FDA Medical Countermeasures Initiative

Protecting National Health and Security

# Program Update


## Fiscal Year 2014

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
Medical Countermeasures Initiative (MCMi)
www.fda.gov/medicalcountermeasures

# Message from Luciana Borio, M.D., Acting Chief Scientist

I am pleased to present the FDA Medical Countermeasures Initiative (MCMi) program update for our fourth year of operations.[a] In addition to our ongoing work to advance the development and availability of medical countermeasures to protect against chemical, biological, radiological, and nuclear (CBRN) threats, we have also responded to emerging public health threats in an unprecedented way.

The Ebola epidemic in West Africa tested systems we've been putting in place since MCMi was launched in 2010, including new legal authorities granted by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA); numerous collaborations with industry, academia, government and international partners; and our investments in regulatory science research—research required to facilitate the development of medical countermeasures and inform their use in emergency situations. International cooperation is critical to address key public health challenges. In FY 2014, in collaboration with numerous partners, we made progress on key global and public health issues, including antimicrobial resistance and pandemic influenza, approving the first adjuvanted vaccine for the prevention of H5N1 influenza.

FDA's response to the Ebola epidemic in West Africa began in FY 2014 and continues today. We continue to take extraordinary steps to be proactive and flexible in our response. FDA's efforts have included work—alongside product sponsors, international regulators, the World Health Organization (WHO) and U.S. government partners—to help expedite the development and availability of Ebola therapeutics, vaccines, and diagnostic tests. These efforts have enabled the launch of clinical trials in record time, including an innovative common clinical protocol to evaluate the most promising investigational treatments for Ebola. FDA also authorized the use of nine Ebola diagnostic tests under our Emergency Use Authority. We are collaborating extensively with WHO and international regulatory counterparts—including counterparts in affected West African countries—to exchange information about investigational products for Ebola in support of international response efforts.

Developing medical countermeasures is highly complex. The Ebola epidemic has demonstrated how critical it is to respond with speed and flexibility—and also how important it is to get it right. There is still a lot of work to do. FDA remains committed to leveraging our deep expertise and authorities to the fullest extent to support our nation's readiness for serious public health threats.

*Cover photo: Centers for Disease Control and Prevention (CDC)/Flickr*

[a] Fiscal year 2014 covers the period from October 1, 2013, to September 30, 2014.

# Contents

**Message from Luciana Borio, M.D., Acting Chief Scientist** ..... II

**FDA's Medical Countermeasures Initiative** ..... 1

**Fiscal Year 2014 Program Update** ..... 1

Background ..... 1

FY 2014 Medical Countermeasure Resources ..... 2

**FY 2014 Objectives, Activities, and Achievements** ..... 3

Objectives and Activities ..... 3

Medical Countermeasure Approvals ..... 4

Supporting an Adequate Supply of Medical Countermeasures ..... 5

Enabling Access to Available Medical Countermeasures ..... 6

Responding to Emerging Public Health Threats ..... 7

Facilitating Medical Countermeasure Development ..... 9

Regulatory Advice and Guidance ..... 12

Collaborations ..... 16

Medical Countermeasure Regulatory Science ..... 16

Medical Countermeasure Regulatory Policy ..... 21

Professional Development ..... 23

**Appendix 1: FY 2014 Medical Countermeasure Approvals** ..... 27

**Appendix 2: Current Emergency Use Authorizations** ..... 31

**Appendix 3: Acronyms** ..... 32

*About references within this document*

*Footnotes contain additional information and are designated with letters (e.g., [a]); each footnote can be found at the bottom of the page on which it is referenced. Endnotes are references, such as links to additional resources, and are designated with numbers (e.g., [1]); all endnotes can be found at the end of the report, beginning on page 24.*

# FDA's Medical Countermeasures Initiative
# Fiscal Year 2014 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. FDA is responsible for ensuring that medical countermeasures—including drugs, therapeutic biologics, vaccines, and devices, such as diagnostic tests—to counter these threats are safe, effective, and secure.[b]

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 (Enterprise) to build and sustain the medical countermeasure programs necessary to respond effectively to public health emergencies.[c] FDA also works closely with the U.S. Department of Defense (DoD) to facilitate the development and availability of medical countermeasures to support the unique needs of the warfighter. FDA supports the Enterprise and DoD by providing subject matter expertise in medical countermeasure development as well as by providing scientific and regulatory input to inform medical countermeasure procurement and stockpiling decisions. In addition, FDA facilitates access to available medical countermeasures 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.[d,e]

---

[b] Medical countermeasures include qualified countermeasures as defined in section 319F–1(a) of the Public Health Service Act (42 USC. § 247d–6a(a)); qualified pandemic or epidemic products as defined in Section 319F–3 of the Public Health Service Act (42 USC. § 247d–6d)), and security countermeasures as defined in Section 319F-2(c)(1)(B) of the Public Health Service Act (42 USC § 247d–6b).

[c] The Enterprise is a coordinated, interagency partnership that fosters the medical countermeasure 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 of Preparedness and Response and includes three primary HHS internal agencies: the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health. Key interagency partners are: the Department of Homeland Security, the Department of Defense, the Department of Veterans Affairs, and the Department of Agriculture.

[d] 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 medical countermeasures in emergencies under certain terms and conditions [21 USCS § 360bbb-3].

[e] For purposes of this document, "approved" refers to "FDA-approved, licensed, or cleared" under sections 505, 510(k), or 515 of the Federal Food, Drug, and Cosmetic Act or of section 351 of the Public Health Service Act.

In 2010, FDA launched its Medical Countermeasures Initiative (MCMi), building on the substantive medical countermeasure work ongoing at FDA and focusing increased resources on promoting the development of medical countermeasures by establishing clear regulatory pathways for medical countermeasures, instituting effective regulatory policies and mechanisms to facilitate timely access to available medical countermeasures, and advancing medical countermeasure 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.[f] 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 medical countermeasures as well as created new authorities to enable FDA to more effectively support preparedness and response efforts. PAHPRA also requires FDA to issue an annual report detailing its medical countermeasure activities. This report responds to that requirement for Fiscal Year (FY) 2014.[1]

## FY 2014 Medical Countermeasure Resources

FDA obligated $136.2 million in FY 2014 to support CBRN and pandemic influenza-related medical countermeasure activities (**Table 1**). These resources comprised a combination of base funding and no-year funding.

**Table 1: FY 2014 Resources Obligated to Medical Countermeasure Activities (dollars in millions)**

| | FY 14 Actuals | FY 14 FTE Actuals |
|---|---|---|
| CBRN Base Funding | $66.5 | 345 |
| Pandemic Influenza Base Funding | $38.3 | 179 |
| MCMi Base Funding | $24.6 | 80.5 |
| No-Year Funding | $6.8 | 0 |
| Total | **$136.2** | **604.5** |

### Base Funding

FDA obligated $129.4 million from its FY 2014 base resources to support CBRN and pandemic influenza-related medical countermeasure activities. This funding included $66.5 million for CBRN preparedness activities, $38.3 million for pandemic influenza preparedness activities, and $24.6 million for the MCMi.

This funding supported 604 full-time equivalents (FTEs) as well as a $1.6 million investment in the MCMi Regulatory Science Program.

[f] Public Law 113-5, 127 Stat. 161.

### No-Year Funding

FDA received $170 million, one-time funding from HHS to commence MCMi activities at the end of FY 2010 when the MCMi was launched. In FY 2014, FDA obligated $6.8 million of the no-year funding to support MCMi activities.[g] This funding supported regulatory science projects and infrastructure for the MCMi Regulatory Science Program and other non-payroll MCMi costs (e.g., professional development).

## FY 2014 Objectives, Activities, and Achievements

### Objectives and Activities

FDA's overarching objective with respect to medical countermeasures—which cuts across all FDA centers and offices engaged in the medical countermeasure mission space—is to facilitate the development of and access to safe and effective medical countermeasures to counter high-priority CBRN and emerging infectious disease threats, as well as medical countermeasures 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 medical countermeasures for CBRN or emerging threat indications, to help clarify requirements for approval
- Reviewing medical countermeasure marketing applications and approving those that meet standards for safety, efficacy, and quality
- Supporting the establishment and sustainment of an adequate supply of medical countermeasures
- Enabling access to available medical countermeasures 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 high-priority medical countermeasures
- Collaborating with U.S. government partners developing medical countermeasures

[g] FDA expended $49.8 million of the $170 million no-year funding during FY 2011, $54.6 million during FY 2012, and $53.2 million during FY 2013. FDA anticipates expending the remaining balance of the no-year funding (approximately $5.6 million) in FY 2015.

- Sustaining the MCMi Regulatory Science Program to develop tools, standards, and approaches to develop and assess medical countermeasure safety, efficacy, quality, and performance
- Ensuring that FDA regulations and policies adequately support medical countermeasure 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 medical countermeasure mission

The following sections provide detail on achievements in FY 2014 with respect to these activities.

## Medical Countermeasure Approvals

FDA approved the majority of medical countermeasure marketing applications under review[h] in FY 2014 (**Appendix 1**).

MCMi promotes development and availability of safe, effective medical countermeasures

In the area of diagnostics for CBRN threats, FDA cleared a U.S. Centers for Disease Control and Prevention (CDC) assay for the qualitative detection of plasmid and chromosomal DNA sequences from *B. anthracis* (anthrax).

In the area of pandemic influenza preparedness, FDA approved the Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (Q-Pan H5N1) manufactured by ID Biomedical Corporation (a subsidiary of GlaxoSmithKline Biologicals), for use in people 18 years of age and older who are at increased risk of exposure to the H5N1 influenza virus. This is the first adjuvanted vaccine approved for the prevention of H5N1 influenza.

With respect to diagnostic tests for influenza, FDA approved three new *in vitro* diagnostic devices for the qualitative detection and differentiation of influenza viruses and 14 modifications of previously approved influenza assays to improve their performance.

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

Ten additional medical countermeasure marketing applications were under review in FY 2014, the reviews for which 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 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.[i]

## Supporting an Adequate Supply of Medical Countermeasures

FDA continued its efforts to support the establishment and sustainment of an adequate supply of medical countermeasures during FY 2014. 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 medical countermeasures 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 2014, as a result of SLEP testing that assured drug stability and quality, FDA granted shelf-life extensions for 1,800 lots (batches) of medical countermeasure drugs.

Another way FDA worked to ensure an adequate supply of medical countermeasures in FY 2014 was by conducting post-marketing current good manufacturing practices (cGMP) inspections for facilities that produce medical countermeasures 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.[j]

---

[i] For updated information about medical countermeasure approvals after the FY 2014 reporting period, visit the MCMi News and Events page at: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm262925.htm

[j] 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.

FDA also works to resolve medical countermeasure shortages as quickly as possible when they occur. In FY 2014, FDA continued its collaboration with U.S. government partners and the product manufacturer of auto-injectors used for the treatment of nerve agent and insecticide poisoning to help prevent shortages of these products after quality issues identified in the manufacturing process resulted in a subset of product being out of specification (i.e., having an insufficient quantity of active drug product). FDA reviewed applicable scientific data and determined that, if properly stored, certain auto-injectors could be used beyond their 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.[2] 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-injectors produced by the same manufacturer. Meanwhile, FDA continued to work with the product manufacturer to help rectify the quality issues in its manufacturing process so production of new product can be resumed.

## Enabling Access to Available Medical Countermeasures

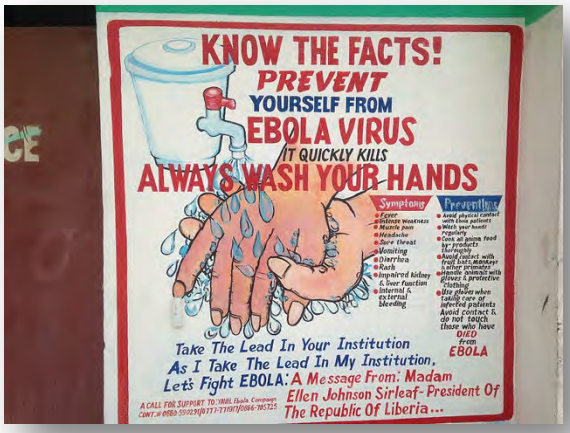
During FY 2014, FDA continued to work with its Enterprise partners, DoD, and product sponsors to enable access to available medical countermeasures when necessary. One way FDA does this is by issuing Emergency Use Authorizations (EUAs), which allow FDA to authorize the use of an unapproved medical countermeasure, or the unapproved use of an approved medical countermeasure, in anticipation of a potential emergency or during an actual emergency involving a specified CBRN agent or agents if certain statutory criteria are met. In FY 2014, FDA issued several EUAs to facilitate preparedness for emerging threats. FDA issued two EUAs for diagnostic tests for the avian influenza A (H7N9) virus. These EUAs are in addition to the EUA issued in FY 2013 for CDC's H7N9 diagnostic test, which remains in effect. FDA also re-issued the EUA for the CDC *in vitro* diagnostic for the Middle East Respiratory Syndrome coronavirus (MERS-CoV) in its entirety with CDC-requested amendments incorporated.[k] Additionally, FDA issued nine EUAs, and subsequently reissued six of these EUAs to address requesters' amendments, for diagnostic tests for the presumptive detection of Ebola virus in response to the 2014 West Africa outbreak; one of these EUAs was issued in the FY 2014 reporting period.[3]

In addition to issuing EUAs when necessary, FDA also works to ensure that the U.S. government is as prepared as possible to deploy medical countermeasures that may need to be used under

[k] The amendments authorize the expanded use of the CDC assay to include testing persons who may not be exhibiting signs and symptoms associated with MERS-CoV infection, but who meet certain epidemiological risk factors. The EUA amendments also include a new fact sheet for contacts of MERS cases and revisions/updates to the instructions for use and fact sheets for patients and health care professionals.

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 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.[I] During FY 2014, FDA continued to work with CDC, the Biomedical Advanced Research and Development Authority (BARDA), DoD, and industry on pre-EUA activities for medical countermeasures against a diverse array of threats including smallpox, anthrax, pandemic influenza, Ebola virus, and nuclear threats.

## Responding to Emerging Public Health Threats




In FY 2014, an Ebola virus outbreak emerged in Guinea and quickly spread to Liberia, Sierra Leone, and nearby countries, becoming the largest Ebola epidemic in history. On August 8, 2014, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern.[4] FDA worked proactively with U.S. government partners, international partners, and medical product developers to facilitate the development and availability of medical countermeasures to respond to the Ebola outbreak. In addition, FDA continued similar activities to respond to the avian influenza A (H7N9) virus and MERS-CoV, both of which emerged in 2013 and continue to pose significant public health threats. Key FDA response activities included:

- Collaborating closely with HHS, other Federal agencies, and international partners such as WHO in preparedness and response decisions regarding medical countermeasure development and use
- Providing technical expertise, regulatory guidance, and interactive review to expedite the development of medical countermeasures including review and feedback on development proposals including clinical trial design and data assessment

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

- Maintaining regular contact with drug, vaccine, device, and diagnostic test developers, and expediting the regulatory review of data for products that are currently in the pipeline and products that are still very early in development (i.e., reviewing data as they are received)
- Enabling access to investigational medical countermeasures—when necessary—through an appropriate mechanism such as under an EUA or under expanded access mechanisms (e.g., enabled access to investigational medical countermeasures under Emergency Investigational New Drug (eIND) applications to respond to the Ebola outbreak during the period of the epidemic before clinical trials were established). FDA issued EUAs for diagnostic tests for the avian influenza A(H7N9) virus, MERS-CoV, and Ebola virus (see **Appendix 2** for a list of current EUAs)
- Preparing to implement safety surveillance programs for adverse events associated with medical countermeasure use and take appropriate action if safety issues are identified
- Monitoring the medical countermeasure supply chain to identify product shortages, distribution of misbranded/counterfeit products, and false product claims, and taking appropriate action when necessary to protect consumers[5]

Agreements established in FY 2014 between FDA and its international counterparts have helped information-sharing and collaboration during the current Ebola epidemic, and have better prepared the international regulatory community to respond to future public health emergencies. For example:

Progress made during the Ebola response will help the U.S. and global health community better prepare for future public health threats

- On August 25, 2014, FDA and the WHO Department of Essential Medicines and Health Products (WHO EMP) signed an agreement (PDF, 550 KB) to help facilitate communications between FDA and WHO EMP regarding an actual or potential public health crisis or public health emergency of international concern, such as the Ebola outbreak in West Africa. The agreement allows sharing of information that is non-public but important to address public health emergencies between the organizations.
- On September 4, 2014, medicines regulators worldwide announced a commitment to enhanced cooperation with the WHO and between regulatory agencies to encourage submission of regulatory dossiers and evaluation of the submitted information on

potential new medicines. The aim is to accelerate access to investigational treatments for patients most in need during the current epidemic. The enhanced cooperation also aims to ensure that in the future, public health authorities in countries affected by Ebola have safe and efficacious medicines at their disposal, strengthening their ability to respond effectively to outbreaks and to save lives. This pledge was made by members of an interim International Coalition of Medicines Regulatory Authorities (ICMRA), including FDA.

- In February and March 2015, respectively, FDA and the Liberian Medicines and Health Products Regulatory Authority (LMHRA) and the Pharmacy Board of Sierra Leone (PBSL) entered into reciprocal agreements as part of cooperative regulatory activities to help facilitate communication on medical products used, or proposed to be used, for Ebola-related purposes.[6,7]

## Facilitating Medical Countermeasure Development

### Action Teams

Under the MCMi, FDA established multidisciplinary Public Health and Security Action Teams (Action Teams) to advance priority medical countermeasures by working with internal and external entities—as appropriate—to identify and catalyze the resolution of regulatory and scientific challenges to medical countermeasure development. During FY 2014, FDA continued or completed tasks assigned to the five Action Teams launched during FY 2011 and FY 2012. The following information summarizes FY 2014 activities of the five Action Teams.

**Multiplex and Microbial Sequencing *In Vitro* Diagnostics Action Team –** This Action Team continued its work to facilitate the development of multiplex and microbial sequencing *in vitro* diagnostic tests. Such diagnostics could be used to test for multiple pathogens simultaneously from a single clinical specimen, providing valuable information when responding to a public health emergency. Key activities during FY 2014 included:

- Hosting a workshop on advancing regulatory science for high throughput sequencing devices for microbial identification and detection of antimicrobial resistance markers to discuss the clinical and public health applications and performance validation of these devices, the quality criteria for establishing the accuracy of reference databases for regulatory use, and ways to streamline testing for microbial identification.[8] Also, worked with the FDA Center for Devices and Radiological Health (CDRH) Network of Experts, a resource that utilizes professional organizations and their networks to obtain outside expertise.

- Continuing a collaboration with the National Center for Biotechnology Information (NCBI) and the Lawrence Livermore National Laboratory (LLNL) to establish quality criteria for microbial reference databases that will be critical to developers seeking to validate their candidate multiplex *in vitro* diagnostic tests.[m]
- Developing quality criteria and establishing publicly available and accessible database through NCBI: FDA-ARGOS, a database for regulatory-grade microbial genomic reference sequences. The sequencing contract was awarded to the Institute of Genomic Sciences at the University of Maryland to sequence and deposit 650 genus-diverse and public health need isolates (350 sequenced, 300 in pipeline at various stages).[n]
- Continuing a collaboration with the Defense Advanced Research Projects Agency (DARPA) to support their Diagnostics on Demand (DxOD)/Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT) program.
- Continuing information exchange with the CDC Laboratory Response Network (LRN) and DHS regarding implementation of Public Health Actionable Assay validation strategies for characterization of biothreat assays for LRN use.
- Sustaining interactive collaboration with the DoD on the development of their Next-Generation Diagnostic System (NGDS) to replace the Joint Biological Agent Identification and Diagnostic System (JBAIDS). DoD awarded a contract to BioFire Defense for NGDS technology development in March 2014.

**Acute Radiation Syndrome (ARS) Action Team –** This Action Team continued its efforts to clarify the regulatory requirements for radiological/nuclear medical countermeasures. Key activities during FY 2014 included:

- Working to clarify the regulatory requirements for candidate MCMs in the development pipeline for the hematopoietic sub-syndrome of ARS.

[m] Through this collaboration, draft quality standards for microbial sequence information have been identified and the framework for a publically available reference database has been established. The FDA MicroDB: Microbial Confirmatory Reference Database is available at http://www.ncbi.nlm.nih.gov/bioproject/231221

[n] 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/NIAID collaboration and USAMRIID/CRP, 4) antimicrobial resistance (AMR) isolates from Children's Hospital, and 5) difficult-to-acquire isolates from the American Type Culture Collection (ATCC).

- Identifying regulatory and scientific issues/gaps for development of MCMs for the gastrointestinal sub-syndrome of ARS.
- Supporting the development of an ARS Questions and Answers guidance to help sponsors develop products for this indication under the Animal Rule.
- Working to facilitate the development of radiation biodosimetry devices that can be used in a radiological/nuclear event to assess the ionizing radiation dose received by individuals or populations at various stages (triage and treatment).
- Supporting the development of a draft guidance for Radiation Biodosimetry Devices.[9]

**Warfighter Action Team –** This Action Team continued its efforts to facilitate the development and regulatory assessment of medical countermeasures and related technologies primarily to support the warfighter and trauma victims. Key FY 2014 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 with DTRA and DoD Health Affairs as needed to discuss regulatory and scientific issues.
- Providing assistance to the DoD on potential approaches for addressing the unique challenges in conducting studies or making available medical countermeasures for the warfighter. Focus areas include traumatic brain injury, hemorrhage, nerve agents, and research that involves minimal risk to human subjects.[o]

**Surveillance and Assessment Action Team –** This Action Team, a collaboration between FDA and CDC, continued its efforts to facilitate the development of systems that can be used to monitor and assess medical countermeasure safety and clinical benefit during public health emergencies. Key FY 2014 activities included:

- Working with Enterprise partners to establish an Integrated Program Team (IPT) to review and refine as necessary the *Action Plan for Developing an Enhanced National Capability for Monitoring and Assessing Medical Countermeasures during Public Health Emergencies* developed by the Action Team and to develop an overarching implementation plan for fulfilling the vision set forth in the *Action Plan.*[p]

[o] 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.

[p] In the summer of 2014, the Action Team completed its primary mission to help stand up an MCM Monitoring and Assessment IPT, and was subsequently deactivated. Many members of the Action Team are now members of the IPT, and efforts to continue expansion of surveillance activities to monitor MCMs will continue through the IPT.

**Pediatrics and Maternal Action Team –** This Action Team continued is efforts to identify and address the medical countermeasure needs of pediatric and maternal populations during public health emergencies. Key FY 2014 activities included:

- Assessing countermeasures in the SNS to identify outstanding issues that may prevent or impede MCM availability and usability for the pediatric population during emergencies. The Action Team presented its final analysis of outstanding pediatric SNS issues to the PHEMCE PedsOB IPT.[q]

## Regulatory Advice and Guidance

During FY 2014, FDA continued to provide regulatory advice and guidance to sponsors and applicants of medical countermeasures and our federal partners funding medical countermeasure development, to help foster the development and availability of various medical countermeasures. 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 medical countermeasure sponsors and applicants throughout the product life cycle. For example, FDA reviews pre-investigational and investigational new product applications and responds to questions from sponsors and 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 medical countermeasures into clinical development and assess progress as these specialized product candidates move through clinical development toward a marketing application. FDA also provides technical assistance to minimize risk during medical countermeasure manufacturing, including pre-approval inspections or site visits to ensure that manufacturing establishments are capable of adequately manufacturing products, and that submitted application data are accurate. 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 medical countermeasures.

FDA has established policies and procedures for conducting formal meetings with product sponsors or applicants.[10] Formal meetings are held—as needed—at the request of a product

[q] The Action Team has completed its initial mission, but may be convened as necessary in the future to coordinate with the PedsOB IPT to address issues identified in the analysis, to help ensure that there is sufficient access to and information about MCMs necessary to treat and/ or prevent illness in the pediatric population during public health emergencies.

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).[r] When FDA denies a request for a meeting, the sponsor or applicant is provided feedback on what they need to do to warrant a meeting.

**Table 2. FY 2014 Formal Meetings Between CBER/CDER and Medical Countermeasure Sponsors or Applicants**

| Meeting Type | CBER | CDER |
|---|---|---|
| Type A | 1 | 1 |
| Type B | 18 | 9 |
| Type C | 21 | 27 |
| Total | **40** | **37** |

The Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) categorize their 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,[s] and a Special Protocol Assessment meeting[11]). 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-Investigational New Drug application meetings, certain end-of-phase 1 meetings, end-of-phase 2 and pre-phase 3 meetings, and pre-New Drug Application/Biologics License Application meetings). 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 2014, CBER held 40 formal meetings with medical countermeasure sponsors or applicants, and 5 other (non-PDUFA) meetings, and CDER held 37 formal meetings (**Table 2**).

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. CDRH received

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

and reviewed 27 Pre-sub applications for medical countermeasure diagnostic devices in FY 2014. FDA provided extensive written feedback on these submissions, and most of the 27 sponsors declined 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 2014, CDRH held 17 formal meetings with medical countermeasure sponsors or applicants (**Table 3**), and provided written feedback for 7 medical countermeasure sponsors.

**Table 3. FY 2014 Formal Meetings Between CDRH and Medical Countermeasure Sponsors or Applicants**

| Meeting Type | CDRH |
|---|---|
| Pre-Submission | 15 |
| Submission | 2 |
| Total | **17** |

Moreover, FDA has significant interactions with medical countermeasure 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.[12]

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.[t] FDA did not receive any written RMP requests in FY 2014.

In addition to its direct work with medical countermeasure sponsors and applicants, FDA also issues guidance documents that help foster medical countermeasure development and

[t] Under PAHPRA, medical countermeasures 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 Public Health Service Act [42 USCS § 247d-6b(c)]; or medical countermeasures with respect to which the Biomedical Advanced Research and Development Authority has provided funding under section 319L of the Public Health Service 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 the Biomedical Advanced Research and Development Authority, in consultation with the Commissioner of FDA, prioritizes which eligible medical countermeasures may receive RMPs if resources are not available to establish RMPs for all eligible medical countermeasures for which requests are submitted.

availability.[u] Guidance documents issued during FY 2014 directly related to, or applicable to, medical countermeasures policies or regulatory issues include:

- Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools (PDF, 499 KB), describing the process for qualifying drug development tools intended for potential use, over time, in multiple drug development programs. Drug development tools (DDTs) are methods, materials, or measures that aid drug development. DDTs include, but are not limited to, biomarkers, clinical outcome assessments (COAs), and animal models for drug development under the Animal Rule[13,14]
- Draft Guidance for Industry, Product Development Under the Animal Rule (PDF, 1.3 MB), addressing a broad scope of issues for products developed under the Animal Rule[15]
- Guidance for Industry and FDA Staff: Highly Multiplexed Microbiological/Medical Countermeasure *In Vitro* Nucleic Acid Based Diagnostic Devices (PDF, 799 KB), providing recommendations for studies to establish the analytical and clinical performance of highly multiplexed microbiological/medical countermeasure *in vitro* nucleic acid-based diagnostic devices intended to simultaneously detect and identify multiple pathogen nucleic acids extracted from a single appropriate human specimen or culture[16]

FDA also holds Advisory Committee meetings and public workshops to obtain independent input and expert advice on scientific, technical, and policy matters to facilitate medical countermeasure development. Key workshops held during FY 2014 include:

- April 1-2, 2014 – Advancing Regulatory Science for High Throughput Sequencing Devices for Microbial Identification and Detection of Antimicrobial Resistance Markers[17]
- May 5, 2014 – Innovative Approaches to Pediatric Drug Development and Pediatric Medical Countermeasures: A Role for Physiologically-Based PK?, a meeting co-sponsored by the University of Maryland and FDA[18]
- May 21-22, 2014 – Respiratory Protective Devices Summit[v]
- July 30-31, 2014 – The Development of New Antibacterial Products: Charting a Course for the Future, a workshop co-hosted by the National Institutes of Health and FDA[19]
- September 3-4, 2014 – Hemostatic Medical Devices for Trauma Use workshop[20]

[u] Guidance documents are documents prepared for FDA staff, applicants/sponsors, and the public that describe the 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) (2011)]

[v] Invitation-only meeting

- September 5, 2014 – Clinical Development of Drugs for the Prevention of Infections Caused by *Staphylococcus aureus* in the Health Care Setting workshop[21]
- September 22-23, 2014 – Addressing Challenges in Antimicrobial Resistance: Overcoming Bottlenecks in Antibacterial Product Development and Coordinated Development of Diagnostics and Therapeutics, a workshop sponsored by the National Institutes of Health (NIH) with FDA participation[22]

## Collaborations

During FY 2014, FDA continued to collaborate extensively with Enterprise and DoD partners to foster the development and availability of medical countermeasures. FDA provided subject matter expertise and technical assistance to 54 standing Enterprise- and DoD-specific committees and working groups that develop medical countermeasure 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 medical countermeasures from threat assessment to requirements setting to product development to procurement, stockpiling, and utilization.

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 medical countermeasures.

## Medical Countermeasure Regulatory Science

In FY 2014, 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.

Medical countermeasures 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 medical countermeasures 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 many threat agents.[w] In these situations, efficacy data from animal studies may be used if the results can reasonably be extrapolated to expected human use.[x] The challenges are even more complex when it comes to developing medical countermeasures 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 medical countermeasures—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 in the pediatric population).[y]

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 medical countermeasure safety, efficacy, quality, and performance and to help translate cutting-edge science and technology into innovative, safe, and effective medical

[w] 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 2014 PHEMCE Strategy and Implementation Plan for more information at http://www.phe.gov/Preparedness/mcm/phemce/Documents/2014-phemce-sip.pdf (see Box 1, page 9)

[x] 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 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 for drugs and 21 CFR 601.90 for biological products).

[y] 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

countermeasures—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 medical countermeasure product quality and related product release assays
- Validating next-generation *in vitro* diagnostics 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 medical countermeasures used during public health emergencies

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.[z] To ensure that the MCMi Regulatory Science Program is appropriately targeted and coordinated with U.S. government medical countermeasure 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.

Examples of ongoing research include:

- Developing a highly sensitive assay to measure the level of the influenza antiviral Tamiflu (oseltamivir phosphate) and its active metabolite (oseltamivir carboxylate) in blood samples to aid in the development of appropriate dosing for specific populations such as pregnant women
- Developing models of radiation damage in lung, gut, and bone marrow organs-on-chips and then using these models to test candidate medical countermeasures to treat such damage[23]

[z] 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/ucm391617.htm

- Mapping immune responses to certain biothreat agents and medical countermeasures in humans and animal models to create species-specific immune function maps[24]
- Examining the scientific basis for the instability of the protective antigen of *B. anthracis* that has hindered efforts to develop next-generation anthrax vaccines and using protein engineering to stabilize the antigen[25,26]

- Developing new approaches for measuring the quality of next-generation smallpox vaccines
- Developing new methods for evaluating the purity and sterility of novel cell substrates that can be used to produce vaccines[27,28,29]
- Developing new and improved tests to detect viruses and mycoplasma in biological samples including cell substrates and other starting materials to support assessment of product quality, safety, and consistency[30,31]
- Developing and characterizing a highly qualified influenza virus panel for the evaluation of influenza detection antigen assays, in collaboration with CDC; these panels are now ready for distribution by CDC
- Constructing and characterizing highly qualified and validated nucleic acid panels for the molecular characterization of bacterial biothreat agents that will aid in the development of diagnostic devices for biothreat agents, in collaboration with USAMRIID; this project was completed in late 2013 (FY 2014)[32]
- Developing and characterizing a repository of microbial-resistant strain panels to be made publicly available for developers of antimicrobial resistant diagnostics and therapies, 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 order isolates.
- Developing methods for real-time detection of medical device surface contamination to decrease the potential for the transmission of infection between patients as well as between patients and healthcare workers
- Assessing the feasibility of using electronic health record systems to conduct near real-time monitoring of health outcomes, including serious or unexpected adverse events associated with medical countermeasures used during public health emergencies[33]

- Developing a mobile device (e.g., smartphone) application for reporting adverse events associated with medical countermeasures to FDA, including an in-depth MCMs module
- 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[34]
- Investigating decontamination and reuse of respirators in public health emergencies, and optimizing respirator decontamination to ensure supplies for emergency preparedness[35]
- Developing methods for obtaining safety and limited efficacy data from patients who receive a medical countermeasure 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[36]

FDA also expanded and sustained medical countermeasure regulatory science collaborations in FY 2014. For example FDA:

- Convened the third annual MCMi Regulatory Science Symposium to showcase medical countermeasure regulatory science under way at FDA and by external partners and to promote scientific engagement.[37]
- Sponsored the second installment of a training program to ensure the integrity and quality of data generated in high-containment (i.e., Animal Biosafety Level (ABSL) 3 and ABSL4) laboratories used to support product approval under the Animal Rule.
- Supported the Animal Model Qualification Program, which will enable the product-independent evaluation of animal models and provide the potential to determine whether a particular model can contribute to the demonstration of efficacy to support approval of classes of products for specific indications.[38]
- 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; NCBI to establish a publicly available, well-curated

reference database that will be critical to developers seeking to validate their candidate high-throughput sequencing-based *in vitro* diagnostic assays; and the National Interagency Confederation for Biological Research (NICBR) to assist in this effort to develop synchronized scientific interaction among Federal partners to enhance public health, medical research, and biotechnology development.

- Collaborated with the National Institute of Standards and Technology (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.
- Held a workshop on advancing regulatory science for high-throughput sequencing devices for microbial identification and detection of antimicrobial resistance markers.
- Held a Respiratory Protective Devices (RPD) Summit to assess the state of the science regarding performance standards, testing, and evaluation of RPDs and to identify strategies for increasing and extending the RPD supply for those involved in the response to public health emergencies.

## Medical Countermeasure Regulatory Policy

During FY 2014, FDA continued its 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 medical countermeasures. FY 2014 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, including requirements to establish processes for sponsor interactions.[39] Implementation efforts have focused on drafting an update to FDA's 2007 Guidance entitled Emergency Use Authorization of Medical Products.
- Finalizing a PHEMCE Memorandum of Understanding (MOU) to establish a clearer framework for information sharing and FDA engagement within the PHEMCE, and to facilitate more robust communications while preserving confidentiality and the integrity of regulatory decisions.[40]

- 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.[41] FDA also published a PAHPRA Q&A document for public health preparedness and response stakeholders in FY 2014,[42] and sustained 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 Institute of Medicine's (IOM) Forum on Medical and Public Health Preparedness for Catastrophic Events, which provides national leadership in coordinating ongoing efforts among members from Federal, state, and local government; business; and professional associations to develop sustainable partnerships between the public and private sector so that communities are adequately prepared for natural or human-made catastrophic events.
- Working 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 MCM development that are unique to the warfighter
    - Issues related to expiration dating that are unique to MCMs and to public health stakeholders
    - Approaches to data collection on MCMs used during public health emergencies
    - Issues related to use of expanded access and EUAs to make available unapproved MCMs
    - MCM import and export issues during emergency responses and to support preparedness for international events
    - 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
    - Enhanced flexibility to conduct minimal risk research in support of product development
    - Harmonizing multi-jurisdictional regulation of certain personal protective equipment

## Professional Development

FDA launched a medical countermeasure Professional Development Program under the MCMi during FY 2011 to ensure that FDA scientists are informed about CBRN threats and associated health impacts as they conduct benefit-risk analyses on medical countermeasures, and that FDA scientists can meet the regulatory challenges posed by new areas of science and technology in the area of medical countermeasure development. Key activities of the MCMi Professional Development Program during FY 2014 include:

- **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 medical countermeasure applications. There were 3 lectures in this series during FY 2014 with 297 attendees, 13 of whom received continuing education (CE) credits.[43]


- **Foundations for Preclinical Review Lecture Series:** This is a monthly lecture series on pre-clinical scientific and technical issues of importance to medical countermeasures, since many medical countermeasures are developed under the Animal Rule. Presentations are invited from both internal and external experts in the field. There were 6 lectures in this series during FY 2014 with 791 attendees, 57 of whom received CE credits.
- **Conference Support**: FDA supported 32 staff to attend 9 MCM-related external conferences during FY 2014.
- **Georgetown University Certificate Program on Biohazardous Threat Agents and Emerging Infectious Diseases**: This 12-credit, online, graduate-level certificate program is available to FDA staff involved in MCM activities to learn more about the science behind and impact of biothreat agents and emerging diseases. At successful course completion, participants receive a Certificate in Biohazardous Threat Agents and Emerging Diseases. Six FDA staff graduated in May 2014 and 5 staff members are currently enrolled in the program.[44]

[1] Detailed information on FDA's medical countermeasure development and review activities in FY 2011, FY 2012 and FY 2013 can be found in the *MCMi Year 1 Status Report*, *MCMi Year 2 Program Update,* and *MCMi Fiscal Year 2013 Program Update* available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm270744.htm

[2] For the latest updates on expiry dating extensions for auto-injectors, see http://www.fda.gov/Drugs/DrugSafety/ucm376367.htm

[3] For more about EUAs see http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm

[4] For more, see the August 8, 2014, WHO Disease Outbreak News report at http://www.who.int/csr/don/2014_08_08_ebola/en/

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

[6] FDA and LMHRA reciprocal agreements, signed in FY 2015 (PDF, 821 KB): http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM441392.pdf

[7] FDA and PBSL reciprocal agreements, signed in FY 2015 (PDF, 702 KB): http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM441396.pdf

[8] Webcast recordings and meeting information (April 1, 2014) available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm386967.htm

[9] Draft guidance published December 2014, available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM427866.pdf

[10] 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

[11] 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

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

[13] Guidance available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

[14] For more on Drug Development Tools qualification programs see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

[15] Revised draft guidance available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf

[16] Guidance available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM327294.pdf

[17] Meeting materials available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm386967.htm

[18] Meeting agenda available at http://www.pharmacy.umaryland.edu/centers/cersievents/pediatricpbpk/agenda.html

[19] Meeting materials available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm403009.htm

[20] Meeting materials available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm396497.htm

[21] Meeting materials available at http://www.fda.gov/Drugs/NewsEvents/ucm407259.htm

[22] Meeting information available at https://respond.niaid.nih.gov/conferences/TherapeuticsWorkshops2014/Pages/default.aspx

[23] The project was funded under the extramural MCMi regulatory science program. For more information see Organs-On-Chips for Radiation Countermeasures at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm364491.htm

[24] The project was funded under the extramural MCMi regulatory science program. For more information see Cross Species Immune Reference at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm332539.htm

[25] Verma, A., et al., *Use of site-directed mutagenesis to model the effects of spontaneous deamidation on the immunogenicity of Bacillus anthracis protective antigen.* Infect Immun, 2013. 81(1): p. 278-84.

[26] Domínguez-Castillo RI, et al., *Ability of ELISA and a toxin neutralization assay to detect changes in immunogenicity of a recombinant Bacillus anthracis protective antigen vaccine upon storage*. Biologicals 2013 Mar;41(2): p.111-4.

[27] Teferedegne B, et al., *MicroRNAs as potential biomarkers for VERO cell tumorigenicity*. Vaccine, 2014. 32(37): p.4799-805

[28] Khan AS, et al., *New technologies and challenges of novel virus detection*. PDA J Pharm Sci Technol, 2014. 68(6):661-6

[29] Taliaferro LP, et. al., *Evaluation of the broad-range PCR-electrospray ionization mass spectrometry (PCR/ESI-MS) system and virus microarrays for virus detection*. Viruses, 2014. 6(5):1876-96

[30] Dabrazhynetskaya, A., et al., *Preparation of reference stocks suitable for evaluation of alternative NAT-based mycoplasma detection methods.* J Appl Microbiol 2014. 116(1):100-8

[31] Dabrazhynetskaya A, et. al., *Collaborative study report: evaluation of the ATCC experimental mycoplasma reference strains panel prepared for comparison of NAT-based and conventional mycoplasma detection methods*. Biologicals 2013. 41(6):377-83

[32] Zhao J, et. al., *Nanomicroarray and multiplex next-generation sequencing for simultaneous identification and characterization of influenza viruses*. Emerg Infect Dis 2015 Mar;21(3):400-8

[33] This research was funded under the extramural MCMi regulatory science program, and through the Mini-Sentinel program. For more information see Adverse Events Monitoring and Analysis Pilot Program at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm377550.htm and Mini-Sentinel at http://www.mini-sentinel.org/

[34] This project was funded under the extramural MCM regulatory science program. For more information see Ensuring Appropriate Public Use of Medical Countermeasures through Effective Emergency Communication at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm400865.htm

[35] These projects were funded under the extramural MCM regulatory science program. For more information see http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm412725.htm and http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm414974.htm

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

[37] Webcast recordings of the 2014 MCMi Regulatory Science Symposium are available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm398996.htm

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

[39] For more information on PAHPRA's MCM provisions see http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm346195.htm

[40] For more information see: http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm402857.htm

[41] 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

[42] View the PAHPRA Q&A at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm418184.htm

[43] For more about MCMi lectures see http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMiProfessionalDevelopmentActivities/ucm399895.htm

[44] For more about additional MCM education opportunities see http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMiProfessionalDevelopmentActivities/ucm400029.htm

## Appendix 1: FY 2014 Medical Countermeasure Approvals[aa]

| FY 2014 Medical Countermeasure Approvals | | | |
|---|---|---|---|
| **Medical Countermeasure** | **Sponsor/Applicant** | **Key Dates** | **Indication** |
| **Biologics** | | | |
| Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (Q-Pan H5N1) | ID Biomedical Corporation (a subsidiary of GlaxoSmithKline Biologicals) | • Received 02/22/2012<br>• Approved 11/22/2013 | For active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. |
| **Devices** | | | |
| Alere BixaNOW Influenza A & B Card | Alere Scarborough, Inc., d/b/a Binax, Inc. | • Received 11/07/2013<br>• Approved 12/05/2013 | A previously FDA-cleared and CLIA-waived immunochromatographic assay for the qualitative detection of Influenza A and B nucleoprotein antigens in nasopharyngeal (NP) swab, nasal swab, and nasal wash/aspirate specimens. |
| Alere I Influenza A & B | Alere Scarborough, Inc., d/b/a Binax, Inc. | • Received 06/09/2014<br>• Approved 06/13/2014 | A new rapid, instrument-based molecular *in vitro* diagnostic test utilizing isothermal nucleic acid amplification technology for the qualitative detection of influenza A and influenza B from direct nasal swab specimens. |
| Alere Influenza A & B Test | Alere Scarborough, Inc., d/b/a Binax, Inc. | • Received 11/07/2013<br>• Approved 12/18/2013 | A previously FDA-cleared and CLIA-waived *in vitro* immunochromatographic assay for the qualitative detection of influenza A and B nucleoprotein antigens in nasal swab specimens collected from symptomatic patients. |

[aa] Includes medical countermeasures approved, licensed, or cleared by FDA in FY 2014 (October 1, 2013 – September 30, 2014).

| FY 2014 Medical Countermeasure Approvals | | | |
|---|---|---|---|
| **Medical Countermeasure** | **Sponsor/Applicant** | **Key Dates** | **Indication** |
| BD Veritor System for the Rapid Detection of Flu A+B | Becton Dickinson & Co. | • Received 08/29/2013<br>• Approved 10/02/2013 | A previously FDA-cleared rapid chromatographic immunoassay for the direct and qualitative detection of influenza A and B viral nucleoprotein antigens from nasopharyngeal wash, aspirate and swab in transport media samples from symptomatic patients. The analytical reactivity performance table was updated to include new analytical reactivity performance data for six H3N2v strains, as well as four H1N1 strains, one H3N2 strain and 12 influenza B strains. |
| BD Veritor System for the Rapid Detection of Flu A+B | Becton Dickinson & Co. | • Received 10/17/2013<br>• Approved 11/13/2013 | A previously FDA-cleared rapid chromatographic immunoassay for the direct and qualitative detection of influenza A and B viral nucleoprotein antigens from nasopharyngeal wash, aspirate and swab in transport media samples from symptomatic patients (new additional procedure for using RSV assay in addition to Flu A+B assay). |
| BioSign Flu A+B, Status Flu A & B | Princeton Biomeditech Corp. | • Received 11/12/2013<br>• Approved 12/10/2013 | A previously FDA cleared *in vitro* rapid qualitative test that detects influenza type A and type B nucleoprotein antigens directly from nasal swab, nasopharyngeal swab, and nasopharyngeal aspirate/wash specimens obtained from patients with signs and symptoms of respiratory infection (modified to add ability to detect avian influenza A/H5N1 strains). |
| CDC *B. anthracis* Real-Time PCR Assay | CDC | • Received 02/19/2014<br>• Approved 05/22/2014 | Assay for the qualitative detection of plasmid and chromosomal DNA sequences from *B. anthracis*. |

| FY 2014 Medical Countermeasure Approvals | | | |
|---|---|---|---|
| **Medical Countermeasure** | **Sponsor/Applicant** | **Key Dates** | **Indication** |
| CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, Influenza A/B Typing Kit | CDC | • Received 12/20/2013<br>• Approved 01/17/2014 | A previously FDA-cleared nucleic acid amplification test panel for the qualitative detection of influenza A and B RNA directly from respiratory specimens from symptomatic patients, for the determination of the subtype of seasonal human influenza A viruses as seasonal A/H1, A/H3, A/H1pdm09, and/or A/H5 (Asian lineage), and for the determination of genetic lineage of human influenza B viruses as B/Victoria or B/Yamagata lineage. |
| CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, Influenza A/H5 Subtyping | CDC | • Received 07/10/2014<br>• Approved 08/01/2014 | A previously FDA-cleared nucleic acid amplification test panel for the qualitative detection of influenza A and B RNA directly from respiratory specimens from symptomatic patients, for the determination of the subtype of seasonal human influenza A viruses as seasonal A/H1, A/H3, A/H1pdm09, and/or A/H5 (Asian lineage), and for the determination of genetic lineage of human influenza B viruses as B/Victoria or B/Yamagata lineage. |
| CDC Influenza A Subtyping Kit, CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel | CDC | • Received 04/03/2014<br>• Approved 04/25/2014 | A previously FDA-cleared nucleic acid amplification test panel for the qualitative detection of influenza A and B RNA directly from respiratory specimens from symptomatic patients, for the determination of the subtype of seasonal human influenza A viruses as seasonal A/H1, A/H3, A/H1pdm09, and/or A/H5 (Asian lineage), and for the determination of genetic lineage of human influenza B viruses as B/Victoria or B/Yamagata lineage. |

| FY 2014 Medical Countermeasure Approvals | | | |
|---|---|---|---|
| **Medical Countermeasure** | **Sponsor/Applicant** | **Key Dates** | **Indication** |
| CDC Influenza B Lineage Genotyping Kit, CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel | CDC | • Received 04/03/2014<br>• Approved 04/25/2014 | A previously FDA-cleared nucleic acid amplification test panel for the qualitative detection of influenza A and B RNA directly from respiratory specimens from symptomatic patients, for the determination of the subtype of seasonal human influenza A viruses as seasonal A/H1, A/H3, A/H1pdm09, and/or A/H5 (Asian lineage), and for the determination of genetic lineage of human influenza B viruses as B/Victoria or B/Yamagata lineage. |
| Sofia Influenza A+B FIA | Quidel Corp. | • Received 10/02/2013<br>• CLIA waived 12/18/2013 | A previously FDA-cleared FIA test that employs immunofluorescence to detect influenza A and influenza B viral nucleoprotein antigens in nasal swab, nasopharyngeal swab, and nasopharyngeal aspirate/wash specimens taken directly from symptomatic patients. |
| TRU FLU | Meridian Bioscience, Inc. | • Received 12/05/2013<br>• Approved 01/03/2014 | A previously FDA-cleared rapid, qualitative, lateral-flow immunochromatographic assay for detecting both influenza A and influenza B viral nucleoprotein antigens in human nasal wash, nasopharyngeal aspirate and nasal and nasopharyngeal swab samples in symptomatic patients (modified to include detection of an influenza A/H7N9 strain). |

## Appendix 2: Current Emergency Use Authorizations

| Year | MCM | Requester | Status |
|---|---|---|---|
| **Anthrax [*Bacillus anthracis*]** | | | |
| 2008 | Doxycycline hyclate 100 mg oral tablets (in National Postal Model home & workplace kits) | HHS (ASPR/ BARDA) | Amended in 2009, 2010, 2011 (Current) |
| 2011 | All oral formulations of doxycycline (mass dispensing) | HHS (CDC) | Current[a] |
| **Novel Influenza A (H7N9) Virus** | | | |
| 2013 | CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel-Influenza A/H7 (Eurasian Lineage) Assay | HHS (CDC) | Current |
| 2014 | Lyra™ Influenza A Subtype H7N9 Assay | Quidel Corporation | Current |
| 2014 | A/H7N9 Influenza Rapid Test | Arbor Vita Corporation | Current |
| **Middle East Respiratory Syndrome Coronavirus [MERS-CoV]** | | | |
| 2013[b] | CDC Novel Coronavirus 2012 Real-time RT-PCR Assay | HHS (CDC) | Current |
| **Ebola Virus** | | | |
| 2014[b] | DoD EZ1 Real-time RT-PCR Assay | DoD | Current |
| 2014[c] | CDC Ebola VP40 rRT-PCR Assay | HHS (CDC) | Current |
| 2014[c] | CDC Ebola NP rRT-PCR Assay | HHS (CDC) | Current |
| 2014[c] | BioFire Defense FilmArray NGDS BT-E Assay | BioFire Defense | Current |
| 2014 | BioFire Defense FilmArray Biothreat-E test | BioFire Defense | Current |
| 2014[b] | RealStar® Ebolavirus RT-PCR Kit 1.0 | altona Diagnostics GmbH | Current |
| 2014 | LightMix® Ebola Zaire rRT-PCR Test | Roche Molecular Systems, Inc. | Current |
| 2015[c] | ReEBOV™ Antigen Rapid Test | Corgenix | Current |
| 2015 | Xpert® Ebola Assay | Cepheid | Current |
| **Enterovirus D68** | | | |
| 2015 | CDC Enterovirus D68 2014 Real-time RT-PCR Assay | HHS (CDC) | Current |

[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.

Note: chart accurate as of publication of this report [June 30, 2015]. View the latest EUAs at: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm182568.htm

## Appendix 3: Acronyms

| | |
|---|---|
| **ABSL** | Animal Biosafety Level |
| **ADEPT** | Autonomous Diagnostics to Enable Prevention and Therapeutics |
| **ARS** | Acute Radiation Syndrome |
| **ASPR** | Assistant Secretary for Preparedness and Response (HHS) |
| **BARDA** | Biomedical Advanced Research and Development Authority |
| **BLA** | Biologics License Application |
| **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 |
| **COA** | Clinical outcome assessment |
| **DARPA** | Defense Advanced Research Projects Agency |
| **DDT** | Drug development tools |
| **DHS** | U.S. Department of Homeland Security |
| **DoD** | U.S. Department of Defense |
| **DTRA** | Defense Threat Reduction Agency |
| **DxOD** | Diagnostics on Demand |
| **eIND** | Emergency Investigational New Drug |
| **EUA** | Emergency Use Authorization |
| **FDA** | U.S. Food and Drug Administration |
| **FDA-ARGOS** | FDA Database for Regulatory Grade Microbial Sequences |
| **FTE** | Full-time equivalent |
| **FY** | Fiscal year |
| **HHS** | U.S. Department of Health and Human Services |
| **ICMRA** | International Coalition of Medicines Regulatory Authorities |
| **IED** | Improvised explosive device |
| **IND** | Investigational New Drug |
| **IPT** | Integrated Program Team |
| **IOM** | Institute of Medicine (National Academy of Medicine) |
| **JBAIDS** | Joint Biological Agent Identification and Diagnostic System |
| **JPEO-CBD** | Joint Program Executive Office for Chemical and Biological Defense |

| | |
|---|---|
| **LLNL** | Lawrence Livermore National Laboratory |
| **LMHRA** | Liberian Medicines and Health Products Regulatory Authority |
| **LRN** | CDC Laboratory Response Network |
| **MCM** | Medical countermeasure |
| **MCMi** | FDA Medical Countermeasures Initiative |
| **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 |
| **NCBI** | National Center for Biotechnology Information |
| **NGDS** | Next-Generation Diagnostic System |
| **NGO** | Non-Governmental Organization |
| **NICBR** | National Interagency Confederation for Biological Research |
| **NIH** | U.S. National Institutes of Health |
| **NIST** | National Institute of Standards and Technology |
| **PAHPRA** | Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 |
| **PBSL** | Pharmacy Board of Sierra Leone |
| **PDUFA** | Prescription Drug User Fee Act |
| **PHEMCE** | Public Health Emergency Medical Countermeasures Enterprise |
| **PK** | Pharmacokinetics |
| **PMA** | Premarket approval |
| **RMP** | Regulatory Management Plan |
| **RPD** | Respiratory protective device |
| **SLEP** | Shelf Life Extension Program |
| **SNS** | Strategic National Stockpile |
| **USCIITG** | United States Critical Illness and Injury Trials Group |
| **UTMB** | University of Texas Medical Branch |
| **WHO** | World Health Organization |
| **WHO EMP** | WHO Department of Essential Medicines and Health Products |



**U.S. Department of Health and Human Services**
**Food and Drug Administration | Office of the Commissioner**
**Office of the Chief Scientist | Office of Counterterrorism and Emerging Threats**
**10903 New Hampshire Avenue, Silver Spring, MD 20993**

**www.fda.gov/MedicalCountermeasures**

**AskMCMi@fda.hhs.gov**

**@FDA_MCMi**

**Email updates**