Protecting National Health and Security

FDA
Medical Countermeasures Initiative (MCMi)

Fiscal Year 2013
Program Update

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., Assistant Commissioner for Counterterrorism Policy

I am pleased to present the Fiscal Year (FY) 2013 Program Update for the Food and Drug Administration (FDA) Medical Countermeasures Initiative (MCMi). As detailed in our previous program updates, FDA has made substantial progress under the MCMi in facilitating the development and availability of safe and effective medical countermeasures for chemical, biological, radiological, and nuclear (CBRN) threats and emerging infectious diseases, such as pandemic influenza. [1,2]

The MCMi has continued to gain momentum in its third year, sustaining critical regulatory science, policy and inter-agency activities that improve preparedness for CBRN and emerging infectious disease threats. FDA approved several medical countermeasures this year, including an anthrax therapeutic and a botulism antitoxin (the first monoclonal and polyclonal antibodies licensed under the Animal Rule, respectively); a next-generation portable ventilator; and several seasonal influenza vaccines, which help increase and sustain production capacity for pandemic influenza vaccines. FDA also expanded the approved use of an influenza antiviral drug to treat infants as young as two weeks old, as well as expanding the use of several influenza diagnostic tests to detect emerging influenza virus strains.

Additional significant achievements in FY 2013 include issuing Emergency Use Authorizations for diagnostic tests for the avian influenza A (H7N9) virus and Middle East Respiratory Syndrome coronavirus (MERS-CoV); funding cutting-edge regulatory science projects and providing medical countermeasure development-specific training for FDA staff; and working with government partners and product developers to identify and resolve regulatory challenges to medical countermeasure development. We also moved forward with implementing new authorities gained under the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 for fostering the development and availability of medical countermeasures.

FDA remains committed to supporting the development of promising medical countermeasures and to facilitating their ready availability should they be needed during a public health emergency.

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[1] MCMi Year 1 Status Report (PDF):
http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM270750.pdf

[2] MCMi Year 2 Program Update (PDF):
http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM381256.pdf

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FDA's Medical Countermeasures Initiative
Fiscal Year 2013 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, vaccines, and diagnostic tests—to counter these threats are safe, effective, and secure.[3]

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.[4] 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.[5] 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.[6]

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[3] 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).

[4] 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.

[5] 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.

[6] 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 countermeasure in emergencies under certain terms and conditions [21 USCS § 360bbb-3].

In 2010, FDA launched its Medical Countermeasures initiative (MCMi), building on the substantive medical countermeasure work ongoing at FDA and focusing increased resources on identifying and resolving regulatory challenges to medical countermeasure development and availability. The MCMi mission is to promote 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.[7] PAHPRA contains key legal authorities that sustain and strengthen the United States' preparedness for public health emergencies involving CBRN agents and emerging infectious disease threats. PAHPRA codified many of the activities already ongoing at FDA under the MCMi to foster the development and availability of medical countermeasures as well as creating new authorities to enable FDA to more effectively support preparedness and response efforts.[8] PAHPRA also requires FDA to issue an annual report detailing its medical countermeasure activities. This report responds to that requirement for Fiscal Year (FY) 2013.[9]

FY 2013 Medical Countermeasure Resources

FDA obligated $169.5 million in FY 2013 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 2013 Resources Obligated to Medical Countermeasure Activities (dollars in millions)

	FY 13 Actuals	FY 13 FTE Actuals
CBRN Base Funding	$62.3	317
Pandemic Influenza Base Funding	$32.1	158
MCMi Base Funding	$21.8	77
No-Year Funding	$53.3	8
Total	**$169.5**	**560**

Base Funding

FDA obligated $116.2 million from its FY 2013 base resources to support CBRN and pandemic influenza-related medical

[7] Public Law 113-5, 127 Stat. 161.
[8] For more information on PAHPRA see http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/BioterrorismAct/ucm346195.htm
[9] Detailed information on FDA's medical countermeasure development and review activities in FY 2011 and FY 2012 can be found in the *MCMi Year-1 Status Report* and *MCMi Year-2 Program Update* available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm270744.htm

countermeasure activities. This funding included $62.3 million for CBRN preparedness activities, $32.1 million for pandemic influenza preparedness activities, and $21.8 million for the MCMi.[10]

This funding supported 452 FTEs as well as a $0.9 million investment in the MCMi regulatory science program.

No-Year Funding

FDA received $170 million, one-time funding from HHS to immediately commence MCMi activities at the end of FY 2010 when the MCMi was launched. In FY 2013, FDA obligated $53.3 million of the no-year funding to support MCMi activities.[11] This funding supported 8 FTEs as well as regulatory science projects and infrastructure for the MCMi Regulatory Science Program and other non-payroll MCMi costs (e.g., professional development).

FY 2013 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:

- Reviewing medical countermeasure marketing applications and approving those that meet standards for safety and efficacy
- 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

[10] In FY 2013, Congress provided FDA with $23.5 million base funding for the MCMi, however, as a result of reductions experienced with the sequester and rescission in FY 2013, the total estimated FY 2013 MCMi budget authority is $21.8 million.

[11] FDA expended $49.9 million of the $170 million no-year funding during FY 2011, and $54.6 million during FY 2012. FDA anticipates expending the remaining balance of the no-year funding (approximately $12.2 million) through FY 2015.

- Responding to emerging public health threats
- Establishing and sustaining Public Health and Security Action Teams to identify and catalyze the resolution of regulatory challenges associated with high-priority medical countermeasures
- Providing regulatory advice, guidance and, when needed, technical assistance to medical countermeasure product sponsors
- Collaborating with U.S. government partners developing medical countermeasures
- Sustaining the MCMi Regulatory Science Program to develop the tools, standards, and approaches to 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

FDA's overarching objective is to facilitate the development of and access to safe and effective medical countermeasures to counter high-priority CBRN and emerging infectious disease threats, and support the warfighter

The following sections provide detail on achievements in FY 2013 with respect to these activities.

Medical Countermeasure Approvals

FDA approved the majority of medical countermeasure marketing applications under review in FY 2013 (Appendix 1). With respect to medical countermeasures to treat diseases caused by CBRN threats, FDA approved raxibacumab, manufactured by GlaxoSmithKline, to treat inhalational anthrax in combination with appropriate antibacterial drugs. Raxibacumab is also approved to prevent inhalational anthrax when alternative therapies are not available or not appropriate. This was the first monoclonal antibody approved under the Animal Rule.[12]

[12] Under the Animal Rule, when human challenge studies would not be ethical and field trials after accidental or hostile 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).

FDA was able to approve raxibacumab for use in children as well as adults—despite the fact that pediatric patients were not studied during the development of raxibacumab for ethical reasons—using computer simulations designed to extrapolate the observed adult dosing to children. FDA also approved Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) (Equine) (BAT), manufactured by Cangene Corporation, to treat adult and pediatric patients showing signs of botulism following exposure to botulinum neurotoxin. This was the first polyclonal antibody approved under the Animal Rule.

In the area of diagnostics for CBRN threats, FDA approved the use of a new sample purification kit as part of the Joint Biological Agent Identification and Diagnostic System, manufactured by BioFire Diagnostics, Inc., for the qualitative *in vitro* diagnostic detection of target DNA sequences of the causative agents of anthrax, plague, and tularemia. FDA also approved an organophosphate test system (Quantitation of Organophosphate Metabolites in Urine by LC/MS/MS), sponsored by the Centers for Disease Control and Prevention (CDC), for the quantitation of specific organophosphate metabolites in human urine from individuals who have signs and symptoms consistent with cholinesterase poisoning—as would occur after exposure to certain chemical threats.

With regard to all-hazards preparedness, FDA approved the Aura Ventilator, manufactured by Newport Medical Instruments, Inc., a next-generation portable ventilator that can provide respiratory support for infant, pediatric, and adult patients. In addition, FDA approved the Burn Resuscitation Decision Support System (BRDSS), manufactured by Areos, Inc., a fluid resuscitation calculator for use in the care of adult patients with 20% or more total body surface area burned—as could occur after the detonation of an improvised nuclear device (IND) or improvised explosive device (IED).

In the area of pandemic influenza preparedness, FDA approved several seasonal influenza vaccines, which helps increase and sustain pandemic influenza vaccine production capacity, including: Flucelvax, manufactured by Novartis Vaccines and Diagnostics, Inc., the first seasonal influenza vaccine licensed in the United States produced using modern cell culture techniques; and Flublok, manufactured by Protein Sciences Corporation, the first seasonal influenza vaccine made through recombinant DNA technology using an insect virus (baculovirus) expression system in a cell-based

substrate. FDA also approved three additional quadrivalent seasonal influenza vaccines (Fluarix Quadrivalent, manufactured by GlaxoSmithKline Biologicals, Fluzone Quadrivalent, manufactured by Sanofi Pasteur, Inc., and FluLaval Quadrivalent, manufactured by ID Biomedical Corporation), which contain four strains of the influenza virus (two influenza A strains and two B strains).

In addition to the seasonal influenza vaccine approvals, FDA expanded approval for use of the influenza antiviral, Tamiflu (oseltamivir), to treat children as young as 2 weeks old. Prior to this approval, Tamiflu had been approved to treat influenza in children ages 1 year and older. FDA was able to expand the approved use of Tamiflu in children younger than 1 year based on the extrapolation of data from previous study results in adults and older children, and additional supporting safety and pharmacokinetic studies sponsored by both industry and non-industry sources. Tamiflu is the only product approved to treat influenza in children younger than 1 year old, providing an important treatment option for this vulnerable population.

With respect to diagnostic tests for influenza, FDA approved a new multiplex nucleic acid assay for the qualitative determination of influenza A, influenza B, and Respiratory Syncytial Virus Type RNA in nasopharyngeal swabs from patients with signs and symptoms of respiratory infection. FDA also approved: (1) a label modification to the CDC Human Influenza Real-Time RT-PCR Diagnostic Panel to interpret results that are positive for influenza A H3 and negative for other influenza markers as presumptive positive for H3N2v influenza A virus detection; (2) the addition of a new influenza B assay within the CDC Diagnostic Panel for the determination of the genetic lineage of human influenza B virus as B/Victoria or B/Yamagata; (3) the addition of a new instrument for the Quidel Molecular Influenza A+B assay, which makes the test more widely available; and (4) modifications of several previously approved influenza assays to improve performance and demonstrate analytical reactivity with influenza A (H7N9) virus and the influenza A (H3N2v) virus.

Three additional medical countermeasure marketing applications were under review in FY 2013 that 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.

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 2013. 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 approved. In FY 2013, FDA tested 1,000 lots of medical countermeasure drugs as part of SLEP and approved shelf-life extension for those that met standards for stability and quality.

Another way FDA worked to ensure an adequate supply of medical countermeasures in FY 2013 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.[13]

FDA also works to resolve medical countermeasure shortages as quickly as possible when they occur. For example, FDA worked 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 an immediate shortage 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 certain lots of these auto-injectors can be used for an additional one year

[13] cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP regulations assures the identity, strength, quality, and purity of medical products by requiring that manufacturers adequately control manufacturing operations.

beyond their original labeled expiration date, if properly stored, to help ensure that the nation's first responders and warfighters will continue to have ready access to these products. Meanwhile, FDA is working with the product manufacturer to help rectify the quality issues in its manufacturing process so production of new product can be resumed.

In another example of FDA's efforts to address medical countermeasure shortages in FY 2013, FDA worked closely with HHS and product manufacturers in the early part of 2013 to monitor and respond to spot shortages of influenza products. Key activities included:

- Providing the manufacturer of Tamiflu regulatory discretion to release 2 million treatment courses of their reserve product with a Dear Healthcare Provider Letter to explain the outdated labeling and provide the most current prescribing information[14]
- Messaging that FDA will not take enforcement action with regard to the storage, distribution or use of certain lots of Tamiflu capsules, held by states or the SNS, that were expired or close to expiring (up to a maximum of 10 years beyond the date of manufacture), provided that the products have been stored under labeled storage conditions and CDC recommends such use[15]
- Reminding health care professionals that the FDA-approved instructions in the labeling for Tamiflu provide directions for pharmacists on how to make a liquid form of Tamiflu from Tamiflu capsules if the commercially manufactured Tamiflu oral suspension is unavailable
- Working with FDA District Offices in Los Angeles and New York to expedite the release of shipments of diagnostic devices for influenza that were being held by Customs and Border Protection

While these activities were in response to seasonal influenza, they also served as real-world preparedness activities providing valuable learning experiences that better position FDA to respond effectively to an influenza pandemic.

[14] Dear Health Care Provider (DHCP) letters are correspondence intended to alert physicians and other health care providers about important new or updated information regarding a human drug or biologic. For more information on DHCP letters see *Guidance for Industry and FDA Staff Dear Health Care Provider Letters: Improving Communication of Important Safety Information* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM233769.pdf

[15] FDA made this determination based on the review of data generated by FDA scientists.

Enabling Access to Available Medical Countermeasures

During FY 2013, 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 declared emergency involving a specified CBRN agent or agents if statutory criteria are met. In FY 2013, FDA issued two EUAs to facilitate preparedness for emerging threats. One was for the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel-Influenza A/H7 (Eurasian Lineage) Assay. The second was for the CDC Novel Coronavirus 2012 Real-Time RT-PCR Assay for the presumptive detection of Middle East Respiratory Syndrome (MERS-CoV) in patients with signs and symptoms of MERS-CoV infection in conjunction with clinical and epidemiological risk factors.

In addition to issuing EUAs when necessary, FDA also works to ensure that the United States government is as prepared as possible to deploy medical countermeasures 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 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.[16] During FY 2013, FDA continued to work with CDC, the Biomedical Advanced Research and Development Authority (BARDA), and DoD on pre-EUA activities for medical countermeasures against a diverse array of threats including smallpox, anthrax, pandemic influenza, and nuclear threats.

[16] 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 in advance of an emergency to begin a review of information and assist in the development of conditions of authorization, fact sheets, and other documentation needed for an EUA.

Responding to Emerging Public Health Threats

The avian influenza A (H7N9) virus and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged in 2013, both of which pose significant public health threats. FDA worked proactively with U.S. government partners, international partners (including national regulatory agencies), and product developers in FY 2013 to help facilitate the development and availability of medical countermeasures to respond. Key FDA response activities included:

- Collaborating closely with HHS and other Federal agencies in preparedness and response decisions regarding medical countermeasure development and use
- Providing technical expertise, regulatory guidance, and interactive review to expedite the development and approval of *in vitro* diagnostic tests
- Facilitating the rapid development of candidate pandemic influenza vaccines for clinical testing and assisting manufacturers through the vaccine production, clinical testing, and the regulatory approval processes
- Working with BARDA, CDC, and potential sponsors to support candidate therapeutic product development by providing advice on assessment of antiviral activity, and offering to provide review and feedback on development proposals including clinical trial design and data assessment.
- Reviewing requests for EUAs for medical countermeasures and issuing EUAs for medical countermeasures that meet statutory criteria (FDA issued EUAs for diagnostic tests for the avian influenza A(H7N9) virus and MERS-CoV)
- 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 and help mitigate product shortages and the distribution of misbranded/counterfeit products

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 challenges to medical countermeasure development. During FY 2013, FDA sustained the five Action Teams launched during FY 2011 and FY 2012. The following information summarizes FY 2013 activities of the five Action Teams.

Multiplex *In Vitro* Diagnostics Action Team – This Action Team continued its work to facilitate the development of multiplex *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 2013 included:

- Publishing Draft Guidance for Industry and FDA Staff; Highly Multiplexed Microbiological/Medical Countermeasure *in Vitro* Nucleic Acid Based Diagnostic Devices (PDF)
- Continuing a collaboration with the Defense Threat Reduction Agency (DTRA) and the National Center for Biotechnology Information (NCBI) to establish a publicly available, well-curated reference database that will be critical to developers seeking to validate their candidate multiplex *in vitro* diagnostic tests
- Continuing 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.[17]

Acute Radiation Syndrome (ARS) Action Team – This Action Team continued its efforts to clarify the regulatory requirements for medical countermeasures to improve survival and mitigate and treat injuries from radiological/nuclear events and their delayed effects, including ARS. Key activities during FY 2013 included:

[17] This program is seeking to enable *in vitro* devices that address current clinical diagnostic needs and are reconfigurable to decrease the time to design, manufacture and rapidly distribute assays in response to emerging diagnostic needs. For more information see: http://www.darpa.mil/Our_Work/BTO/Programs/Autonomous_Diagnostics_to_Enable_Prevention_and_Therapeutics_ADEPT.aspx

- Working to clarify the regulatory requirements for candidate medical countermeasures in the development pipeline for the hematopoietic sub-syndrome of ARS
- Holding a joint meeting of the Medical Imaging Drugs Advisory Committee (MIDAC) and the Oncologic Drugs Advisory Committee (ODAC) to discuss the safety and efficacy of currently approved leukocyte growth factors (LGFs) as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident[18]
- Working to facilitate the development and regulatory assessment of biodosimetry devices that can be used in a radiological/nuclear event to assess exposure to radiation and facilitate response activities

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 2013 activities included:

- Holding standing meetings with the U.S. Army Medical Research and Materiel Command (MRMC) and the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD) and as-needed meetings with DTRA and DoD Health Affairs 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[19]

[18] Meeting minutes available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM363898.pdf

[19] 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.

Surveillance and Assessment Action Team – This Action Team, which is 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 2013 activities included:

- Finalizing an *Action Plan for Developing an Enhanced National Capability for Monitoring and Assessing Medical Countermeasures during Public Health Emergencies*
- Working with Enterprise partners to establish a working group to review and refine as necessary the *Action Plan* and develop an overarching implementation plan for fulfilling the vision set forth in the *Action Plan*

Pediatrics and Maternal Action Team – This Action Team continued is efforts to identify and address the medical countermeasure needs of at-risk populations, such as pediatric and maternal populations, during public health emergencies. Key FY 2013 activities included:

- Developing a prioritized list of medical countermeasures in the SNS for which to pursue pediatric indications based on greatest public health benefit and feasibility of achieving a pediatric indication, such as medical countermeasures for Acute Radiation Syndrome and nerve agent exposures
- Engaging the Pediatric Trials Network (PTN) regarding the potential to leverage the PTN for data regarding the safety and efficacy of specific drugs used in the pediatric population as potential medical countermeasures
- Holding a meeting of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee to discuss ethical issues in pediatric product development, including medical countermeasures[20]

Regulatory Advice and Guidance

During FY 2013, FDA continued to provide regulatory advice and guidance to sponsors and applicants of medical countermeasures and U.S. government agencies funding medical countermeasure development to help foster development and approval. FDA provides regulatory advice and guidance through a variety of mechanisms including direct engagement

[20] Meeting minutes available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM369509.pdf

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. When necessary, FDA medical product review centers have extensive interactions to discuss testing, data requirements, and scientific issues related to moving candidate medical countermeasures into clinical development and assessing progress as these specialized product candidates move through clinical development toward 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 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.[21] 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).[22] 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 2013 Formal Meetings Between CBER/CDER and Medical Countermeasure Sponsors or Applicants

Meeting Type	CBER	CDER
Type A	1	1
Type B	21	9
Type C	20	21
Total	**42**	**31**

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

[21] See for example, *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants* available at http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf and *Draft Guidance for Industry and FDA Staff - Medical Devices: The Pre-Submission Program and Meetings with FDA Staff* available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

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

as a dispute resolution meeting, a meeting to discuss a clinical hold,[23] and a Special Protocol Assessment meeting[24]). 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.). In FY 2013, CBER held 42 formal meetings with medical countermeasure sponsors or applicants and CDER held 31 formal meetings (Table 2).

The Center for Devices and Radiological Health (CDRH) categorizes its formal meetings with product sponsors as Pre-Submission (Pre-sub) and 510(k) / 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. 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 2013, CDRH held 21 formal meetings with medical countermeasure sponsors or applicants (Table 3).

Table 3. FY 2013 Formal Meetings Between CDRH and Medical Countermeasure Sponsors or Applicants

Meeting Type	CDRH
Pre-Submission	21
Submission	0
Total	**21**

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

[23] 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.
[24] 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

increased interaction between FDA and applicants, including the exchange of scientific and regulatory information.[25]

In addition, PAHPRA created a new mechanism—the Regulatory Management Plan (RMP)—whereby medical countermeasure sponsors or applicants can interact with FDA regarding the development and regulatory requirements for eligible medical countermeasures.[26] RMPs—which must be agreed to by FDA and the product sponsor or applicant—delineate developmental milestones that trigger meetings, written feedback, and decisions by FDA, or other activities (e.g., developing a plan to demonstrate safety and effectiveness in pediatric populations) conducted as part of the development and review process; associated performance targets and goals for such responses and activities; and how the plan will be modified if necessary. RMPs are initiated upon a written request from a product sponsor or applicant and requests for an RMP are granted according to the prioritization framework established in PAHPRA.[27] FDA did not receive any written requests for an RMP in FY 2013.

In addition to its direct work with medical countermeasure sponsors and applicants, FDA also issues guidance documents that help foster medical countermeasure development and availability.[28] Guidance documents issued during FY 2013 directly related to, or applicable to, medical countermeasures policies or regulatory issues include:

- Draft Guidance for Industry and Food and Drug Administration Staff; Highly Multiplexed Microbiological/Medical Countermeasure *in Vitro* Nucleic Acid Based Diagnostic Devices (PDF)
- Draft Guidance for Industry; Expanded Access to Investigational Drugs for Treatment Use – Qs & As (PDF)

[25] 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

[26] 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)]

[27] Under PAHPRA, 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.

[28] 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)]

- Draft Guidance for Industry; Expedited Programs for Serious Conditions – Drugs and Biologics (PDF)

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 Advisory Committee meetings and workshops held during FY 2013 include:

- Anti-Infective Drugs Advisory Committee to discuss Biologics License Application (BLA) for Raxibacumab[29]
- Vaccines and Related Biological Products Advisory Committee to discuss the safety and immunogenicity of an adjuvanted Influenza A (H5N1) Virus Monovalent Vaccine manufactured by GlaxoSmithKline[30]
- Public Workshop on *Burkholderia* to present the most current information on melioidosis (caused by *Burkholderia pseudomallei*) and glanders (caused by *B. mallei*), with the general purpose of identifying future areas of research needed to advance animal model development and to advance candidate medical countermeasures[31]
- Blood Products Advisory Committee to discuss Cangene Corporation's BLA for Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) (Equine) (BAT), to treat botulism caused by these botulinum neurotoxin serotypes[32]
- Device Good Manufacturing Advisory Committee meeting to address the effects of extreme weather and natural disasters on the production and supply of medical devices and to identify steps that FDA, manufacturers, and the public can take to prepare for such events[33]

[29] Meeting minutes available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM334800.pdf
[30] Meeting minutes available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM333704.pdf
[31] Workshop agenda and program available at http://www.fda.gov/downloads/EmergencyPreparedness/MedicalCountermeasures/UCM328087.pdf
[32] Meeting minutes available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm349043.htm
[33] Meeting minutes available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/DeviceGoodManufacturingPracticeAdvisoryCommittee/UCM347961.pdf

- Joint meeting of the Medical Imaging Drugs Advisory Committee and the Oncologic Drugs Advisory Committee to discuss the safety and efficacy of currently approved leukocyte growth factors as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident[34]
- Microbiology Devices Advisory Committee meeting to discuss and make recommendations regarding the possible reclassification of rapid influenza detection devices, currently regulated as Class I, to Class II[35]
- Public workshop entitled *Battery-Powered Medical Devices Workshop: Challenges and Opportunities* to create awareness of the potential challenges related to battery-powered medical devices—that play a significant role in the overall safety, performance, and reliability of many life-saving and life-sustaining medical devices—and to collaboratively develop ways of ensuring the continued performance and reliability of these devices[36]
- Pediatric Ethics Subcommittee of the Pediatric Advisory Committee to discuss ethical issues in pediatric product development, including medical countermeasures[37]

Collaborations

During FY 2013, FDA collaborated extensively with Enterprise and DoD partners to foster the development and availability of medical countermeasures. FDA provided subject matter expertise and technical assistance to 66 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

[34] Meeting minutes available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM363898.pdf
[35] Meeting summary available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/UCM357228.pdf
[36] A webcast of this event is available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm355183.htm
[37] Meeting minutes available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM369509.pdf

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 the World Health Organization to foster the development and availability of medical countermeasures.

Medical Countermeasure Regulatory Science

In FY 2013, 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 such threat agents.[38] Instead, efficacy studies must be done in animals and the results extrapolated to humans.[39] And the challenges are even more complex when it comes to developing medical countermeasures for use in at-risk 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 appropriate to conduct clinical trials to obtain data that can be used for approving pediatric indications for medical countermeasures—such as

[38] High-priority threats identified by the Enterprise for which medical countermeasures are needed include: *Bacillus anthracis* (anthrax); *Clostridium botulinum* toxin (botulism); cyanide; emerging infectious diseases (including pandemic influenza); gram negative organisms (*Francisella tularensis* (tularemia), *Yersinia pestis* (plague), *Burkholderia mallei* (glanders), *Burkholderia pseudomallei* (meliodosis), and *Rickettsia prowazekii* (typhus)); multi-drug resistant *Bacillus anthracis* (MDR anthrax); nerve agents; radiological agents (e.g., radiological dispersal devices); nuclear agents; Variola virus (smallpox); and Viral Hemorrhagic Fevers (Marburg and Ebola). See the 2012 PHEMCE Strategy for more information available at http://www.phe.gov/Preparedness/mcm/phemce/Documents/2012-PHEMCE-Strategy.pdf

[39] Under the Animal Rule, when human challenge studies would not be ethical and field trials after accidental or hostile 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).

safety or dosing information—and FDA must rely on the extrapolation of data from adult populations and, at times, animals for making regulatory decisions when scientifically feasible.

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 countermeasures—including for at-risk populations. Priority research areas being supported under the MCMi Regulatory Science Program include:

- Developing animal models and tools to evaluate safety and efficacy
- Identifying and qualifying biomarkers for safety and efficacy
- 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

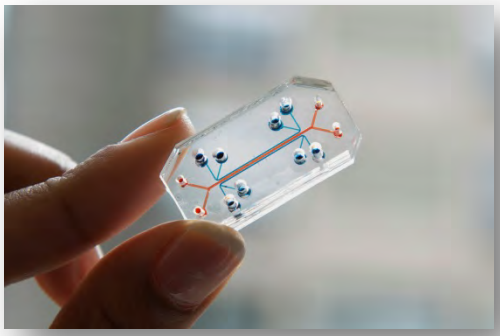
FDA has established a broad and robust research portfolio under the MCMi Regulatory Science Program

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.[40] 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 the National Institutes of Health (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.

[40] Intramural FDA medical countermeasure regulatory science is funded through a competitive challenge grant process. Extramural medical countermeasure regulatory science is primarily funded through a Broad Agency Announcement (Food and Drug Administration Broad Agency Announcement for the Advanced Research and Development of Regulatory Science) available at https://www.fbo.gov/?s=opportunity&mode=form&id=862c0ec16447bad7c7196f5d451ec601&tab=core&_cview=0.

Examples of ongoing research include:

- Developing a highly sensitive assay to quantitate the level of the influenza antiviral Tamiflu (oseltamivir) and its active metabolite (oseltamivir carboxylate) in blood samples to aid in the development of appropriate dosing for at-risk 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[41]



- Mapping immune responses to certain biothreat agents and medical countermeasures in humans and animal models to create species-specific immune function maps[42]
- Examining the scientific basis for the instability of the protective antigen that have hindered efforts to develop next-generation anthrax vaccines and using protein engineering to stabilize the antigen[43]
- 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
- 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
- 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

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[41] The project was funded under the extramural MCMi regulatory science program. For more information see Organs-On-Chips for Radiation Countermeasures available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ProtectingNationalHealthandSecurity/ucm263071.htm

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

[43] 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.

- 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[44]
- Developing a mobile device (e.g., smartphone) application for reporting adverse events associated with medical devices to FDA including an in-depth module for products associated with medical countermeasures

FDA also expanded and sustained medical countermeasure regulatory science collaborations in FY 2013. For example FDA:

- Convened the second annual MCMi Regulatory Science Symposium in May 2013 to showcase medical countermeasure regulatory science under way at FDA and by external partners and to promote scientific engagement.[45]
- Designed, developed, and executed a pilot training program under an educational grant with the University of Texas Medical Branch (UTMB) Galveston National Laboratory to identify and share best practices for ensuring data quality and integrity in Biosafety Level (BSL) 3/4 facilities for animal studies being conducted to support medical countermeasure development using the Animal Rule.

- Sustained the animal model qualification program, which will enable the product-neutral evaluation of animal models and provide the potential for product-neutral determination of whether a particular model is appropriate for the demonstration of efficacy to support approval of classes of products for specific indications.[46]

[44] The project was funded under the extramural MCMi regulatory science program. For more information see Adverse Events Monitoring and Analysis Pilot Program available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm377550.htm

[45] A webcast of the 2013 MCMi Regulatory Science Symposium is available at http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm330195.htm

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

- 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; the DTRA and the NCBI to establish a publicly available, well-curated reference database that will be critical to developers seeking to validate their candidate multiplex *in vitro* diagnostic tests; 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.

Medical Countermeasure Regulatory Policy

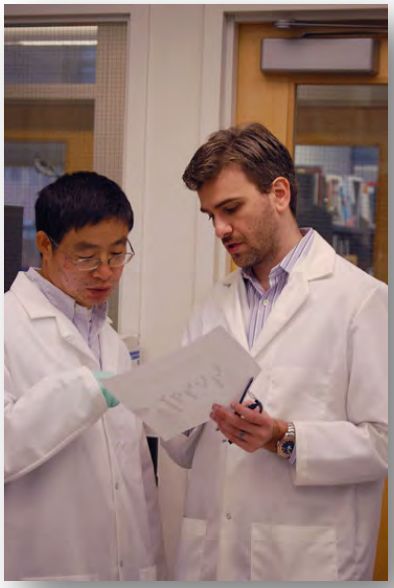
During FY 2013, FDA continued its efforts to ensure that U.S. laws, regulations, and policies enable the application of advances in regulatory science to the regulatory review process and adequately support preparedness for and response to CBRN and emerging infectious disease threats by facilitating the availability of medical countermeasures. FY 2013 activities included:

- Initiating 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 medical countermeasures, including requirements to establish processes for sponsor interactions.
- Working with state and local public health authorities and responders and public health NGOs to support medical countermeasure preparedness and response capabilities at the state and community levels, including responding to numerous EUA-related inquiries and participating in multiple national-level workshops, meetings, and webinars on legal preparedness, FDA's roles in medical countermeasure distribution and dispensing, and enactment of the PAHPRA.
- Sustaining participation in the Institute of Medicine's (IOM) 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 partnerships between the public and private sector so that communities are adequately prepared for natural or human-made catastrophic events.

FDA works with state and local public health authorities, first responders, and public health NGOs to support medical countermeasure preparedness and response capabilities at state and community levels

- Working with appropriate partners to develop and propose new approaches for addressing legal, regulatory, and policy challenges associated with the development, distribution, administration, stockpiling, or use of specific medical countermeasures. Examples of areas where FDA provided policy assistance include: first responders' ready access to and use of medical countermeasures; issues related to medical countermeasure development that are unique to the warfighter; issues related to expiration dating that are unique to medical countermeasures and to public health stakeholders; approaches to data collection on medical countermeasures used during public health emergencies; medical countermeasure import and export issues during emergency responses; 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; and 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 of CBRN threats and risks 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 2013 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 five lectures in this series during FY 2013 with 387 attendees, 78 of whom received continuing education (CE) credits.
- **Foundations for Pre-Clinical 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 seven lectures in this series during FY 2013 with 568 attendees, 99 of whom received CE credits.

- **Conference Support:** FDA supported 54 staff to attend 12 medical countermeasure-related external conferences during FY 2013.
- **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 MCMi 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. Ten FDA staff are currently enrolled in the program. The first cohort of seven staff graduated in May 2013.
- **Training Course on the Emergency Management of Radiation Accident Victims**: This course was taught by experts from Oak Ridge Institute of Science and Education; approximately 100 FDA staff members attended.

Appendix 1: FY 2013 Medical Countermeasure Approvals

FY 2013 Medical Countermeasure Approvals			
Medical Countermeasure	**Sponsor/Applicant**	**Key Dates**	**Indication**
Biologics			
Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) (Equine) (BAT)	Cangene Corporation	• Received 09/20/2012 • Approved 03/22/2013	Approved for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G in adults and pediatric patients
Flucelvax	Novartis Vaccines and Diagnostics, Inc.	• Received 02/26/2009 • Withdrawn 04/27/2009 • Resubmitted 11/22/2011 • Approved 11/20/2012	Approved for the active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine in persons 18 years of age and older
Flublok	Protein Sciences Corporation	• Received 04/18/2008 • Complete Response Letter Issued 08/29/2008 • Resubmitted 04/27/2009 • Complete Response Letter Issued 01/11/2010 • Resubmitted 07/16/2012 • Approved 01/16/2013	Approved for the active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine in persons 18 through 49 years of age

FY 2013 Medical Countermeasure Approvals			
Medical Countermeasure	**Sponsor/Applicant**	**Key Dates**	**Indication**
Fluarix Quadrivalent	GlaxoSmithKline Biologicals	• Received 02/14/2012 • Approved 12/14/2012	Approved for the active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons 3 years of age and older
Fluzone Quadrivalent	Sanofi Pasteur, Inc.	• Received 08/10/2012 • Approved 06/07/2013	Approved for the active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons 6 months of age and older
FluLaval Quadrivalent	ID Biomedical Corporation	• Received 10/16/2012 • Approved 08/15/2013	Approved for the active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons 3 years of age and older
Drugs			
Raxibacumab	GlaxoSmithKline	• Received 05/14/2009 • Complete Response Letter Issued 11/14/2009 • Resubmitted 06/15/2012 • Approved 12/14/2012	Approved to treat adult and pediatric patients with inhalational anthrax in combination with appropriate antibacterial drugs and to prevent inhalational anthrax when alternative therapies are not available or not appropriate

FY 2013 Medical Countermeasure Approvals			
Medical Countermeasure	**Sponsor/Applicant**	**Key Dates**	**Indication**
Tamiflu (oseltamivir)	Hoffmann-La Roche, Inc.	• Received 06/21/2012 • Approved 12/21/2012	Expanded approval for use of Tamiflu to treat children as young as 2 weeks old (previously approved for ages 1 year and older)
Devices			
Aura Ventilator	Newport Medical Instruments, Inc.	• Received 06/29/2012 • Approved 11/09/2012	Approved to provide ventilatory support for infant, pediatric and adult patients in hospital, sub-acute, emergency response, transport and homecare environments under the direction of a physician
Burn Resuscitation Decision Support System (BRDSS)	Arcos, Inc.	• Received 06/05/2012 • Approved 04/18/2013	Approved for use in the care of adult patients with 20% or more Total Body Surface Area (TBSA) burned as a fluid resuscitation calculator for hourly fluid recommendations
JBAIDs Anthrax Detection Kit	BioFire Diagnostics, Inc.	• Received 06/28/2013 • Approved 08/05/2013	Modified the previously approved JBAIDS Anthrax Detection Kit for use with the IT *1-2-3"1*Platinum Path Sample Purification Kit Accessory for the qualitative *in vitro* diagnostic detection of *Bacillus anthracis*
JBAIDs Plague Detection Kit	BioFire Diagnostics, Inc.	• Received 06/14/2013 • Approved 07/31/2013	Modified the previously approved JBAIDS Plague Detection Kit for use with the IT *1-2-3"1*Platinum Path Sample Purification Kit Accessory for the qualitative *in vitro* diagnostic detection of *Yersinia pestis*

FY 2013 Medical Countermeasure Approvals			
Medical Countermeasure	**Sponsor/Applicant**	**Key Dates**	**Indication**
JBAIDs Tularemia Detection Kit	BioFire Diagnostics, Inc.	• Received 06/27/2013 • Approved 07/31/2013	Modified the previously approved JBAIDS Tularemia Detection Kit for use with the IT *1-2-3"1*Platinum Path Sample Purification Kit Accessory for the qualitative *in vitro* diagnostic detection of *Francisella tularensis*
CDC Quantitation of Organophosphate Metabolites in Urine by LC/MS/MS	CDC	• Received 07/30/2012 • Approved 08/08/2013	Approved for the quantitation of specific organophosphate metabolites by LC/MS/MS. Measures the concentration of specific organophosphate metabolites in human urine from individuals who have signs and symptoms consistent with cholinesterase poisoning
CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel	CDC	• Received 12/19/2012 • Approved 1/14/2013	Modified the previously approved CDC Human Influenza Real-Time RT-PCR Diagnostic Panel to interpret results positive for influenza A H3 and negative for other influenza markers as presumptive positive for H3N2v influenza A virus detection
CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel	CDC	• Received 03/04/2013 • Approved 05/22/2013	Modified the previously approved CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel to allow the use of an alternative enzyme in the assay

FY 2013 Medical Countermeasure Approvals			
Medical Countermeasure	**Sponsor/Applicant**	**Key Dates**	**Indication**
CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel	CDC	• Received 08/12/2013 • Approved 09/23/2013	Modified the previously approved CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel to add a new assay for the determination of the genetic lineage of human influenza B virus as B/Victoria or B/Yamagata lineage. An additional positive control was also added to the panel for use with the new assay
QuickVue Influenza A+B Test	Quidel Corporation	• Received 06/03/2013 • Approved 06/28/2013	Modified the previously approved QuickVue Influenza A+B to add new analytical reactivity data testing for the influenza A (H7N9) virus
QuickVue Influenza Test	Quidel Corporation	• Received 06/05/2013 • Approved 07/05/2013	Modified the previously approved QuickVue Influenza to add new analytical reactivity data testing for the influenza A (H7N9) virus
Sofia Influenza A/B FIA	Quidel Corporation	• Received 06/05/2013 • Approved 07/05/2013	Modified the previously approved Sofia Influenza A/B FIA to add new analytical reactivity data testing for the influenza A (H7N9) virus
Remel Xpect Flu A&B	Remel, Inc.	• Received 06/19/2013 • Approved 07/12/2013	Modified the previously approved Xpect Influenza A&B to add new analytical reactivity data testing for the influenza A (H7N9) virus
BD Veritor System Flu A+B Assay Clinical Kit	Becton, Dickinson and Company	• Received 07/19/2013 • Approved 08/07/2013	Modified the previously approved BD Veritor System for the Rapid Detection of Flu A+B to add new analytical reactivity data testing for the influenza A (H7N9) virus

FY 2013 Medical Countermeasure Approvals			
Medical Countermeasure	**Sponsor/Applicant**	**Key Dates**	**Indication**
BD Veritor System for Rapid Detection of Flu A+B POC kit	Becton, Dickinson and Company	• Received 07/19/2013 • Approved 08/07/2013	Modified the previously approved BD Veritor System for the Rapid Detection for Rapid Detection of Flu A+B POC kit to add new analytical reactivity data testing for the influenza A (H7N9) virus
BD Veritor System Flu A+B Assay	Becton, Dickinson and Company	• Received 09/04/2013 • Approved 10/02/2013	Modified the previously approved BD Veritor System for Rapid Detection of Flu A+B assay to add new analytical reactivity data testing for the H3N2v influenza A virus and minimal concentration detected for all viruses in the reactivity table
BD Veritor System Flu A+B Assay	Becton, Dickinson and Company	• Received 08/29/2013 • Approved 09/23/2013	Modified the previously approved BD Veritor System for the Rapid Detection for Rapid Detection of Flu A+B POC kit to new analytical reactivity data testing for the H3N2v influenza A virus and minimal concentration detected for all viruses in the reactivity table
Prodesse ProFlu+ Assay	Gen-Probe Prodesse, Inc.	• Received 07/10/2013 • Approved 08/09/2013	Modified the previously approved ProFlu+ Assay to add new analytical reactivity data testing for the influenza A (H7N9) virus and modify the internal control
Prodesse ProFast+ Assay	Gen-Probe Prodesse, Inc.	• Received 07/30/2013 • Approved 08/26/2013	Modified the previously approved Prodesse ProFast+ Assay to add new analytical reactivity data testing for the influenza A (H7N9) virus and modify the internal and positive controls

FY 2013 Medical Countermeasure Approvals			
Medical Countermeasure	**Sponsor/Applicant**	**Key Dates**	**Indication**
SAS FluAlert A & B Test, SAS Influenza A Test	SA Scientific, Ltd.	• Received 08/02/2013 • Approved 08/22/2013	Modified the previously approved SAS FluAlert A & B, SAS Influenza A Test to add new analytical reactivity data testing for the influenza A (H7N9) virus
BioSign Flu A + B and Status Flu A & B assays	Princeton Biotech Corporation	• Received 08/13/2013 • Approved 09/09/2013	Modified the previously approved BioSign Flu A + B and Status Flu A & B assays to add new analytical reactivity data testing for the influenza A (H7N9) virus
Quidel Molecular Influenza A + B Assay	Quidel Corporation	• Received 06/12/2013 • Approved 08/29/2013	Approved for the *in vitro* qualitative detection and differentiation of influenza A and influenza B viral RNA in nasal and nasopharyngeal swabs from patients with signs and symptoms of respiratory infection using the Life Technologies QuantStudio Dx Real-Time PCR Instrument
IMDx Flu A/B and RSV for Abbott m2000	Intelligent Medical Devices, Inc.	• Received 05/31/2013 • Approved 08/21/2013	Approved for the qualitative determination of influenza A, influenza B, and Respiratory Syncytial Virus Type RNA in nasopharyngeal swabs from patients with signs and symptoms of respiratory infection

Appendix 2: Acronyms

ADEPT	Autonomous Diagnostics to Enable Prevention and Therapeutics
ARS	Acute Radiation Syndrome
ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BAT	Botulism Antitoxin Heptavalent
BLA	Biologics License Application
BRDSS	Burn Resuscitation Decision Support System
BSL	Biosafety level
CBRN	Chemical, biological, radiological, and nuclear
CBER	Center for Biologics Evaluation and Research
CDC	U.S. Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CE	Continuing education
cGMP	Current good manufacturing practices
DARPA	Defense Advanced Research Projects Agency
DTRA	Defense Threat Reduction Agency
DHS	Department of Homeland Security
DoD	Department of Defense
DxOD	Diagnostics on Demand
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
FTE	Full-time equivalent
FY	Fiscal year
HHS	U.S. Department of Health and Human Services
IED	Improvised explosive device
IND	Improvised nuclear device
IOM	Institute of Medicine
JBAIDS	Joint Biological Agent Identification and Diagnostic System
JPEO-CBD	Joint Program Executive Office for Chemical and Biological Defense
LGF	Leukocyte growth factor
MCMi	Medical Countermeasures Initiative
MERS-CoV	Middle East Respiratory Syndrome coronavirus
MIDAC	Medical Imaging Drugs Advisory Committee
MRMC	U.S. Army Medical Research and Materiel Command
NCBI	National Center for Biotechnology Information

NGO	Non-Governmental Organization
NICBR	National Interagency Confederation for Biological Research
NIH	U.S. National Institutes of Health
ODAC	Oncological Drugs Advisory Committee
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act of 2013
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PTN	Pediatric Trials Network
RMP	Regulatory Management Plan
SLEP	Shelf Life Extension Program
SNS	Strategic National Stockpile
TBSA	Total body surface area
UTMB	University of Texas Medical Branch

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