimicrobials	Antibiotics	$287.9	$339.5	$236.3	$243.4	$251.2	$1,358.3
NIH	NIAID	Direct Appropriation, Annual	Broad Spectrum Antimicrobials	Antivirals	$105.7	$109.9	$76.5	$78.8	$81.3	$452.3
NIH	NIAID	Direct Appropriation, Annual	Cross-Cutting Science	Animal Models/Regulatory Science	$28.0	$29.1	$20.3	$20.9	$21.5	$119.8
NIH	NIAID	Direct Appropriation, Annual	Cross-Cutting Science	Basic/Other Research	$286.9	$298.3	$199.7	$205.7	$212.3	$1,202.8
NIH	NIAID	Direct Appropriation, Annual	Cross-Cutting Science	Product Development	$157.7	$164.0	$114.2	$117.6	$121.4	$674.9
NIH	NIAID	Direct Appropriation, Annual	Cross-Cutting Science	Translational	$50.5	$52.5	$36.6	$37.6	$38.9	$216.0
NIH	NIAID	Direct Appropriation, Annual	Filoviruses	Basic/Other Research	$38.6	$40.1	$27.9	$28.8	$29.7	$165.2
NIH	NIAID	Direct Appropriation, Annual	Filoviruses	Vaccine	$31.7	$33.0	$23.0	$23.7	$24.4	$135.8

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY'16	FY'17	FY'18	FY'19	FY'20	FY'16-'20 Total
NIH	NIAID	Direct Appropriation, Annual	Multiplex Diagnostics	Diagnostics	$70.3	$73.2	$50.9	$52.5	$54.1	$301.0
NIH	NIAID	Direct Appropriation, Annual	Other Threats	Basic/Other Research	$343.4	$339.8	$236.6	$243.6	$251.4	$1,414.9
NIH	NIAID	Direct Appropriation, Annual	Other Threats	Vaccine	$91.0	$94.7	$65.9	$67.9	$70.1	$389.5
NIH	NIAID	Direct Appropriation, Annual	Pandemic Influenza	Basic/Other Research	$100.2	$104.2	$72.5	$74.7	$77.1	$428.7
NIH	NIAID	Direct Appropriation, Annual	Pandemic Influenza	Vaccine	$83.0	$96.3	$75.1	$77.3	$79.8	$411.5
NIH	NIAID	Direct Appropriation, Annual	Plague/Tularemia	Basic/Other Research	$8.6	$9.0	$6.2	$6.4	$6.6	$36.9
NIH	NIAID	Direct Appropriation, Annual	Plague/Tularemia	Vaccine	$2.6	$2.7	$1.9	$1.9	$2.0	$11.0
NIH	NIAID	Direct Appropriation, Annual	Smallpox	Basic/Other Research	$14.4	$15.0	$10.4	$10.8	$11.1	$61.7
NIH	NIAID	Direct Appropriation, Annual	Smallpox	Vaccine	$0.8	$0.8	$0.6	$0.6	$0.6	$3.3
NIH	NIAID	Pandemic Influenza - PHSSEF, Sup Bal No-Year	Pandemic Influenza	Vaccine	$8.5	$66.0	$0.0	$0.0	$0.0	$74.5
NIH	Non-NIAID	Direct Appropriation, Annual	Broad Spectrum Antimicrobials	Antibiotics/Antiviral	$2.7	$2.8	$2.0	$2.0	$2.1	$11.6
NIH	Non-NIAID	Direct Appropriation, Annual	Multiplex Diagnostics	Diagnostics	$1.0	$1.1	$0.7	$0.8	$0.8	$4.4
NIH	Non-NIAID	Direct Appropriation, Annual	Other Threats	Basic/Other Research	$28.9	$30.0	$20.9	$21.5	$22.2	$123.6
NIH	Non-NIAID	Direct Appropriation, Annual	Other Threats	Vaccine	$3.9	$4.0	$2.8	$2.9	$3.0	$16.5
NIH	OD	Direct Appropriation, Annual	Chemical	Chemical Countermeasures Research	$47.5	$47.5	$33.1	$34.1	$35.2	$197.2
NIH	OD	Direct Appropriation, Annual	Rad/Nuc	Nuclear/Radiological Countermeasures	$45.9	$45.9	$32.0	$32.9	$34.0	$190.7

Agency	Office	Funding Source	Portfolio	Sub Portfolio	FY'16	FY'17	FY'18	FY'19	FY'20	FY'16-'20 Total
NIH	OD	Ebola Emergency Funding, Multiyear, Direct	Broad Spectrum Antimicrobials	Antivirals	$12.4	$0.0	$0.0	$0.0	$0.0	$12.4
NIH	OD	Ebola Emergency Funding, Multiyear, Direct	Filoviruses	Basic/Other Research	$13.0	$0.0	$0.0	$0.0	$0.0	$13.0
NIH	OD	Ebola Emergency Funding, Multiyear, Direct	Filoviruses	Vaccine	$26.4	$0.0	$0.0	$0.0	$0.0	$26.4
NIH	OD	Ebola Emergency Funding, Multiyear, Direct	Multiplex Diagnostics	Diagnostics	$3.2	$0.0	$0.0	$0.0	$0.0	$3.2
NIH	OD	Zika Emergency Funding, Multiyear, Direct	Multiplex Diagnostics	Diagnostics	$5.0	$11.0	$0.0	$0.0	$0.0	$16.0
NIH	OD	Zika Emergency Funding, Multiyear, Direct	Other Threats	Basic/Other Research	$12.0	$5.0	$0.0	$0.0	$0.0	$17.0
NIH	OD	Zika Emergency Funding, Multiyear, Direct	Other Threats	Vaccine	$30.0	$136.0	$0.0	$0.0	$0.0	$166.0

‡ **Figures above are estimates and subject to change. Future year projections were developed without regard to competing priorities that are considered throughout the budget development and submission process.**