FDA Medical Countermeasures Initiative (MCMi)
Protecting National Health and Security

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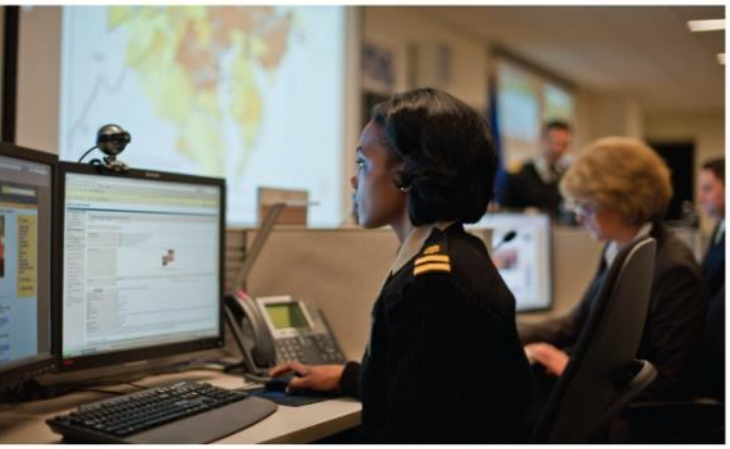
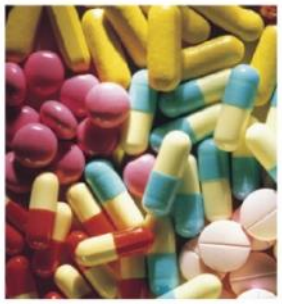
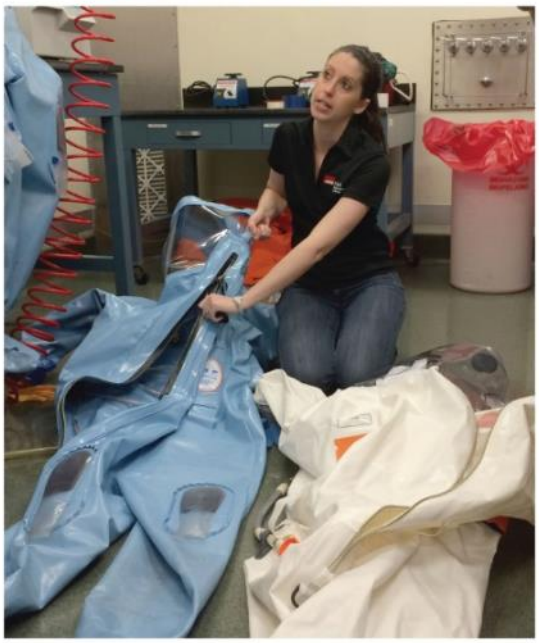
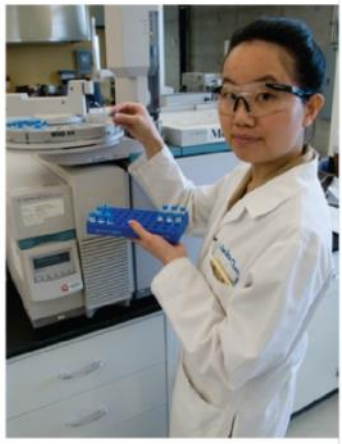
MCMi Program Update

Fiscal Year 2016





U.S. FOOD & DRUG ADMINISTRATION

Message from Luciana Borio, MD, Acting Chief Scientist, and

RADM Carmen T. Maher, MA, BSN, RN, RAC, Acting Assistant Commissioner for Counterterrorism Policy

We are pleased to present the Food and Drug Administration (FDA) Medical Countermeasures Initiative (MCMi) program update for our sixth year of operations.[1] As we have since MCMi was launched in 2010, FDA continues our ongoing work to advance the development and availability of medical countermeasures to protect against chemical, biological, radiological, and nuclear (CBRN) threats. This report covers these activities including medical countermeasure (MCM)-related regulatory science and legal and policy actions.

FDA continues to respond to emerging public health threats in an unprecedented way. The tragic Ebola epidemic in West Africa was declared over in early 2016, and the World Health Organization (WHO) declared in November 2016 that Zika is no longer an international public health emergency.[2] However, this doesn't mean that these diseases are no longer a concern. Vaccines for Ebola are still under development. WHO has identified—and the global public health community agrees—that Zika is a serious public health issue that will require sustained and long-term efforts moving forward. We must continue to expedite development of MCMs to detect, treat, and prevent emerging diseases—particularly Zika, which is likely to become endemic in much of North America, with devastating and life-altering consequences for some of our most vulnerable populations.

We cannot lose momentum when it comes to supporting development and testing of new products to combat emerging diseases

We cannot lose momentum, especially when it comes to supporting development and testing of new products to combat these emerging infectious diseases—and we are not. FDA has a critical role in helping to facilitate the development and availability of investigational products for use against emerging infectious diseases. We remain committed to working with the global community as we collaborate to rapidly respond to emerging threats, including the current outbreak of Zika virus.[3]

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[1] Fiscal year 2016 covers the period from October 1, 2015, to September 30, 2016.
[2] World Health Organization, "Fifth Meeting of the Emergency Committee Under the International Health Regulations Regarding Microcephaly, Other Neurological Disorders, and the Zika Virus," November 18, 2016, http://who.int/mediacentre/news/statements/2016/zika-fifth-ec/en/
[3] For more information about FDA's Zika virus response updates, visit: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm

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FDA's Medical Countermeasures Initiative
Fiscal Year 2016 Program Update

Background

The U.S. Food and Drug Administration (FDA) plays a critical role in protecting the United States from chemical, biological, radiological, nuclear (CBRN), and emerging infectious disease threats such as pandemic influenza, Ebola virus disease (EVD), and Zika virus infections. FDA is responsible for assessing the safety and effectiveness of medical countermeasures (MCMs) — including drugs, therapeutic biologics, vaccines, and devices, such as diagnostic tests—to counter these threats.[4]

In addition to its regulatory responsibilities, FDA works closely with interagency partners through the U.S. Department of Health and Human Services (HHS) Public Health Emergency Medical Countermeasures Enterprise (PHEMCE, or Enterprise) to build and sustain the MCM programs necessary to respond effectively to public health emergencies.[5] FDA also works closely with the U.S. Department of Defense (DoD) to facilitate the development and availability of MCMs to support the unique needs of the warfighter. FDA supports the Enterprise and DoD by providing subject-matter expertise in MCM development and by providing scientific and regulatory input to inform MCM procurement and stockpiling decisions. In addition, FDA facilitates access to available MCMs to respond to public health and military emergencies, even when products are still investigational or not yet approved for that particular use, provided certain criteria are met.[6,7]

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[4] MCMs include qualified countermeasures as defined in section 319F–1(a)(2)(A) of the Public Health Service Act (42 USC. § 247d–6a(a))(2)(A); qualified pandemic or epidemic products as defined in section 319F–3(i)(7) of the Public Health Service Act (PHS Act) (42 USC. § 247d–6d(i)(7)), and security countermeasures as defined in section 319F-2(c)(1)(B) of the PHS Act (42 USC § 247d–6b(c)(1)(B)). Some items included in this report, such as traumatic brain injury diagnostics and some activities discussed, such as combatting antimicrobial resistance, may not meet the statutory definition of MCMs or relate directly to products defined as MCMs, but were included in this report as examples of additional work supported by MCMi staff. Inclusion of such examples is not intended as comprehensive reporting on Agency activities related to these topics.

[5] The Enterprise is a coordinated, interagency partnership that fosters the MCM programs necessary to improve public health emergency preparedness as well as to prevent and mitigate the adverse health consequences associated with CBRN threats and emerging infectious diseases. The Enterprise is led by the Office of the Assistant Secretary for Preparedness and Response and includes three primary HHS internal agencies: the Centers for Disease Control and Prevention (CDC), FDA, and the National Institutes of Health (NIH). Key interagency partners are: the Department of Homeland Security (DHS), the Department of Defense (DoD), the Department of Veterans Affairs, and the Department of Agriculture (USDA).

[6] See e.g., sections 561 and 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

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

In 2013, the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) was enacted.[8] PAHPRA contains key legal authorities to strengthen the United States' preparedness for public health emergencies involving CBRN agents and emerging infectious disease threats. PAHPRA also codified many of the activities already ongoing at FDA under the MCMi to foster the development and availability of MCMs as well as created new authorities to enable FDA to more effectively support preparedness and response efforts. PAHPRA requires FDA to issue an annual report detailing its MCM activities. This report responds to that requirement for Fiscal Year (FY) 2016.[9]

FY 2016 Resources for Medical Countermeasures Activities

FDA obligated an estimated $124.1 million in FY 2016 to support CBRN and pandemic influenza-related MCM activities (**Table 1**). These resources comprised a combination of base funding and no-year funding.

Table 1: FY 2016 Resources Obligated to Medical Countermeasure Activities (dollars in millions)

	FY 16 Estimate	FY 16 FTE Estimate
CBRN Base Funding	$53.0	229
Pandemic Influenza Base Funding	$35.7	158
MCMi Base Funding	$24.6	80.5
Subtotal	$113.3	467.5
Ebola Supplemental Funding (No-Year)	$10.3	10.7
Total	**$123.6**	**478.2**

Base Funding

FDA obligated an estimated $113.3 million from its FY 2016 base resources to support CBRN and pandemic influenza-related MCM activities. This funding included

[7] For purposes of this document, "approved" refers to "FDA-approved, licensed, or cleared" under sections 505, 510(k), or 515 of the FD&C Act or of section 351 of the PHS Act.
[8] Public Law 113-5, 127 Stat. 161.
[9] Detailed information on FDA's MCM development and review activities for covering fiscal years 2011-2015 can be found in the *MCMi Year 1 Status Report*, *MCMi Year 2 Program Update, MCMi Fiscal Year 2013 Program Update*, *MCMi Fiscal Year 2014 Program Update, and MCMi Fiscal Year 2015 Program Update* available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm270744.htm

$53.0 million for CBRN preparedness activities, $35.7 million for pandemic influenza preparedness activities, and $24.6 million for the MCMi.

This funding supported 467.5 full-time equivalents (FTEs) as well as a $1.6 million investment in the MCMi Regulatory Science Program.

No-Year Funding

In FY 2015, FDA received $25 million in emergency supplemental, no-year funding to support activities related to responding to the Ebola epidemic in West Africa including conducting medical product review and funding regulatory science research to help expedite the development and availability of medical products for Ebola. FDA spent an estimated $11.3 million of this funding in FY 2015 and an estimated $10.3 million in FY 2016. This funding supported 10.7 FTEs as well as a $5.7 million investment in regulatory science research to support Ebola response activities. In addition, FDA reprogrammed $2.4 M of its Ebola supplemental funding to support regulatory science for Zika virus response, and obligated $1.7 million of those funds in FY 2016.

FY 2016 Objectives, Activities, and Achievements

Objectives and Activities

FDA's overarching objective with respect to MCMs—which cuts across all FDA centers and offices engaged in the MCM mission space—is to facilitate the development of and access to safe, effective, and quality MCMs to counter high-priority CBRN and emerging infectious disease threats, as well as MCMs to support the warfighter. FDA pursues this objective through a variety of activities including:

- Providing regulatory advice, guidance, and technical assistance to sponsors developing investigational MCMs for CBRN or emerging threat indications
- Discussing questions with potential product sponsors to help clarify requirements for approval
- 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 for use—when necessary—through an appropriate mechanism

- Responding to emerging public health threats
- Establishing and sustaining Public Health and Security Action Teams to identify and catalyze the resolution of regulatory and scientific challenges associated with MCMs to address high-priority threats
- Collaborating with U.S. government partners developing MCMs
- Sustaining the MCMi Regulatory Science Program to create tools, standards, and approaches to develop and assess MCM safety, efficacy, quality, and performance
- Ensuring that FDA laws and policies adequately support MCM development and enable preparedness and response activities
- Sustaining the MCMi Professional Development Program to ensure that FDA personnel maintain the requisite skills and abilities to support the MCM mission

The following sections provide detail on achievements in FY 2016 with respect to these activities.

Medical Countermeasure Approvals

During FY 2016, FDA continued to review marketing applications for MCMs against CBRN and emerging infectious disease threats and to approve applications that met standards for safety, efficacy, and quality. FDA approved the majority of MCM marketing applications under review[10] in FY 2016 (**Appendix 1**: FY 2016 Medical Countermeasure Approvals).[11]

FDA facilitates the development of and access to safe, effective, and quality MCMs

In the area of MCMs to treat diseases or conditions caused by CBRN threats, FDA approved Anthim (obiltoxaximab) to treat inhalational anthrax in combination with appropriate antibacterial drugs, and reduce the risk of inhalational anthrax when alternative

[10] "Under review" indicates that a marketing application has been submitted to FDA for approval by the product's sponsor.

[11] More information is available at: Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/, Biologics Products & Establishments: http://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm, and Medical Device Databases: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm

therapies are not available or not appropriate. Anthim is a monoclonal antibody that neutralizes toxins produced by *Bacillus anthracis*.[12] FDA also expanded the indication for BioThrax (Anthrax Vaccine Adsorbed) to include post-exposure prophylaxis (PEP) of disease resulting from suspected or confirmed *B. anthracis* exposure, when combined with the recommended course of antimicrobial therapy in persons 18 – 65 years of age.[13] Both of these indications were approved under the Animal Rule.[14] BioThrax was the first vaccine to receive FDA approval for a new indication based on the Animal Rule.[15] In addition, FDA approved a new indication for Neulasta (pegfilgrastim), for the treatment of adult and pediatric patients at risk of developing myelosuppression after a radiological/nuclear incident.[16]

With regard to all-hazards preparedness, FDA approved the Ahead 300 device, which analyzes a patient's electroencephalograph (EEG) using a sensor attached to a smartphone to provide an interpretation of the structural condition of the patient's brain after a head injury at the point of care. This device can help rapidly identify patients who may have traumatic brain injury, as would be expected to occur after detonation of an improvised explosive device.[17] FDA also expanded approval of the XSTAT 30 device from use by the military only to use in adults and adolescents in the general population. The XSTAT 30 is an expandable, multi-sponge wound dressing used to control severe, life-threatening bleeding from wounds in areas that a tourniquet cannot be placed (such as the groin or armpit) in battlefield and civilian trauma settings.[18] FDA also approved the ER-REBOA (Resuscitative Endovascular Balloon Occlusion of the Aorta) Catheter for the temporary occlusion of large vessels and monitoring of blood pressure providing a minimally invasive technique to temporarily occlude the aorta and stop bleeding.

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[12] For more information, view the FDA news release: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm491470.htm

[13] For more information, view the FDA news release: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm474027.htm

[14] Under the Animal Rule, when human challenge studies would not be ethical and field trials after accidental or intentional exposure have not been feasible, FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans. Demonstration of the product's safety in humans is still necessary (see 21 CFR 314.600--650 for drugs and 21 CFR 601.90--95 for biological products).

[15] FDA also expanded the license to include the manufacture of BioThrax (Anthrax Vaccine Adsorbed) in the sponsor's large-scale manufacturing facility.

[16] Myelosuppression occurs when radiation damages internal organs, including bone marrow. Suppression of the bone marrow blocks the production of blood cells.

[17] In addition to EEG capabilities provided in previously approved BrainScope products, the Ahead 300 includes additional assessments providing clinicians with a digitized, streamlined report, delivering a comprehensive and objective panel of results to facilitate their differential diagnosis, according to the company. More information: http://brainscope.com/media/2016/9/26/brainscope-announces-fda-clearance-of-the-first-handheld-medical-device-for-assessment-of-the-full-spectrum-of-traumatic-brain-injury

[18] For more information, see the FDA news release: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm475810.htm

In the area of diagnostics for CBRN threats, FDA approved a Shiga Toxin Direct Test for the detection of nucleic acids and toxin gene sequences found in Shiga toxin producing strains of *E. coli* 0157 and *Shigella dysenteriae*, in stool specimens.

In the area of re-emerging threats, FDA approved three modifications to a *Bordetella pertussis* assay: a change to the sample preparation, addition of an acceptable specimen collection and transport system, and addition of an optional sample pre-treatment to neutralize the interfering activity of biological substances found in the nasopharynx (upper part of the throat) of some patients.

In the area of pandemic influenza preparedness, FDA approved Fluad, the first seasonal influenza vaccine containing an adjuvant. Fluad, a trivalent vaccine produced from three influenza virus strains (two subtype A and one type B), is approved for the prevention of seasonal influenza in people 65 years of age and older. [19] FDA also approved a new indication for another influenza vaccine to include a quadrivalent formulation (Afluria Quadrivalent) for use in people 18 years of age and older, and approved Flucelvax quadrivalent for use in patients aged four years and older.

FDA also approved five nucleic acid-based new influenza tests: three qualitative *in vitro* diagnostic (IVD) tests for the detection and differentiation of influenza A, influenza B, and respiratory syncytial viruses (ARIES Flu A/B & RSV Assay, Cobas Influenza A/B & RSV, and Xpert Flu+RSV); a qualitative IVD test for the detection and differentiation of influenza A and B viral RNA (Solana Influenza A+B Assay); and a multiplexed device for the qualitative detection of influenza A (with sub-type differentiation), influenza B, and other respiratory viruses and bacteria (NxTag Respiratory Pathogen Panel). FDA also approved modifications to nine previously cleared influenza detection IVD devices to include additional specimen types, redesign primes and probes, remove the detection of an influenza sub-type from the assay, increase instrument throughput, update the Limitations section of the labeling, and revise labeling changes to add results of testing new strains of influenza viruses. These steps forward in influenza treatments and diagnostics facilitate preparedness for both seasonal and pandemic influenza, as new tests and technologies may be applied more rapidly to emerging pandemic influenza strains once approved for seasonal influenza use.

Six additional marketing applications for new MCMs or new MCM indications were under review in FY 2016; these reviews were still ongoing at the end of the reporting period for this report. While FDA anticipates meeting the goal date for a decision for each of these

[19] For more information, view the FDA news release: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm474295.htm

submissions, FDA is generally prohibited from disclosing any determinations regarding the filing or approvability of any marketing application for a medical product under applicable statutory and regulatory provisions unless the application is approved or other grounds for disclosure apply.[20]

Supporting an Adequate Supply of Medical Countermeasures

FDA continued efforts to support the establishment and sustainment of an adequate supply of MCMs during FY 2016. One way FDA does this is by supporting the Shelf-Life Extension Program (SLEP). SLEP is a Federal fee-for-service program for extending the useful shelf life of military-significant and contingency use medical products, including MCMs that are owned by components of DoD or other Federal program participants such as the Strategic National Stockpile (SNS). SLEP is designed to defer drug replacement costs for date-sensitive stockpiles of drugs by extending their useful shelf life beyond the manufacturer's original expiration date. FDA laboratory personnel test and evaluate drugs submitted for shelf-life extension to assure stability and quality before a shelf-life extension is granted. In FY 2016, as a result of SLEP testing that assured drug stability and quality, FDA granted shelf-life extensions for 2,020 lots (batches) of MCM drugs.

A variety of auto-injector products – FDA reviewed scientific data and determined that, if properly stored, certain auto-injectors could be used beyond their original labeled expiration date, to help ensure that the nation's warfighters and first responders continue to have ready access to these potentially life-saving products. (FDA photo)

Another way FDA worked to ensure an adequate supply of MCMs in FY 2016 was by conducting post-marketing current good

[20] For updated information about MCM approvals after the FY 2016 reporting period, visit the MCMi News and Events page at: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm262925.htm

manufacturing practices (cGMP) inspections for facilities that produce MCMs to ensure that these products were produced under cGMP and to help identify and resolve any issues that could potentially lead to a shortage due to manufacturing issues.[21]

In addition, FDA continued efforts to better secure the drug supply chain to protect consumers from counterfeit or substandard drugs, including MCMs. For example, FDA obtained spectral data on foreign-manufactured, FDA-approved MCM drugs and added that information to its spectral library, which will help facilitate the prevention of the introduction of counterfeit or substandard MCM drugs into the supply chain by providing a reference standard. [22]

FDA also works to resolve MCM shortages as quickly as possible when they occur. In FY 2016, FDA continued to collaborate with U.S. government partners and the manufacturer of auto-injector products used for the treatment of nerve agent and insecticide poisoning to help prevent shortages of these products when production stopped after quality issues were identified in the manufacturing process. FDA reviewed applicable scientific data and determined that, if properly stored, certain lots of this manufacturer's auto-injector products held for emergency use could be used beyond the original labeled expiration date for a period specified by FDA, to help ensure that the nation's warfighters and first responders continue to have ready access to these products.[23] FDA also provided information on such expiry dating extensions to international military and public health partners to assist them in their determinations about whether they should extend the shelf life of their stockpiled auto-injector products produced by the same manufacturer. Meanwhile, FDA continued to work with the product manufacturer so production of new product can be resumed.

[21] cGMPs provide for systems that ensure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP regulations ensures the identity, strength, quality, and purity of medical products by requiring that manufacturers adequately control manufacturing operations.
[22] Spectral data provides information about the molecular make-up of compounds, such as drugs, and can be used to help identify counterfeit MCMs, or MCMs that do not meet quality objectives.
[23] For the latest updates on expiry dating extensions for auto-injectors, see http://www.fda.gov/Drugs/DrugSafety/ucm376367.htm

Enabling Access to Available Medical Countermeasures Under FDA's Emergency Use Authorization[24]

During FY 2016, FDA continued to work with Enterprise partners, including DoD, and product sponsors to enable access to available MCMs when necessary. One way FDA does this is by issuing Emergency Use Authorizations (EUAs), which allow FDA to authorize the use of an unapproved MCM, or the unapproved use of an approved product, in anticipation of a potential emergency or during an actual emergency involving a specified CBRN agent or agents if certain statutory criteria are met.[25] In FY 2016, FDA issued 12 EUAs for diagnostic tests to detect Zika virus and/or diagnose Zika virus infection, and 2 EUAs for diagnostic tests for detection of Ebola virus (in addition to 10 similar EUAs issued in previous fiscal years).[26]

During FY 2016, FDA provided feedback to sponsors on 36 pre-EUAs for Zika diagnostic tests

In addition to issuing EUAs when necessary, FDA also works to ensure that the U.S. government is as prepared as possible to deploy MCMs that may need to be used under an EUA. To facilitate the issuance of EUAs, FDA has developed a pre-EUA submission process by which FDA works with product sponsors or government agencies, such as the CDC and DoD, to facilitate the development of pre-EUA packages that will form the basis of an EUA request and issuance when circumstances justify.[27] During FY 2016, FDA continued to work with CDC, the Biomedical Advanced Research and Development Authority (BARDA), DoD, and industry on pre-EUA activities for MCMs against a diverse array of threats including

[24] Section 564 of the FD&C Act

[25] Under the Project BioShield Act of 2004 [PL 108-276], which was amended by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 [PL 113-5], the Secretary of HHS has the authority to authorize the "emergency use" of MCMs in emergencies under certain terms and conditions [21 USCS § 360bbb-3].

[26] This support includes numerous activities including availability of pre-IND consultations for drug development proposals, and pre-EUA discussions in areas where product technology is sufficiently mature and generalizable (and need among potential U.S. users sufficiently widespread) to justify an HHS determination and declaration. For more about EUAs, including additional Zika diagnostic EUAs issued after FY 2016, see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm

[27] Pre-EUA packages contain data and information about the safety, quality, and efficacy of the product, its intended use under an EUA, and information about the potential emergency situation that might unfold. The pre-EUA process allows FDA scientific and technical subject matter experts to begin a review of information and assist in the development of conditions of authorization, fact sheets, and other documentation needed for an EUA in advance of an emergency.

smallpox, anthrax, pandemic influenza, Ebola virus, Zika virus, and nuclear threats. For example, during FY 2016 FDA provided feedback to sponsors on 36 pre-EUAs for Zika diagnostic tests, and 4 pre-EUAs for Ebola diagnostic tests.

Responding to Emerging Public Health Threats

FDA is actively supporting the national and international response to Zika virus.[28] As of late September 2016, FDA has mobilized more than 400 staff members to support the agency's critical contributions to the U.S. Government's Zika virus response.[29]

In addition to its role facilitating the development and availability of investigational products and protecting the blood supply, FDA communicates with key stakeholders including healthcare providers and product sponsors about emergency response activities.

In FY 2016, FDA also continued to support the international response to the Ebola epidemic in West Africa, which emerged in 2014. Throughout the epidemic response, FDA has worked proactively with U.S. government partners, medical product developers, and international partners (including the World Health Organization (WHO) and international regulatory counterparts) providing scientific and regulatory advice to help facilitate the development and availability of MCMs to respond to the epidemic.[30]

In addition, FDA continued similar activities to respond to the Middle East Respiratory Syndrome coronavirus (MERS-CoV) outbreak, which was first noted in the Middle East in 2012, with subsequent importations by international travel into a number of other countries.

Key FDA response activities include:

- Collaborating closely with HHS, other Federal agencies, and international partners in preparedness and response decisions regarding MCM development and use
- Providing review and feedback on development proposals including clinical trial design and data assessment

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

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

[30] View the latest updates on FDA's Ebola response at http://www.fda.gov/ebola

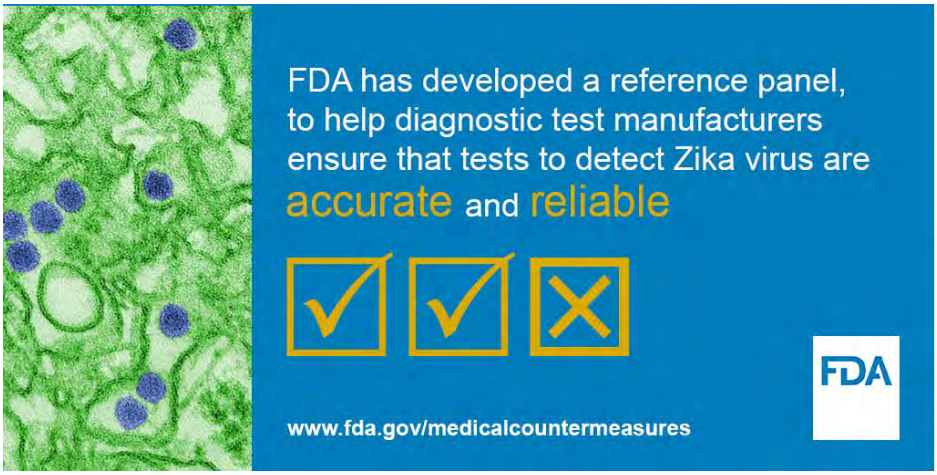
- Maintaining regular contact with drug, vaccine, and device (including diagnostic test) developers, via established mechanisms, and expediting the regulatory review of data for products that are currently in the pipeline and products that are still very early in development
- Advising on design and set-up of clinical trials for establishing the safety and efficacy of investigational products for the treatment and/or prevention of emerging infectious diseases, including Ebola and Zika
- Supporting FDA's ongoing efforts to protect the safety of the nation's blood supply and human cells, tissues, and cellular/tissue-based products for transplantation, including issuing guidance recommending universal testing of donated whole blood and blood components for Zika virus in the U.S. and its territories,[31] and guidance providing recommendations to reduce the potential transmission risk of Zika virus from human cells, tissues, and cellular and tissue-based products (HCT/Ps)[32]
- Enabling access to investigational MCMs—when necessary—through an appropriate mechanism such as under an EUA or under expanded access mechanisms (e.g., FDA enabled access to investigational MCMs under Emergency Investigational New Drug (eIND) applications to treat Ebola patients in the United States during the period of the Ebola epidemic before clinical trials were established, when the clinical circumstances warranted)
- Issuing EUAs for diagnostic tests for Zika and EVD (see **Appendix 2**: Current Emergency Use Authorizations for a list of current EUAs)
- Addressing issues related to the export of investigational MCMs
- Preparing to implement safety surveillance programs for adverse events associated with MCM use and take appropriate action if safety issues are identified
- Protecting consumers from fraudulent products related to the Ebola and Zika viruses
- Monitoring the MCM supply chain to identify product shortages, distribution of misbranded/counterfeit products, and false product claims, and taking appropriate action when necessary to protect consumers

[31] The guidance *Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components* is available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf

[32] The guidance *Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by HCT/Ps* is available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf

- Reviewing the use of innovative strategies that fall under FDA's regulatory authorities to help suppress the population of virus-carrying mosquitoes[33]

In addition, to help Zika diagnostic manufacturers assess traceability of their tests (a requirement for Zika virus EUA), FDA developed the FDA Zika Virus Reference Materials for nucleic acid (NAT)-based IVD devices, available upon request to Zika device developers who have a pre-EUA submission with the agency and have established the analytical and clinical performance of their assay.[34]



Throughout the Ebola epidemic, and more recently to support Zika response activities, FDA has worked to establish and maintain good lines of communication with regulatory authorities in the affected countries to enable technical and information exchange, and to make sure that the needs of the affected countries are understood and addressed.

Agreements established in FY 2016 between FDA and its international counterparts have helped information-sharing and collaboration, and have better prepared the international regulatory community to respond to future public health emergencies. For example, in October 2015, FDA and the Saudi Food and Drug Authority (SFDA) signed reciprocal confidentiality commitments to help facilitate communications between the two agencies on medical products used, or proposed to be used, for Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

[33] For more information, view FDA Releases Final Environmental Assessment for Genetically Engineered Mosquito: http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm490246.htm
[34] An infographic about these reference materials is available at: http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/UCM507010.pdf

as part of cooperative regulatory activities.[35] In April 2016, FDA and the Brazilian Health Regulatory Agency (ANVISA) signed a statement of continued cooperation to offer mutual support and to collaborate to address the public health emergency presented by the Zika virus disease outbreak in the Americas.

Facilitating Medical Countermeasure Development

Action Teams

Under the MCMi, FDA established multidisciplinary Public Health and Security Action Teams (Action Teams) as necessary to advance MCMs for priority threats by working with internal and external entities—as appropriate—to identify and catalyze the resolution of regulatory and scientific challenges to MCM development. The following information summarizes activities of the Action Teams that were active in FY 2016.

Microbial Sequencing and Multiplex *In Vitro* Diagnostics Action Team – This Action Team continued its work to make available a vetted, validated, and curated database of high-quality genomic sequence data for MCM and clinically significant bacterial pathogens to support sequenced-based diagnostic device development. Such diagnostics may include multiplex diagnostic devices, which test for multiple pathogens simultaneously from a single clinical specimen, providing valuable information when responding to a public health emergency. Key activities during FY 2016 included:

- Continuing a collaboration with the National Center for Biotechnology Information (NCBI), the Lawrence Livermore National Laboratory (LLNL), and the Institute for Genome Sciences at the University of Maryland to establish quality criteria for microbial reference databases that will be critical to developers seeking to validate their candidate next-generation sequencing (NGS)-based IVD tests.

- Continuing to facilitate the population of a publicly available database for regulatory-grade microbial genomic reference sequences (FDA-ARGOS), established in FY 2014, through NBCI. The sequencing contract was awarded to the Institute of Genomic Sciences at the University of Maryland to sequence and deposit additional genus-diverse and public health need isolates. Approximately 2,000 isolates will be sequenced as part

[35] FDA and SFDA reciprocal agreements, signed in FY 2016 (PDF, 185 KB): http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/UCM469577.pdf

of the FDA-ARGOS project. [36] This database is being expanded to generate 150 high-quality, nearly-complete draft genome sequences of mosquito-borne viral pathogens, including Zika virus sequences.

- Continuing a collaboration with the National Institute of Standards and Technology (NIST) to develop mixed microbial reference materials that will be critical to developers seeking to validate their candidate NGS-based IVD tests.
- Continuing a collaboration with the Defense Advanced Research Projects Agency (DARPA) to support its Diagnostics on Demand (DxOD)/Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT) program.
- Sustaining an interactive collaboration with the DoD on the development of its Next-Generation Diagnostic System (NGDS) to replace the Joint Biological Agent Identification and Diagnostic System (JBAIDS).

Acute Radiation Syndrome (ARS) Action Team – This Action Team continued its efforts to clarify the regulatory requirements for development of MCMs for ARS indications, to improve survival and mitigate and treat injuries from radiological/nuclear events. Key activities during FY 2016 included:

- Supporting the development of an ARS Questions and Answers guidance to help sponsors develop products for ARS indications under the Animal Rule.
- Supporting the issuance of the final guidance Radiation Biodosimetry Medical Countermeasure Devices (PDF, 514 KB), issued on April 18, 2016.
- Providing input to BARDA on the development of MCMs for radiation and thermal burn injuries.
- Discussing regulatory strategies for gastrointestinal acute radiation syndrome (GI-ARS), with particular regard to appropriate models and associated issues.
- Providing FDA reviewers with training and information on the national concept of operations during/after radiological and nuclear mass casualty incidents and the current

[36] As part of this project, FDA set up collaborations to acquire the following prospective samples: 1) clinical isolates from Children's Hospital and George Washington University in Washington, D.C., to enhance diversity of GenBank, 2) biothreat and near-neighbor isolates/gDNA from USAMRIID/CRP, 3) Ebola isolates/gDNA from Public Health Canada/ National Institute of Allergy and Infectious Diseases (NIAID) collaboration and U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)/Critical Reagents Program (CRP), 4) antimicrobial resistance (AMR) isolates from Children's Hospital, and 5) difficult-to-acquire isolates from the American Type Culture Collection (ATCC). The FDA-ARGOS database is available at http://www.ncbi.nlm.nih.gov/bioproject/231221

status on the operational aspects for post-marketing requirement for Neulasta and Neupogen.

Warfighter Action Team – FDA continued this Action Team's efforts to facilitate the development and regulatory assessment of MCMs and related technologies primarily to support the warfighter and trauma victims. Key FY 2016 activities included:

- Meeting with the U.S. Army Medical Research and Materiel Command (MRMC), the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD), and the Defense Threat Reduction Agency (DTRA) to discuss regulatory and scientific issues.
- Providing assistance to the DoD on potential approaches for addressing the unique challenges in conducting studies or making MCMs available for the warfighter. Focus areas include traumatic brain injury, hemorrhage, nerve agents, and research that involves minimal risk to human subjects.[37]
- Working to establish a formal fellowship program between FDA and the DoD to support the training of DoD scientific and medical personnel in medical product development and FDA's regulatory processes.

FDA also participated in the Military Health System Research Symposium in August 2016, and provided expert speakers on topics including traumatic brain injury, digital health, physiological monitoring, and the regulatory review process for MCMs, to help facilitate interagency coordination.

Regulatory Advice and Guidance

During FY 2016, FDA continued to provide regulatory advice and guidance to sponsors and applicants of MCMs and our federal partners funding MCM development, to help foster the development and availability of various MCMs. FDA provides regulatory advice and guidance through a variety of mechanisms including direct engagement with sponsors and applicants, issuing guidance documents, and holding Advisory Committee meetings and public workshops.

FDA medical product review centers engage with MCM sponsors and applicants throughout the product life cycle. For example, FDA reviews Investigational New Drug (IND) applications and

[37] Minimal risk research is research in which the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. See, 45 CFR 46.303(d).

Investigational Device Exemptions (IDEs) and responds to questions from sponsors, applicants and federal agencies supporting product development. FDA medical product review centers have extensive interactions to discuss testing, data requirements, and nonclinical development plans to move candidate MCMs into clinical development and assess progress as these specialized product candidates move through clinical development toward a marketing application. FDA also continues to engage with sponsors and applicants to address any issues that arise during regulatory review as well as during the post-marketing phase for these MCMs.

FDA has established policies and procedures for conducting formal meetings with product sponsors or applicants. For detailed information on meetings about product development with CDER and CBER, see FDA's guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants* (Revision 1). In the *Federal Register* of March 11, 2015 (80 FR 12822), FDA published a notice announcing the availability of a draft guidance *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (Revision 2). The revised draft guidance updates the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants* (Revision 1) and, when finalized, will represent the Agency's current thinking on the topic.[38] Formal meetings are held—as needed—at the request of a product sponsor or applicant, and requests for meetings are granted unless there is a substantive reason for denying the request (e.g., the product for which the meeting is requested is not sufficiently developed to warrant the type of meeting sought).[39] When FDA denies a request for a meeting, the sponsor or applicant is provided feedback on steps required to warrant a meeting.

The Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) categorize formal meetings with product sponsors and applicants as Type A, B, and C. Type A meetings are meetings to help an otherwise stalled product development program proceed (such as a dispute resolution meeting, a meeting to discuss a clinical hold,[40] and a Special Protocol Assessment meeting[41]).

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[38] See for example, *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM437431.pdf and *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff* available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

[39] Formal meetings may also be rescheduled or cancelled based on criteria described in FDA guidance.

[40] A clinical hold is an order issued by FDA to a product sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. See 21 CFR 312.42 for more information on clinical holds.

[41] For more information on Special Protocol Assessments see *Guidance for Industry – Special Protocol Assessment* available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080571.pdf

Type B meetings are meetings held at pivotal points during product development to help products move into and through clinical development to marketing application (i.e., pre-IND application meetings, certain end-of-phase 1 meetings, end-of-phase 2/pre-phase 3 meetings, and pre-New Drug Application (NDA)/Biologics License Application (BLA) meetings). Type B meetings also include pre-EUA meetings, Risk Evaluation and Mitigation Strategies (REMS) meetings, and certain meetings for breakthrough therapy-designated products, under the draft guidance Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (PDF, 336 KB), issued in March 2015.

Type C meetings are any meetings other than a Type A or Type B meeting and can address a range of issues related to product development (e.g., discussions related to data requirements, scientific issues related to product development and manufacturing, post-marketing commitments or requirements, etc.). Meetings that are not categorized as Type A, B, or C are non-Prescription Drug User Fee Act (PDUFA) meetings such as meetings on a sponsor's compliance status or follow-up on post-marketing commitments. In FY 2016, CBER held 34 formal meetings with MCM sponsors or applicants, and 1 other (non-PDUFA) meeting, and CDER held 33 formal meetings (**Table 2**) and 14 other (non-PDUFA) meetings.

Table 2. FY 2016 Formal Meetings Between CBER/CDER and Medical Countermeasure Sponsors or Applicants

Meeting Type	CBER	CDER
Type A	1	0
Type B	17	5
Type C	16	28
Total	**34**	**33**

The Center for Devices and Radiological Health (CDRH) categorizes its formal meetings with product sponsors as Pre-Submission (Pre-sub) and 510(k)/Premarket Approval (PMA) Submission issues. Pre-sub meetings are designed for FDA staff to provide feedback in response to specific questions related to product development, including planned nonclinical evaluations, proposed clinical study protocols, regulatory pathways, or data analysis recommendations prior to making a submission.

In addition to 36 Pre-EUAs, which is a form of Pre-sub application, CDRH received and reviewed 41 Pre-submission applications for MCM medical devices in FY 2016. FDA provided extensive written feedback on these submissions, and many of these sponsors elected to cancel additional formal follow-up meetings after receiving this information. Submission issue meetings are held to discuss deficiencies identified during premarket review of device

marketing applications and to provide clarification of FDA's questions or to discuss an approach to address any complex issues identified. In FY 2016, CDRH held 28 formal meetings with MCM sponsors or applicants (**Table 3**), and provided written feedback for 41 MCM Pre-submission applications.

Moreover, FDA has significant interactions with MCM sponsors and applicants outside of the formal meeting process to address issues and provide assistance. For example, CDRH has established an Interactive Review Process to facilitate the efficient and timely review and evaluation of premarket submissions and pre-EUA submissions through increased interaction between FDA and sponsors, including the exchange of scientific and regulatory information.[42]

Table 3. FY 2016 Formal Meetings Between CDRH and Medical Countermeasure Sponsors or Applicants*

Meeting Type	CDRH
Pre-Submission	28
Submission	0
Total	**28**

**The number of formal meetings included in this table does not include most Ebola- and Zika-related meetings, such as pre-EUA meetings.*

In addition, eligible MCM sponsors or applicants can request a Regulatory Management Plan (RMP), setting forth a process whereby the terms for interactions between FDA and the product sponsor or applicant can be delineated.[43] FDA did not receive any written RMP requests in FY 2016.

FDA also conducted enhanced inspection and compliance activities to support early identification of any problems that might impede MCM product development. FDA provided technical advice to minimize risk during MCM product manufacturing, including pre-approval inspections or site visits to ensure that manufacturing establishments are capable of adequately manufacturing MCM products, and that submitted application data are accurate.

[42] For more information on the Interactive Review Process see *Types of Communication during the Review of Medical Device Submissions - Guidance for Industry and Food and Drug Administration Staff* available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM341948.pdf

[43] Under PAHPRA, MCMs eligible for RMPs are security countermeasures with respect to which the Secretary of HHS has entered into a procurement contract under section 319F-2(c) of the PHS Act (42 USCS § 247d-6b(c)); or MCMs with respect to which BARDA has provided funding under section 319L of the PHS Act (42 USCS § 247d-7e) for advanced research and development. (FD&C Act Sec. 565(f); 21 U.S.C. § 360bbb-4(f)). The Director of BARDA, in consultation with the Commissioner of FDA, prioritizes which eligible MCMs may receive RMPs if resources are not available to establish RMPs for all eligible MCMs for which requests are submitted.

In addition to its direct work with MCM sponsors and applicants, FDA also issues guidance documents that help foster MCM development and availability.[44] Guidance documents issued during FY 2016 directly related or applicable to MCMs policies or regulatory issues include:

- Guidance for Industry: Product Development Under the Animal Rule (PDF, 574 KB) – to provide information and recommendations on drug and biological product development when human efficacy studies are not ethical or feasible[45]
- Draft Guidance for Industry: Recommendations for Assessment of Blood Donor Suitability, Donor Deferral and Blood Product Management in Response to Ebola Virus (PDF, 92 KB) - The draft guidance document provides blood establishments that collect blood and blood components for transfusion or further manufacture, including source plasma, with FDA recommendations for assessing blood donor suitability, donor deferral, and blood product management in the event that an outbreak of EVD with widespread transmission is declared in at least one country.[46]
- Guidance for Industry and FDA Staff: Premarket Notification Requirements Concerning Gowns Intended for Use in Health Care Settings (PDF, 319 KB) – to describe the Agency's premarket regulatory requirements and the performance testing needed to support liquid barrier claims for gowns intended for use in health care settings
- Draft Guidance for Industry and FDA Staff: Postmarket Management of Cybersecurity in Medical Devices (PDF, 952 KB) - this draft guidance details the Agency's recommendations for monitoring, identifying, and addressing cybersecurity vulnerabilities in medical devices once they have entered the market

[44] Guidance documents are documents prepared for FDA staff, applicants/sponsors, and the public that describe FDA's interpretation of or policy on a regulatory issue. Guidance documents include, but are not limited to, documents that relate to: the design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies. (21 C.F.R. § 10.115(b))

[45] This guidance was finalized in FY 2016 (October 27, 2015). More information about the Animal Rule: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm391604.htm

[46] Gowns are examples of personal protective equipment (PPE) used in health care settings, including during public health emergencies such as the Ebola epidemic. Gowns protect the wearer from the spread of infection or illness if the wearer comes in contact with potentially infectious liquid and solid material. More information about gowns is available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/PersonalProtectiveEquipment/ucm452775.htm

- Draft Guidance for Industry: Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax (PDF, 565 KB) – to assist sponsors in the development of new drugs for the prophylaxis of inhalational anthrax[47]
- Guidance for Industry: Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus (PDF, 111 KB) – for blood establishments that collect Whole Blood and blood components, with recommendations for donor screening, donor deferral, and product management to reduce the risk of transfusion-transmitted Zika virus (a Questions and Answers document (PDF, 310 KB) was also published along with this guidance)[48]
- Guidance for Industry: Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (PDF, 76 KB) - for establishments that make donor eligibility determinations for donors of HCT/Ps, with recommendations for screening donors for evidence of, and risk factors for, infection with Zika virus[49]
- Draft Guidance: Emergency Use Authorization of Medical Products and Related Authorities – to explain FDA's policies applicable to the authorization of the emergency use of certain medical products under sections 564, 564A, and 564B of the FD&C Act as amended or added by PAHPRA[50]
- Guidance for Industry and FDA Staff: Radiation Biodosimetry Medical Countermeasure Devices (PDF, 514 KB) – to provide recommendations for the types of information that should be submitted to support marketing authorization (e.g., clearance or approval) for radiation biodosimetry medical countermeasure devices[51]

[47] This draft guidance supersedes the draft guidance entitled *Inhalational Anthrax (Post-Exposure)—Developing Antimicrobial Drugs* issued in March 2002.
[48] This guidance was superseded by the *Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components* issued on August 26, 2016, which recommended universal testing of donated whole blood and blood components for Zika virus in the U.S. and its territories.
[49] This guidance identifies Zika virus as a relevant communicable disease agent or disease (RCDAD) as defined in 21 CFR Part 1271. For additional information, see Safety of the Blood Supply on FDA's Zika virus response updates page at:
http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm#blood
[50] Draft guidance was issued in FY 2016, and finalized in January 2017. To avoid confusion, the previously issued draft guidance is no longer available on the FDA website.
[51] This guidance applies to premarket submissions for medical device systems intended to measure biological responses to unintended (non-therapeutic) radiation absorption. Biodosimetry devices are devices used for the purpose of reconstructing the ionizing radiation dose received by individuals or populations using physiological, chemical, or biological markers of exposure found in humans.

- Draft Guidance: Special Protocol Assessment (SPA)(PDF, 640 KB) - to provide information on the procedures and general policies adopted by CDER and CBER for SPA (this draft guidance includes adding Animal Rule efficacy protocols intended to support approval under 21 CFR part 314, subpart I, and 21 CFR part 601, subpart H, for drugs and biological products, respectively)[52]
- Draft Guidance: Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers (PDF, 1.4 MB) - to provide recommendations for studies to establish the analytical and clinical performance characteristics of infectious disease next-generation sequencing-based diagnostic devices for microbial identification and detection of antimicrobial resistance and virulence markers
- Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use Q&A (PDF, 180 KB) – for industry, researchers, physicians, institutional review boards, and patients, to provide information about the implementation of FDA's regulations on expanded access to investigational drugs for treatment use under an IND, which went into effect on October 13, 2009[53]
- Draft Guidance: Principles for Codevelopment of an *In Vitro* Companion Diagnostic Device With a Therapeutic Product (PDF, 1 MB) – to provide a practical guide to assist therapeutic product sponsors and IVD sponsors in developing a therapeutic product and an accompanying IVD companion diagnostic[54]

[52] SPA is a process in which sponsors may request to meet with FDA to reach agreement on the design and size of certain clinical trials, clinical studies, or animal trials to determine if they adequately address scientific and regulatory requirements. This draft guidance revises the guidance for industry *Special Protocol Assessment* issued in May 2002. After it has been finalized, this guidance will replace the May 2002 guidance.

[53] A related statement from FDA Commissioner Robert Califf, MD, on the release of the final individual patient expanded access form is available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm504579.htm

[54] View a press release about this guidance at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm509814.htm

- Guidance for Industry: Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components (PDF, 279 KB) – for blood establishments that collect Whole Blood and blood components, with recommendations to reduce the risk of transmission of Zika virus by Whole blood and blood components (this guidance recommends universal testing of donated whole blood and blood components for Zika virus in the U.S. and its territories)[55]
- Draft Guidance: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary (PDF, 129 KB) – to clarify how FDA applies the factors set forth in the FD&C Act in determining whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks

FDA held webinars for industry to discuss many of the guidances issued in FY 2016.[56]

FDA also holds Advisory Committee meetings and public workshops to obtain independent input and expert advice on scientific, technical, and policy matters to facilitate MCM development. Key meetings and public workshops held during FY 2016 include:

- October 16, 2015 – Public workshop – Non-Microbial Biomarkers of Infection for *In Vitro* Diagnostic Device Use – A workshop to receive input from stakeholders and discuss approaches to establish the performance of non-microbial biomarker assays for differentiating viral from bacterial infections and for diagnosis and assessment of sepsis.
- October 13-14, 2015 – Public workshop – Physiological Closed-Loop Controlled (PCLC) Devices – A workshop to discuss the challenges related to the design, development, and evaluation of critical care PCLC devices. This workshop focused on the design, development, and performance evaluation of PCLC systems intended for use in critical care environments. Such devices include closed-loop anesthetic delivery, closed-loop vasoactive drug and fluid delivery, and closed-loop mechanical ventilation.
- October 27-28, 2015 – Public workshop co-sponsored by NIST and FDA – Standards for Pathogen Detection Via Next-Generation Sequencing (NGS) - A workshop to receive input from stakeholders and discuss how to define reference materials, reference data,

[55] This guidance document superseded the guidance document entitled, *Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus* (dated February 2016) and the guidance document entitled, *Questions and Answers Regarding "Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion Transmission of Zika Virus* (dated March 2016).

[56] For example, see this list of CDRH medical device webinars and stakeholder calls: http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm411063.htm

and reference methods for assessing analytical sensitivity, specificity, and relative performance of NGS-based pathogen detection devices/assays.

- November 9-10, 2015 – Public workshop – Clinical Trial Designs for Emerging Infectious Diseases – A workshop to explore the ethical and methodological assumptions behind the choice of different trial designs, describe different types of emerging infectious diseases of concern, and explore several clinical trial designs for both vaccines and therapeutic products.
- November 12, 2015 – Public workshop – Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing *In Vitro* Diagnostic Tests – A workshop to obtain feedback on possible analytical standards and approaches to develop or build on existing standardization efforts in order to optimize FDA's regulation of NGS-based IVDs.[57]
- January 20-21, 2016 – Public workshop – Moving Forward: Collaborative Approaches to Medical Device Cybersecurity – A workshop to highlight past collaborative efforts, increase awareness of existing maturity models (i.e. frameworks leveraged for benchmarking an organization's processes) which are used to evaluate cybersecurity status, standards, and tools in development, and to engage the multi-stakeholder community in focused discussions on unresolved gaps and challenges that have hampered progress in advancing medical device cybersecurity.[58]
- March 3, 2016 – Public workshop – Advancing the Development of Biomarkers in Traumatic Brain Injury – A workshop to examine potential biomarkers, discuss the challenges and solutions related to biomarker development methodologies, and establish strategies for data standardization, sharing, and analysis of big data sets for traumatic brain injury (TBI).
- March 28-29, 2016 – Zika Virus in the Americas: An HHS Expert Consultation to Accelerate the Development of Countermeasures – Co-sponsored by HHS, NIH, CDC, BARDA, and FDA, a workshop to review current information about epidemiology of Zika virus, and clinical manifestations and pathogenesis of Zika virus. Participants also discussed strategies to accelerate the development of vaccines, diagnostics, therapeutics and novel vector control methods and ensure blood supply safety.

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

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

- April 5-6, 2016 – Public workshop – Proposed Pilot Project(s) under the Drug Supply Chain Security Act – to discuss proposed design objectives of pilot projects that will explore and evaluate methods to enhance the safety and security of the pharmaceutical distribution supply chain.
- April 14-15, 2016 – Public workshop – Developing an Evidentiary Standards Framework for Safety Biomarkers Qualification – co-hosted by FDA and the NIH Biomarkers Consortium, a workshop to elaborate a general framework for biomarker qualification along with specific application to different contexts of use related to drug safety, including assessment of several specific case studies involving qualifying clinical markers of toxicity in different organ systems.
- August 16, 2016 – Advisory Committee meeting – Microbiology Devices Panel of the Medical Devices Advisory Committee – to discuss and make recommendations regarding the appropriateness of clearing or approving over-the-counter diagnostic tests for the detection of pathogens causing infectious diseases, focusing on respiratory and sexually transmitted infections.
- September 23, 2016 – Public Workshop – Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests –A workshop to obtain feedback on two FDA draft guidances, Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics (IVDs) Used for Diagnosing Germline Diseases (PDF, 707 KB) and Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based *In Vitro* Diagnostics (PDF, 499 KB) that describe new approaches to regulate NGS-based tests.

Collaborations

During FY 2016, FDA continued to collaborate extensively with Enterprise and DoD partners to foster the development and availability of MCMs. FDA provided subject matter expertise and technical assistance to 68 standing interagency and Enterprise- and DoD-specific committees and working groups that develop MCM requirements, plans, priorities, and policies and conduct program oversight and integration. These standing committees and working groups met on a weekly, monthly, bimonthly, quarterly, semi-annually, or as-needed basis depending on the requirements of the issues at hand. These committees and working groups addressed a range of topics across the full spectrum of activities associated with MCMs including threat assessment, requirements setting, product development, procurement, stockpiling, and utilization, and monitoring and assessment of MCMs after they have been dispensed or administered.

In addition to working with federal partners, FDA collaborated with state agencies and non-government organizations (NGOs), as well as with international partners such as WHO to foster the development and availability of MCMs. Examples of FDA's key MCM collaborations include:

- Working with HHS to help establish an international framework for the sharing of MCMs during an international public health emergency
- Coordinating participation in the International Health Regulations (IHR) Joint External Evaluation of the United States (i.e., an assessment of the ability of existing national structures and resources to meet IHR minimum requirements)
- Implementing CBER-WHO Cooperative Agreements[59] to advance global access to safe and effective vaccines and build capacities for the import, registration, and emergency use of prequalified MCMs

Medical Countermeasure Regulatory Science

In FY 2016, FDA continued to implement the MCMi Regulatory Science Program through both intra- and extramural collaborative research, as well as through partnerships with U.S. government agencies, academia, and industry.

MCMs often present unique and complex challenges with respect to developing the data necessary to support regulatory decision-making. For example, many of the high-priority threats for which MCMs are being developed do not occur naturally to an extent that would support the conduct of field efficacy studies in humans, and it is not ethical to conduct human challenge studies with threat agents that would pose unacceptable risks to study volunteers.[60] In these situations, efficacy data from animal studies may be used if the results can reasonably be extrapolated to expected human use.

[59] For example, CBER-WHO Cooperative Agreement: Supporting Influenza Vaccine Introduction to Low-Middle Income Countries (http://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm342894.htm); for more about CBER's WHO Cooperative Agreements, see: http://www.fda.gov/biologicsbloodvaccines/internationalactivities/whoengagements/ucm274213.htm

[60] High-priority threats identified by the Enterprise for which medical countermeasures are needed include biological threats: *Bacillus anthracis* (anthrax); *Clostridium botulinum* toxin (botulism); emerging infectious diseases (including pandemic influenza); gram-negative organisms (*Francisella tularensis* (tularemia), *Yersinia pestis* (plague), *Burkholderia mallei* (glanders), *Burkholderia pseudomallei* (melioidosis), *Rickettsia prowazekii* (typhus)); multi-drug resistant *Bacillus anthracis* (MDR anthrax); Variola virus (smallpox); and viral hemorrhagic fevers (Marburg and Ebola); chemical threats including: nerve agents and cyanide; radiological agents (e.g., radiological dispersal devices); nuclear agents. See the 2015 PHEMCE Strategy and Implementation Plan for more information at http://www.phe.gov/Preparedness/mcm/phemce/Documents/2015-PHEMCE-SIP.pdf (see Box 1, page 8).

The challenges are even more complex when it comes to developing MCMs for use in specific populations, such as children or pregnant women. For example, ethical evaluation of the participation of children in clinical trials depends on both the level of risk and the prospect of direct benefit to the participant. Thus, in some circumstances it may not be ethical to conduct clinical trials to obtain data that can be used for approving pediatric indications for MCMs—such as safety or dosing information—and FDA may rely on the extrapolation of efficacy data from adult populations, along with information and experience the agency has with the use of a particular class of product (e.g., monoclonal antibodies for use in the pediatric population).[61]

The MCMi Regulatory Science Program helps translate cutting-edge technology into innovative, safe, and effective medical countermeasures

The goal of the MCMi Regulatory Science Program is to develop the tools, standards, and approaches to assess MCM safety, efficacy, quality, and performance and to help translate cutting-edge science and technology into innovative, safe, and effective MCMs, including for specific populations. Priority research areas being supported under the MCMi Regulatory Science Program include:

- Identifying, developing, and qualifying drug development tools (such as animal models and biomarkers to evaluate products for safety and efficacy, and using protein engineering to stabilize vaccine proteins)
- Developing methods to assess MCM product quality and related product release assays
- Validating NGS-based IVD platforms
- Assessing the performance of emergency medical equipment
- Enhancing emergency preparedness and response capabilities, including risk communication and tracking and evaluating the safety and clinical benefit of MCMs used during public health emergencies

[61] For example, pharmacokinetic modeling was the basis for pediatric labeling of the monoclonal antibody raxibacumab, approved in 2012 to treat inhalational anthrax, in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. Label information is available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125349s000lbl.pdf

- Supporting activities related to responding to the Ebola epidemic in West Africa, including medical product review and regulatory science research to help expedite the development and availability of medical products to treat, prevent, and detect Ebola
- Supporting activities related to responding to the Zika outbreak in multiple countries,[62] including the U.S. and its territories, including medical product review and regulatory science research to help expedite the development and availability of medical products to treat, prevent, and detect Zika

In addition, FDA awarded a research project cooperative agreement to the Critical Path Institute to refine and complete FDA's preliminary work in developing data standards for the animal efficacy studies and the natural history studies used to establish the animal models of the diseases or conditions of interest for products developed under the Animal Rule and to publish a complete set of voluntary consensus standards for data generated in these studies. Incorporating such data standards in the design, conduct, and analysis of studies benefits FDA and its MCM stakeholders by allowing more efficient data collection, management, and analysis, and by supporting the electronic submission of the data for regulatory review.

FDA has established a broad and robust intra- and extramural research portfolio under the MCMi Regulatory Science Program to meet its goals in these priority research areas.[63] To ensure that the MCMi Regulatory Science Program is appropriately targeted and coordinated with U.S. government (USG) MCM priorities, FDA established a Steering Committee for Advancing MCMi Regulatory Science—which includes representatives from NIH, CDC, BARDA, and DoD—that evaluates MCMi Regulatory Science Program research proposals for scientific/technical merit and feasibility as well as for alignment with Enterprise priorities. FDA continually engages with our USG stakeholders to maintain a MCMi Regulatory Science Program that actively addresses current regulatory science gaps in a timely manner.

FY 2016 MCMi Regulatory Science program activities included:

[62] A list of all countries and territories with active Zika virus transmission is available from CDC at: http://www.cdc.gov/zika/geo/active-countries.html

[63] Intramural FDA medical countermeasure regulatory science is funded through a competitive challenge grant process. Extramural medical countermeasure regulatory science is funded primarily through a Broad Agency Announcement (Food and Drug Administration Broad Agency Announcement for the Advanced Research and Development of Regulatory Science). More information is available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm391600.htm and https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm391318.htm

- Developing models of radiation damage in lung, gut, and bone marrow organs-on-chips and then using these models to test candidate MCMs to treat such damage[64,65]
- Completing a project mapping immune responses to certain biothreat agents and MCMs in humans and animal models to create species-specific immune function maps.[66] The final report for this project was received and the data sets are available to the public via a web-accessible database.[67] FDA continues to conduct outreach to inform USG, academic, and industry stakeholders of the availability of this important countermeasure development tool
- Determining correlates of immunity to aid in the development of next generation tularemia vaccines
- Developing diagnostics that can detect botulism neurotoxin at low levels in food
- Examining the utility of thermal processes for inactivating *Staphylococcal* enterotoxin B in milk
- Expanding a database of regulatory-grade nucleic acid sequences to include antimicrobial-resistant organisms as well as Ebola- and Zika-related sequences

CyTOF mass cytometer – Mass cytometry enables scientists to take simultaneous measurements of dozens of cell features and analyze immune cells in far more detail than previously possible (Credit: Stanford)

- Developing and characterizing a repository of antimicrobial-resistant strains and panels to be made publicly available for developers of diagnostics and therapies to identify and treat antimicrobial-resistant bacteria, in collaboration with CDC. The FDA-CDC Antimicrobial Resistance Isolate Bank website containing available information on strains and panels was recently launched as a pilot to allow interested stakeholders to

[64] The project was funded under the extramural MCMi regulatory science program. For more information see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm364491.htm

[65] Studies with organs-on-chips are not considered adequate replacement for animal efficacy studies required under the Animal Rule.

[66] The project was funded under the extramural MCMi regulatory science program, and was completed in June 2016. For more information see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm332539.htm

[67] Antibody screening and cross-species datasets are available at: https://immuneatlas.org/

order isolates. CDC continues to process and fulfill orders for panels upon request by various organization types including diagnostic and pharmaceutical companies and public health departments. Additional isolates and panels are being incorporated into the Bank, and efforts are underway to generate regulatory grade genomic sequence data for the isolates in the bank

- Developing a rapid and comprehensive method for detection of antimicrobial resistance genes in bacterial pathogens in order to successfully treat secondary bacterial infections associated with influenza infection; the studies have been completed and the data are being analyzed
- Developing and validating assays for Ebola that can be utilized outside of specialized, high-containment Biosafety Level 4 (BSL-4) laboratories
- Developing mobile device applications to bi-directionally collect and communicate MCM product information and analyze CBRN and emerging infectious disease patterns and clusters in real-time
- Cataloging the most likely and serious difficulties that may complicate emergency administration of MCMs, and developing communication strategies to help ensure appropriate public use of life-saving MCMs in emergency situations[68]
- Investigating decontamination and reuse[69] of respirators in public health emergencies, and optimizing respirator decontamination[70] to ensure supplies for emergency preparedness

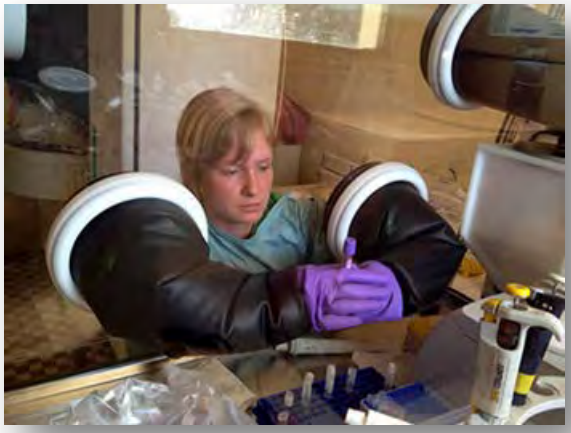
N95 face mask respirators - These respirators protect people who wear them by removing contaminants from the air. (Credit: CDC/ Debora Cartagena)

[68] This project was funded under the extramural MCMi regulatory science program, and was completed in June 2016. For more information, including the final report, see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm400865.htm

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

[70] This project was funded under the extramural MCMi regulatory science program. For more information, see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm414974.htm

- Developing methods for obtaining safety and limited efficacy data from patients who receive MCMs during a public health emergency through a collaboration with the United States Critical Illness and Injury Trials Group (USCIITG) and critical care physicians at 20 hospitals throughout the United States[71]
- Developing reference materials to facilitate diagnostic development for emerging infectious diseases like Ebola and Zika
- Continuing the development of improved small animal models for Ebola and Zika
- Developing bioassays and identifying potential markers of disease progression by evaluating cellular factors affecting Ebola virus surface glycoprotein mediated-cell fusion under BSL-2 conditions
- Evaluating the use of chimeric viruses to improve production of influenza B vaccines
- Evaluating alternative garment testing methods that may predict Ebola penetration without use of live Ebola virus and high-containment facilities
- Testing and comparing how effective different antibiotics are against melioidosis acquired by different routes of exposure[72]
- Developing a toolkit to assess efficacy of Ebola vaccines and therapeutics[73]
- Supporting field laboratory testing of Ebola antibodies in Sierra Leone[74]



Scientist processing Ebola virus disease samples at Donka Hospital in Conakry, Guinea as part of the EVIDENT project. (Credit: EVIDENT)

[71] This project was funded under the extramural MCMi regulatory science program. For more information see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm414015.htm

[72] This project, initiated in FY 2016, was funded under the extramural MCMi regulatory science program. For more information see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm471653.htm

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

- Conducting survivor studies to better understand Ebola's after-effects, to help find new treatments[75]
- Sponsoring nonclinical research studies to help inform FDA recommendations regarding potential transmission of Zika virus via organs and tissues[76]
- Developing an animal model of pregnancy to study the pharmacokinetics of MCMs for influenza and CBRN threats in the "at-risk" population of pregnant women
- Developing phantom-based test methods for evaluation of near-infrared diagnostic devices for TBI and cerebral monitoring
- Developing techniques for the preclinical evaluation of physiological closed-loop controlled supportive therapy devices, particularly related to the computational patient model
- Generating reference materials to standardize and qualify immune assays for Zika detection[77]
- Identifying target peptide sequences for a Zika immunoglobulin M (IgM) diagnostic device

FDA also expanded and sustained MCM regulatory science collaborations in FY 2016. For example FDA:

- Sponsored the fourth installment of a program with the University of Texas Medical Branch (UTMB) to provide training on best practices to ensure the quality and integrity of data generated in maximum-containment (i.e., Animal Biosafety Level 3 and 4) laboratories used to support product approval under the Animal Rule.
- Supported the Animal Model Qualification Program, which provides a mechanism for the evaluation of product-independent animal models for use in drug and biological product development under the Animal Rule.[78]

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[74] This project, initiated in FY 2016, was funded under the extramural MCMi regulatory science program. For more information see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm471621.htm

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

[76] Two contracts were awarded in FY 2016; work began in FY 2017.

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

[78] For more information on FDA's Animal Model Qualification Program see: http://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm284078.htm

- Established and continued to expand a publicly available, well-curated reference database of regulatory-grade sequences from diverse microorganisms. This database, called FDA dAtabase for Regulatory Grade micrObial Sequences (FDA-ARGOS), will be critical to developers seeking to validate their candidate high-throughput sequencing-based IVD assays. This database is being hosted by NCBI.[79] The FDA-ARGOS database was expanded to include Ebola-related sequences in 2015, and Zika-related sequences in 2016.
- Continued collaborations with DARPA on regulatory science research for the development of innovative regulatory tools, such as biomimetic models, as well as to support their DxOD/ ADEPT program, and the National Interagency Confederation for Biological Research (NICBR) to help develop synchronized scientific interaction among Federal partners to enhance public health, medical research, and biotechnology development.
- Collaborated with NIST to produce sequence-based microbial challenge materials for diagnostic tests; two clinical (CDRH FDA-ARGOS) and two environmental (FDA Center for Food Safety and Nutrition (CFSAN)) isolates were selected, sourced, and advanced to the NIST reference material production pipeline.

Medical Countermeasure Regulatory Policy

During FY 2016, FDA continued efforts to ensure that U.S. laws, regulations, and policies enable the application of advances in regulatory science to the regulatory review process and adequately support preparedness for and response to CBRN and emerging infectious disease threats by facilitating the availability of MCMs. FY 2016 activities included:

- Continuing efforts to implement PAHPRA authorities to support emergency preparedness and response capabilities for public health emergencies involving CBRN and emerging infectious disease threats and to foster the development of MCMs.[80] Implementation efforts have focused on:

FDA works with state and local public health authorities to support MCM preparedness and response at community levels

[79] NCBI BioProject 231221 (FDA-ARGOS): http://www.ncbi.nlm.nih.gov/bioproject/231221
[80] For more information on PAHPRA's MCM provisions see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm346195.htm

- Developed a draft guidance on Emergency Use Authorization of Medical Products and Related Authorities, which, when finalized in January 2017, replaced the current guidance, Emergency Use Authorization of Medical Products (July 2007) and Emergency Use Authorization Questions and Answers (April 2009)[81]
- Established a Memorandum of Understanding[82] (MOU) with CDC for developing and issuing Emergency Use Instructions (EUI)[83]
- Issued emergency dispensing orders for doxycycline and ciprofloxacin for anthrax preparedness (utilizing section 564A authorities) on April 13, 2016
- Drafting a guidance on doxycycline expiry dating extension for state and local public health stakeholders
- Finalized the 2014 revised draft guidance Product Development Under the Animal Rule (PDF, 563 KB)[84]

- Working with state and local public health authorities and responders and public health NGOs to support MCM preparedness and response capabilities at the state and community levels, including responding to numerous EUA- and other emergency use-related inquiries and participating in multiple national-level workshops and meetings on legal preparedness, FDA's roles in MCM distribution and dispensing, and enactment of PAHPRA[85]
- Sustaining support for and participation in the annual Public Health Preparedness Summit convened by the National Association of County and City Health Officials (NACCHO)
- Sustaining support for and participation in the National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division (NASEM-HMD) Forum on Medical and Public Health Preparedness for Catastrophic Events, to provide national leadership in coordinating ongoing efforts among members from Federal, state, and local government; business; and professional associations to develop sustainable

[81] The draft guidance was made available for public comment in April 2016, and was finalized in January 2017. View the guidance at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm
[82] This MOU was signed February 19, 2016. View the MOU at: http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm487464.htm
[83] For more on Emergency Use Instructions and emergency dispensing orders, see: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm495126.htm
[84] This guidance was finalized on October 27, 2015.
[85] For a list of MCM-related legal and policy presentations, publications and Q&As, see http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm411508.htm

partnerships between the public and private sector so that communities are adequately prepared for natural or human-made catastrophic events[86]

- Supporting and participating in FDA's Global Health Security agenda and strategy, as well as other HHS-led efforts related to global MCM policies, including efforts to finalize the WHO operational framework for deployment of smallpox vaccine, and based on this work, establish a generic international framework for sharing MCMs during public health emergencies
- Continuing to work with appropriate partners to develop and propose new approaches for addressing legal, regulatory, and policy challenges associated with the development and use of specific MCMs. Examples of areas where FDA provided policy assistance include:
    - Issues related to product development of MCMs that meet the unique needs of the warfighter
    - Issues related to expiration dating that are unique to MCMs and to public health stakeholders
    - Advancing efforts to create a national capability to track, collect, analyze, and evaluate information related to MCMs used during public health emergencies, in order to make real-time decisions about the safety and effectiveness of these MCMs
    - Issues related to use of expanded access and EUA mechanisms to make available unapproved MCMs for investigational Ebola products in FY 2016
    - MCM import and export issues during emergency responses and to support preparedness for international events, with a focus on export issues related to the Ebola and Zika response in FY 2016
    - Novel issues related to the Zika response, including ensuring FDA regulations do not interfere with programs to provide FDA-approved long-acting reversible contraception to Puerto Rico, regulation of genetically engineered mosquitos, and ensuring the safety of the nation's blood supply
    - Issues related to information disclosure and liability protections
    - FDA expectations for ensuring data quality and integrity for certain studies in animals to support approval under the Animal Rule
    - FDA expectations for qualification of animal models under the Animal Model Qualification Program

[86] NASEM-HMD was previously known as the Institute of Medicine (IOM).

- Enhanced flexibility to conduct minimal risk research in support of product development, included within the 21st Century Cures Act legislative package
- Issues related to expanded EUA authorities to include new animal drugs, included within the 21st Century Cures Act legislative package
- Issues related to expanding the Priority Review Voucher Program to include MCMs, included within the 21st Century Cures Act legislative package
- Harmonizing multi-jurisdictional regulation of certain personal protective equipment
- Issuing guidance clarifying and describing the premarket regulatory requirements for gowns regulated under 21 CFR 878.4040[87]
- Establishing an MOU to support NIH and BARDA's challenge incentive for development of diagnostics for antimicrobial-resistant pathogens,[88] and to provide a framework for coordination and collaborative efforts to spur innovation in the development of diagnostic devices that would be of great clinical and public health utility in combating the development and spread of bacteria that are resistant to antimicrobial drugs[89]
- Establishing an MOU with NIH, the Animal and Plant Health Inspection Service (APHIS), and the USDA to set forth a framework for reciprocal cooperation that will assist each agency in meeting its responsibilities in promoting proper laboratory animal care and welfare; implementation of this agreement is intended to maintain and enhance agency effectiveness while avoiding duplication of efforts to achieve required standards for the care and use of laboratory animals[90]
- Establishing an international confidentiality commitment (PDF, 185 KB) with the SFDA to help facilitate communications between the two agencies on medical products used, or proposed to be used, for MERS-CoV as part of cooperative regulatory activities[91]

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[87] This guidance was finalized in FY 2016 (December 9, 2015). Final guidance is available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM452804.pdf

[88] View the MOU at: http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm505271.htm (see also: HHS. *Announcement of Requirements and Registration Antimicrobial Resistance Rapid, Point-of-Need Diagnostic Test Challenge*. 81 Fed. Reg. 62150 (September 8, 2015)).

[89] CDC is also a participant in this MOU, signed May 19, 2016. View the MOU at: http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm505271.htm

[90] This MOU was signed April 29, 2016. View the MOU at: http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm504805.htm

[91] The reciprocal confidentiality commitments were signed on October 20, 2015, and are available at: http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/UCM469577.pdf

- Signing a joint statement of continued cooperation between FDA and the Brazilian ANVISA to offer mutual support and to collaborate to address the public health emergency presented by the Zika virus disease outbreak in the Americas[92]

Professional Development

FDA launched the MCMi Professional Development Program during FY 2011 to ensure that FDA scientists are informed about CBRN threats and associated health impacts as they conduct benefit-risk analyses on MCMs, and that FDA scientists can meet the regulatory challenges posed by new areas of science and technology in the area of MCM development. Key activities in FY 2016 included:

- **MCMi Lecture Series:** These lectures, presented by highly respected leaders in their fields, broaden the understanding of the policies, procedures, and U.S. governmental preparedness and response framework for FDA reviewers who are assessing MCM applications. FDA held 1 lecture in this series during FY 2016 with 59 attendees, 48 of whom received continuing education (CE) credits.[93]
- **Foundations for Preclinical Review Lecture Series:** Focuses on preclinical scientific and technical issues of importance to MCMs, since many MCMs are developed under the Animal Rule. Presentations are designed to educate researchers and reviewers on issues of humane animal care and reproducibility. Speakers include internal and external experts in the field. FDA held 4 lectures in this series during FY 2016 with 247 attendees, 95 of whom received CE credits.
- **Hot Topics Lecture Series:** Hot Topics is a series of timely scientific presentations and discussions to help inform FDA staff about technologies and issues that may impact MCM development. These sessions are designed for an FDA audience, including scientists involved in the review of medical product applications, and include a variety of expert speakers from industry, academia, and government. FDA held 8 lectures in this series during FY 2016, with nearly 1,000 attendees.

[92] The joint statement was issued on April 11, 2016, and is available at: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm495211.htm

[93] For more about MCMi lectures see http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMiProfessionalDevelopmentActivities/default.htm

Appendix 1: FY 2016 Medical Countermeasure Approvals

Medical Countermeasure[94]	Sponsor/ Applicant	Key Dates	Indication
Biologics and Drugs[95]			
Afluria Quadrivalent Influenza Vaccine	Seqirus Pty Ltd.	• Submitted October 27, 2015 • Approved August 26, 2016	New indication to include a quadrivalent formulation (Afluria® Quadrivalent) for use in persons 18 years of age and older. (approval letter)
Anthim (obiltoxaximab) injection	Elusys Therapeutics, Inc.	• Submitted March 20, 2015 • Approved March 18, 2016	For adult and pediatric patients for the treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs; for prophylaxis of inhalational anthrax due to *B. anthracis* when alternative therapies are not available or not appropriate. (FDA news release) (approval letter) (Drug Trials Snapshot[96])
BioThrax Anthrax Vaccine Adsorbed	Emergent BioDefense Operations Lansing LLC	• Submitted October 30, 2014 • Approved November 23, 2015	To include post-exposure prophylaxis (PEP) of disease resulting from suspected or confirmed *B. anthracis* exposure, when combined with the recommended course of antimicrobial therapy in persons 18 through 65 years of age. BioThrax is the first vaccine to receive approval of a new indication based on the Animal Rule. (FDA news release) (approval letter)

[94] Includes medical countermeasures approved, licensed, or cleared by FDA in FY 2016 (October 1, 2015 – September 30, 2016).

[95] For products (biologics) regulated by CBER, additional information can be found at: http://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm; for products (drugs and biologics) regulated by CDER, additional information can be found at: http://www.accessdata.fda.gov/scripts/cder/daf/

[96] Drug Trials Snapshots provide consumers with information about who participated in clinical trials that supported the FDA approval of new drugs. For more information, see: http://www.fda.gov/drugs/informationondrugs/ucm412998.htm

Medical Countermeasure[94]	Sponsor/ Applicant	Key Dates	Indication
FLUAD Influenza Vaccine, Adjuvanted	Seqirus, Inc.	• Submitted November 25, 2014 • Approved November 24, 2015	For active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and B contained in the vaccine. This is the first seasonal influenza vaccine approved by FDA that contains an adjuvant. (FDA news release) (approval letter)
Flucelvax Influenza Vaccine	Seqirus, Inc.	• Submitted November 20, 2014 • Approved May 23, 2016	Expanded to include persons 4 years of age and older, for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine (approval letter)
Neulasta (pegfilgrastim)	Amgen, Inc.	• Submitted February 13, 2015 • Approved November 13, 2015	New indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation (approval letter)
Q-Pan (Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted)	ID Biomedical Corporation	• Submitted November 10, 2015 • Approved September 9, 2016	BLA supplement to extend the age range for use to include persons 6 months through 17 years of age at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine. (approval letter)
Devices[97]			
Ahead 300	BrainScope Company, Inc.	• Received April 15, 2016 • Cleared September 22, 2016	Using commercial smartphone hardware, the Ahead 300 records and analyzes a patient's EEG using a custom sensor attached to the handheld to provide an interpretation of the structural condition of the patient's brain after head injury. In addition to EEG capabilities, the Ahead 300 includes additional assessments providing clinicians with a digitized, streamlined report, delivering a comprehensive and objective panel of results to facilitate their differential diagnosis. Ahead 300 was developed in partnership with DoD.

[97] Additional information about device approvals can be found in Medical Devices Databases: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm, including the 510(k) Premarket Notification Database: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm

Medical Countermeasure[94]	Sponsor/ Applicant	Key Dates	Indication
ARIES® Flu A/B & RSV Assay	Luminex Corporation	• Received April 29, 2016 • Cleared August 2, 2016	A nucleic acid-based device for the detection and differentiation of influenza A virus, influenza B virus, and respiratory syncytial virus (RSV) in nasopharyngeal swabs from patients with signs and symptoms of respiratory tract infection.
BD Veritor System for the Rapid Detection of Flu A + B	Becton Dickinson, and Co.	• Received September 30, 2015 • Cleared October 27, 2015	A previously 510(k)-cleared and Clinical Laboratory Improvement Amendments of 1988 (CLIA)-waived device instrument-based antigen detection test for influenza A and B using nasopharyngeal and nasal swabs. This special 510(k) was to update the analytical reactivity section of the Instructions for Use (IFU) with six additional influenza strains.
BD Veritor System for the Rapid Detection of Flu A + B Laboratory kit	Becton Dickinson, and Co.	• Received September 30, 2015 • Cleared October 27, 2015	A previously 510(k)-cleared and CLIA waived device instrument-based antigen detection test for influenza A and B using nasopharyngeal wash/aspirate samples. This special 510(k) was to update the analytical reactivity section of the IFU with six additional influenza strains.
BD Veritor System for the Rapid Detection of Flu A + B Laboratory kit	Becton Dickinson, and Co.	• Received January 27, 2016 • Cleared February 25, 2016	This special 510(k) was to update the analytical reactivity section of the IFU with two additional influenza strains.
CDC Human Influenza Virus Real-time RT-PCR Diagnostic Panel, Influenza A Subtyping Kit	Centers for Disease Control and Prevention (CDC)	• Received June 6, 2016 • Cleared June 30, 2016	A previously 510(k)-cleared device for determination of the subtype of seasonal human influenza A viruses as seasonal A/H1, A/H3, and/or A/H1pdm09 in upper respiratory tract specimens. This special 510(k) was to redesign primes and probes, to improve reactivity, replace a positive control, and eliminate the A/H1 assay, among other changes.
CDC Human Influenza Virus Real- time RT-PCR Diagnostic Panel, Influenza A/H5 Subtyping	CDC	• Received October 30, 2015 • Cleared December 1, 2015	A previously 510(k)-cleared device for detection of influenza A subtype A/H5 (Asian lineage) in respiratory specimens and viral culture. This special 510(k) was for small changes to the primers and probes of the assay.

Medical Countermeasure[94]	Sponsor/ Applicant	Key Dates	Indication
Cobas Influenza A/B & RSV Nucleic Acid Test for Use on the Cobas Liat System	IQuum, Inc.	• Received December 11, 2015 • Cleared July 25, 2016 • CLIA waived July 25, 2016	A nucleic acid-based device for the detection of influenza A, influenza B and RSV RNA from nasopharyngeal swabs. This test was CLIA-waived along with the approval.
ER-REBOA™ Catheter	Pryor Medical Devices	• Received July 6, 2015 • Cleared October 23, 2015	A large vessel balloon occlusion catheter designed for temporary occlusion of large vessels and arterial pressure monitoring, which provides a minimally invasive technique to temporarily occlude the aorta and stop bleeding
FilmArray Respiratory Panel (RP) for use with FilmArray Torch	BioFire Diagnostics, LLC	• Received January 13, 2016 • Cleared February 8, 2016	A previously 510(k)-cleared nucleic acid multiplexed device for influenza A, influenza A subtype H1, influenza A subtype H3, influenza A subtype 2009 H1, influenza B, and other respiratory viruses. This special 510(k) was to reconfigure the FilmArrayTorch instrument to increase throughput and reduce workspace.
Great Basin Shiga Toxin Direct Test	Great Basin Scientific, Inc.	• Received October 7, 2015 • Cleared March 22, 2016	A device for the detection of nucleic acids and toxin gene sequences from enteric pathogens (Shiga toxin 1/Shiga toxin 2 genes found in Shiga toxin producing strains of *E. coli* 0157 and *Shigella dysenteriae*) in stool specimens.
illumigene Pertussis DNA Amplification Assay	Meridian Bioscience, Inc.	• Received August 12, 2015 • Cleared November 10, 2015	A previously 510(k)-cleared device for the detection of *Bordetella pertussis* DNA in nasopharyngeal swabs. This 510(k) is for three modifications made to the upfront sample preparation, one of them being a sample treatment to neutralize the interfering activity of biological substances found in the nasopharynx.
ImPACT	ImpACT Applications	• Received August 11, 2015 • *De novo* cleared August 22, 2016	First-of-kind computerized cognitive tests for assessments of cognitive function following concussion or suspected brain injury. Two devices were cleared (one for adult and one for pediatric populations). These devices are not intended to diagnose concussion and not intended to determine appropriate treatments.

Medical Countermeasure[94]	Sponsor/ Applicant	Key Dates	Indication
JBAIDS Influenza A & B Detection Kit	U.S. Army Medical Materiel Development Activity	• Received September 3, 2015 • Cleared October 1, 2015	A previously 510(k)-cleared nucleic acid-based device for the detection of influenza A and influenza B from nasopharyngeal swabs and washes from patients with signs and symptoms of respiratory infection. This special 510(k) is to update the analytical reactivity section of the IFU with five additional influenza strains.
NxTAG® Respiratory Pathogen Panel	Luminex Molecular Diagnostics, Inc.	• Received August 24, 2015 • Cleared December 17, 2015	A multiplexed nucleic acid-based device for the detection of influenza A (with subtype differentiation), influenza B and other respiratory viruses and bacteria in nasopharyngeal swabs from symptomatic patients.
ProFlu+ Assay	Hologic, Inc.	• Received November 5, 2015 • Cleared November 20, 2015	A previously 510(k)-cleared nucleic-acid-based device for the detection and discrimination of influenza A, influenza B, and RSV in nasopharyngeal swabs from symptomatic patients. This special 510(k) is to update the analytical reactivity section of the IFU with one additional influenza strain.
Sofia Influenza A+B FIA	Quidel Corporation	• Received October 14, 2015 • Cleared January 12, 2016	A previously 510(k)-cleared instrument-based antigen detection test for influenza A and B using nasal/nasopharyngeal swab and nasopharyngeal aspirate/wash specimens from symptomatic patients. This special 510(k) was to include specimens in viral transport media.
Solana Influenza A+B Assay	Quidel Corporation	• Received July 1, 2016 • Cleared September 27, 2016	A nucleic acid-based device for the detection and differentiation of influenza A and B in nasal and nasopharyngeal swabs from patients with signs and symptoms of respiratory infection.
Xpert Flu+RSV Xpress, Xpert Nasopharyngeal Sample Collection Kit, GeneXpert Xpress System (GX-I)	Cepheid	• Received May 7, 2015 • Cleared December 3, 2015 • CLIA waived December 3, 2015	A nucleic acid-based device for detection and differentiation of influenza A, influenza B and RSV in swab specimens from patients with signs and symptoms of respiratory infection. Includes a sample collection kit.

Medical Countermeasure[94]	Sponsor/ Applicant	Key Dates	Indication
XSTAT 12	Revmedx, Inc	• Received April 12, 2016 • Cleared July 28, 2016	An expandable, multi-sponge wound dressing used to control severe, life-threatening bleeding from wounds in areas that a tourniquet cannot be placed (such as the groin or armpit) in battlefield and civilian trauma settings. The clearance includes a difference in the applicator to allow XSTAT mini-sponges to be used in smaller-diameter wounds.
XSTAT 30	Revmedx, Inc	• Received September 14, 2015 • Cleared December 7, 2015	An expandable, multi-sponge wound dressing used to control severe, life-threatening bleeding from wounds in areas that a tourniquet cannot be placed (such as the groin or armpit) in battlefield and civilian trauma settings. The clearance expands the device's indication from use by the military only to use in adults and adolescents in the general population. (FDA news release)

Appendix 2: Current Emergency Use Authorizations

Year	MCM	Requester
Anthrax [*Bacillus anthracis*]		
2008	Doxycycline hyclate 100 mg oral tablets (in National Postal Model home & workplace kits)	HHS (Assistant Secretary for Preparedness and Response (ASPR)/ BARDA)
2011[a]	All oral formulations of doxycycline (mass dispensing)	HHS (CDC)
Novel Influenza A (H7N9) Virus		
2013	CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel-Influenza A/H7 (Eurasian Lineage) Assay	HHS (CDC)
2014	Lyra™ Influenza A Subtype H7N9 Assay	Quidel Corporation
2014	A/H7N9 Influenza Rapid Test	Arbor Vita Corporation
Middle East Respiratory Syndrome Coronavirus [MERS-CoV]		
2013[b]	CDC Novel Coronavirus 2012 Real-time RT-PCR Assay	HHS (CDC)
2015[d]	RealStar® MERS-CoV RT-PCR Kit U.S.	altona Diagnostics GmbH
Ebola Virus		
2014[b]	DoD EZ1 Real-time RT-PCR Assay	DoD
2014[c]	CDC Ebola VP40 rRT-PCR Assay	HHS (CDC)
2014[c]	CDC Ebola NP rRT-PCR Assay	HHS (CDC)
2014[c]	BioFire Defense FilmArray NGDS BT-E Assay	BioFire Defense
2014	BioFire Defense FilmArray Biothreat-E test	BioFire Defense
2014[b]	RealStar® Ebolavirus RT-PCR Kit 1.0	altona Diagnostics GmbH
2014	LightMix® Ebola Zaire rRT-PCR Test	Roche Molecular Systems, Inc.
2015[c,d]	ReEBOV™ Antigen Rapid Test	Zalgen LLC (formerly Corgenix)
2015	Xpert® Ebola Assay	Cepheid
2015	OraQuick® Ebola Rapid Antigen Test – whole blood	OraSure Technologies, Inc.
2016 [d]	OraQuick® Ebola Rapid Antigen Test – cadaveric oral fluid	OraSure Technologies, Inc.
2016	Idylla™ Ebola Virus Triage Test	Biocartis NV

[a] To be terminated after issuance of doxycycline emergency dispensing order, cGMP waiver, and CDC EUI (sec. 564A of the FD&C Act)

[b] Re-issued in 2014

[c] Re-issued in 2015

[d] Re-issued/amended in 2016

[e] Re-issued/amended in 2017

(table continues on next page)

Year	MCM	Requester
Enterovirus D68		
2015	CDC Enterovirus D68 2014 Real-time RT-PCR Assay	HHS (CDC)
Zika Virus		
2016[d]	CDC Zika Immunoglobulin M (IgM) Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA)	HHS (CDC)
2016[d,e]	CDC Trioplex Real-time RT-PCR Assay (Trioplex rRT-PCR)	HHS (CDC)
2016[d]	Zika Virus RNA Qualitative Real-Time RT-PCR	Focus Diagnostics, Inc.
2016[d,e]	RealStar Zika Virus RT-PCR Kit U.S.	altona Diagnostics GmbH
2016[d]	Aptima Zika Virus assay	Hologic, Inc.
2016[e]	Zika Virus Real-time RT-PCR Test	Viracor Eurofins
2016[d]	VERSANT® Zika RNA 1.0 Assay (kPCR) Kit	Siemens Healthcare Diagnostics Inc.
2016[e]	xMAP® MultiFLEX™ Zika RNA Assay	Luminex Corporation
2016	ZIKV Detect™ IgM Capture ELISA	InBios International, Inc.
2016[d]	LightMix® Zika rRT-PCR Test	Roche Molecular Systems, Inc.
2016	Sentosa® SA ZIKV RT-PCR Test	Vela Diagnostics USA, Inc.
2016	Zika Virus Detection by RT-PCR Test	ARUP Laboratories
2016[e]	Abbott RealTi*m*e ZIKA	Abbott Molecular, Inc.
2016	Zika ELITe MGB® Kit U.S.	ELITechGroup Inc. Molecular Diagnostics

[a] To be terminated after issuance of doxycycline emergency dispensing order, cGMP waiver, and CDC EUI (sec. 564A of the FD&C Act)
[b] Re-issued in 2014
[c] Re-issued in 2015
[d] Re-issued/amended in 2016
[e] Re-issued/amended in 2017

Note: chart is accurate as of March 8, 2017, including EUAs issued in FY 2017. View the latest EUAs.

Appendix 3: Acronyms

ADEPT	Autonomous Diagnostics to Enable Prevention and Therapeutics
AMR	Antimicrobial resistance
ANVISA	Brazilian Health Regulatory Agency
APHIS	Animal and Plant Health Inspection Service
ATCC	American Type Culture Collection
ARS	Acute radiation syndrome
ASPR	Assistant Secretary for Preparedness and Response (HHS)
AST	Antimicrobial susceptibility test
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
BSL	Biosafety level
CBRN	Chemical, biological, radiological, and nuclear
CBER	FDA Center for Biologics Evaluation and Research
CDC	U.S. Centers for Disease Control and Prevention
CDER	FDA Center for Drug Evaluation and Research
CDRH	FDA Center for Devices and Radiological Health
CE	Continuing education
CFSAN	FDA Center for Food Safety and Nutrition
cGMP	Current good manufacturing practices
CLIA	Clinical Laboratory Improvement Amendments of 1988
CRP	Critical Reagents Program
CFR	Code of Federal Regulations
DARPA	Defense Advanced Research Projects Agency
DHS	U.S. Department of Homeland Security
DoD	U.S. Department of Defense
DTRA	Defense Threat Reduction Agency
DxOD	Diagnostics on Demand
EEG	Electroencephalograph
eIND	Emergency Investigational New Drug
EUA	Emergency Use Authorization
EVD	Ebola virus disease
FDA	U.S. Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic Act
FDA-ARGOS	FDA dAtabase for Regulatory Grade micrObial Sequences
FTE	Full-time equivalent
FY	Fiscal year
GI-ARS	Gastrointestinal acute radiation syndrome
HCT/P	Human cells, tissues, and cellular and tissue-based products

HDE	Humanitarian Device Exemptions
HHS	U.S. Department of Health and Human Services
IDE	Investigational Device Exemption
IFU	Instructions for Use
IgM	Immunoglobulin M
IHR	International Health Regulations
IND	Investigational New Drug
IVD	*In vitro* diagnostic
JBAIDS	Joint Biological Agent Identification and Diagnostic System
JPEO-CBD	Joint Program Executive Office for Chemical and Biological Defense
LLNL	Lawrence Livermore National Laboratory
MCM	Medical countermeasure
MCMi	FDA Medical Countermeasures Initiative
MDR	Multi-drug-resistant
MERS-CoV	Middle East Respiratory Syndrome coronavirus
MOU	Memorandum of Understanding
MRMC	U.S. Army Medical Research and Materiel Command
NACCHO	National Association of County and City Health Officials
NASEM-HMD	National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division
NAT	Nucleic acid-based test
NCBI	National Center for Biotechnology Information
NDA	New Drug Application
NGDS	Next-generation diagnostic system
NGO	Non-governmental organization
NGS	Next-generation sequencing
NIAID	National Institute of Allergy and Infectious Diseases
NICBR	National Interagency Confederation for Biological Research
NIH	U.S. National Institutes of Health
NIST	National Institute of Standards and Technology
NLM	National Library of Medicine
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act of 2013
PCLC	Physiological closed-loop controlled
PDUFA	Prescription Drug User Fee Act
PEP	Post-exposure prophylaxis
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PMA	Premarket Approval
PPE	Personal protective equipment
REMS	Risk Evaluation and Mitigation Strategies
RCDAD	Relevant Communicable Disease Agent or Disease

RMP	Regulatory Management Plan
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SLEP	Shelf-Life Extension Program
SFDA	Saudi Food and Drug Authority
SNS	Strategic National Stockpile
SPA	Special Protocol Assessment
TBI	Traumatic brain injury
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USDA	U.S. Department of Agriculture
USCIITG	United States Critical Illness and Injury Trials Group
USG	United States Government
UTMB	University of Texas Medical Branch
WHO	World Health Organization

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