MCMi

FDA's Medical Countermeasures Initiative

Year-2 Program Update—November 2012

—Protecting National Health and Security

US Department of Health and Human Services
Food and Drug Administration

Message from Dr. Luciana Borio

Assistant FDA Commissioner for Counterterrorism Policy

— FDA's commitment is to protecting national health and security

In January 2010, the Secretary of the Department of Health and Human Services ordered a comprehensive review of the US Public Health Emergency Medical Countermeasures Enterprise to assess the nation's readiness to handle public health emergencies. The review also answered a charge by President Obama to improve our nation's capacity to respond faster and more effectively to chemical, biological, radiological, nuclear, and emerging infectious disease threats, like pandemic influenza.

The following August, in support of the Secretary's findings and the President's charge, FDA launched its Medical Countermeasures Initiative (MCMi). Our goal was to build on relevant activities already underway at FDA and devote additional resources to foster the development and availability of the medical products that will be needed to counter a public health emergency, no matter its origin. As reflected in our MCMi Year-1 Status Report, FDA achieved substantial progress during its first year. During this second year, the initiative has gained momentum.

This report describes our activities for fiscal year 2012 and highlights a number of particularly important achievements. We have made the report available on our MCMi web page, where we track progress and share many of our MCMi activities. For those interested in following our progress, I recommend signing up on that web site to receive electronic updates on key activities.

FDA plays a critical role in the nation's effort to protect national health and security. We are committed to doing everything we can to support the development of promising medical countermeasures and to ensure ready availability should they be needed during a public health emergency.

FDA's Medical Countermeasures Initiative (MCMi) Year-2 Program Update—November 2012

Background

In 2010, following a year-long review of the nation's Public Health Emergency Medical Countermeasures Enterprise (Enterprise) by the Secretary of the Department of Health and Human Services (HHS), FDA tasked its Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Chief Scientist with implementing a new FDA initiative, the Medical Countermeasures Initiative (MCMi). OCET provides strategic leadership, oversight, and coordination of FDA's counterterrorism and pandemic influenza policy and planning activities. FDA set as its goal to build on programs already underway at FDA, providing additional resources and support to the development, evaluation, and approval[1] of medical countermeasures and national preparedness and response efforts. Key MCMi activities include clarifying regulatory requirements for countermeasure development and providing guidance to developers of medical countermeasures — especially at the earliest stages of product development so they can gather the necessary data for a determination of product safety, efficacy, and quality.

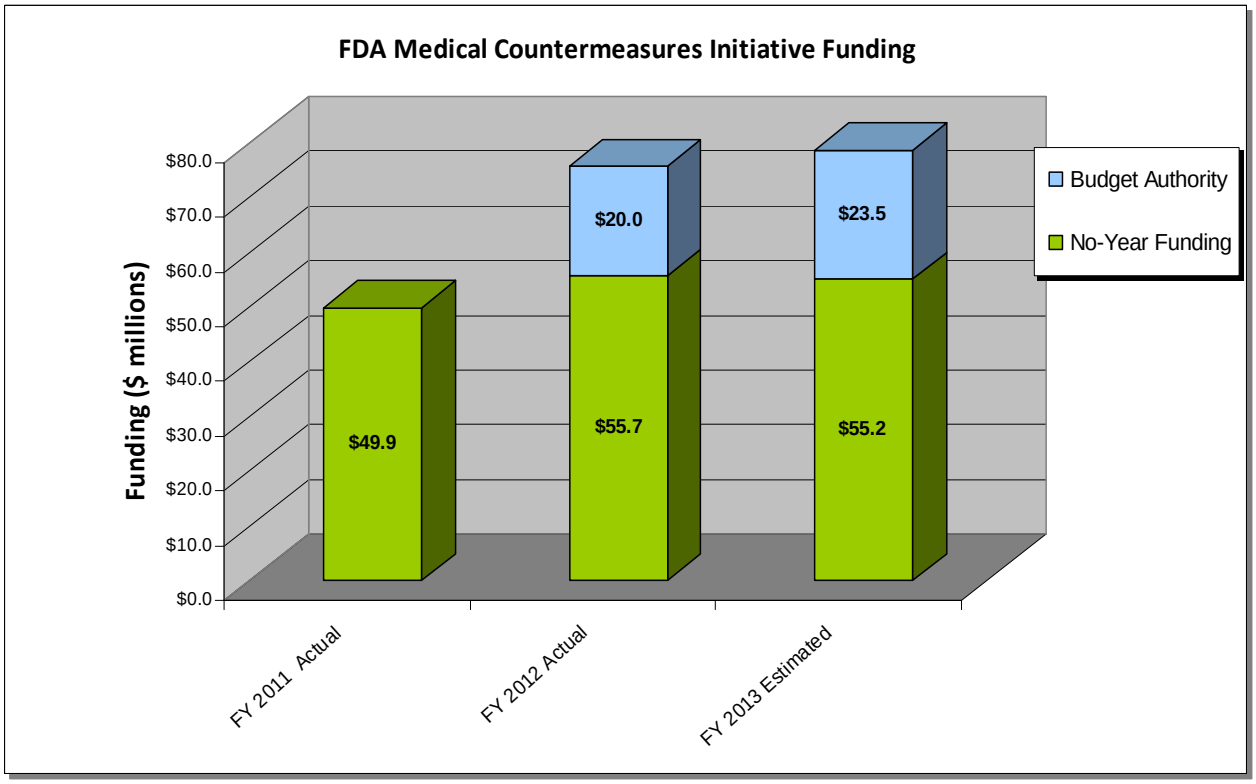
One of FDA's responsibilities is to support the Enterprise by providing subject matter expertise in medical countermeasure product development and approval and by conducting targeted regulatory science research, both vital to increasing access to and availability of safe and effective countermeasures.[2] For example, FDA provides regulatory advice and guidance to industry and other federal agencies to:

- Foster development of new medical countermeasures (with the goal of product approval, licensure, or clearance)
- Help expand the use of already approved products to include new indications against chemical, biological, radiological, or nuclear (CBRN) threats
- Ensure an adequate inventory of medical countermeasures for potential use in an emergency
- Increase medical countermeasure production capacity and ensure product quality
- Support policies that support ready access to life-saving medical countermeasures during public health emergencies.

[1] For purposes of this document, *approval* refers to "FDA-approval, licensure, or clearance" 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.
[2] Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

When FDA's MCMi was launched at the end of fiscal year (FY) 2010, FDA received one-time funding of $170 million from HHS to immediately commence MCMi activities. FDA has used this funding to develop the MCMi infrastructure and hire additional staff with expertise in medical countermeasure development to support the broad range of medical countermeasure-related activities at FDA. FDA has also been using the balance of the $170 million for medical countermeasure regulatory science and related infrastructure, scientific workshops, and activities to enhance the professional development and training of FDA staff involved in MCMi activities.

In addition to one-time funding, FDA received an appropriation from Congress of $20.038 million in FY 2012 to support MCMi activities. This funding enabled FDA to sustain the majority of the additional staff hired under MCMi and support a $327,000 investment in medical countermeasure regulatory science. The President's FY 2013 budget request would increase MCMi funding by $3.5 million to $23.5 million. This will enable FDA to sustain all of the additional staff hired under MCMi and support a continuing $1.6 million annual investment in medical countermeasure regulatory science, once the one-time funding of $170 million is fully expended. The following table displays actual and estimated obligations for MCMi activities by fiscal year.



Budget Authority is appropriated base funding
No-Year Funding is one-time funding from HHS[3]

One of FDA's first tasks under MCMi was to work closely with the Office of the HHS Assistant Secretary for Preparedness and Response (ASPR) to identify the high-priority threats[4] to focus

[3] At the end of FY 2013, FDA estimates the remaining balance of the $170M will be $9.2M. Based on discussions with HHS, FDA will expend this remaining balance during FY 2014.

on. In addition, FDA developed a 5-year MCMi Strategic Plan, which was released in January 2012. The plan lays out in detail the MCMi goals and objectives. As the Strategic Plan explains, FDA's MCMi adopted an approach with three overarching and interrelated goals:

1. Enhance the regulatory review processes for medical countermeasures to advance the development of high-priority countermeasures and related technologies. To do so, FDA (1) increased regulatory review capacity and expertise in the medical review divisions responsible for evaluating medical countermeasures and (2) established multidisciplinary Public Health and Security Action Teams (action teams) to advance priority countermeasures by working with internal and external entities, as appropriate, to identify and catalyze the resolution of challenges to medical countermeasure development pathways.
2. Advance regulatory science to foster development and approval of medical countermeasures by developing solutions to complex scientific regulatory problems and incorporating new, cutting-edge science into the regulatory review process to simplify and speed product development. This program is being implemented through both intra- and extramural collaborative research and through partnerships with U.S. governmental agencies, academia, non-governmental organizations, and industry.
3. Modernize the statutory, regulatory, and policy environment to support an effective public health response. This effort involves identifying possible changes to U.S. laws, regulations, and policies that will enable and foster the application of advances in regulatory science to the regulatory review processes and support efforts for preparedness and response to CBRN and emerging infectious disease threats by facilitating the availability of medical countermeasures.

Achieving such important goals requires extensive internal coordination. MCMi is a broad FDA collaboration involving OCET, the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health, FDA's Office of Regulatory Affairs, and other FDA offices, as appropriate. FDA is also involved in multiple collaborations, including with academia, State and local response agencies, and other HHS agencies and Federal partners involved in the Enterprise, which is led by the HHS Assistant Secretary of Preparedness and Response.[5]

During its first year, FDA reported substantial progress in MCMi. For example, FDA reached out extensively to relevant experts and interested stakeholders through public meetings, workshops, and other interactions to identify scientific gaps and specific opportunities for advancing regulatory science for medical countermeasure development, reduce regulatory uncertainties, and expand communication among relevant stakeholders. Action teams began

[4] Highest priority threats include anthrax, smallpox, radioactive/nuclear agents, and pandemic influenza. For a more detailed list see the *2012 Public Health Emergency Medical Countermeasures Enterprise (Enterprise) Strategy*.

[5] The Enterprise also includes three primary HHS internal agencies: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH). Key interagency partners are the Department of Homeland Security, the Department of Defense, the Department of Veterans Affairs, and the Department of Agriculture.

identifying key challenges in specific topic areas with the goal of identifying options for clarifying regulatory requirements along medical countermeasure development pathways.

In addition, FDA established an MCMi Steering Committee comprising key members of the Enterprise to help guide the medical countermeasure regulatory science program and ensure that it aligns with the highest priorities set by the larger federal Enterprise. With extensive input from the Steering Committee, FDA evaluated and approved funding for more than 80 regulatory science projects in its first year. FDA funded 46 of those projects in FY 2011, which are designed to support a variety of medical countermeasure development activities, including, for example:

- Developing and refining protocols to assess the quality and stability of countermeasures that may be stored over long time periods
- Developing methods for evaluating the purity and sterility of novel cell substrates that can be used to produce medical countermeasures
- Developing modeling tools to determine appropriate dosing of medical countermeasures for children
- Developing new methods to evaluate the safety of next-generation influenza vaccines

Finally, FDA established an FDA expert team dedicated to identifying statutory, regulatory, and policy areas that could be modernized or optimized to enhance the nation's capacity to prepare for and respond to public health emergencies. This group proposed legislative changes in collaboration with HHS to be included as part of the Pandemic and All-Hazards Preparedness Reauthorization Act of 2011 that would facilitate the availability of medical countermeasures for preparedness and response.[6] The team also worked regularly with its many Federal, State, and local partners to gain a common understanding of the needs of local communities and the impact of FDA's regulations and policies on those communities and on their ability to deploy medical countermeasures. For more detail on MCMi's first year, see FDA's MCMi Year-1 Status Report.

MCMi Activities and Achievements in 2012

During 2012, FDA built on achievements in 2011 and continued to break new ground.

To leverage available expertise in identifying, exploring, and addressing the many challenges of medical countermeasure development and evaluation, FDA sponsored and/or collaborated in public meetings and workshops on identified scientific issues with relevant stakeholders and subject matter experts from around the world. FDA also forged partnerships with a variety of organizations (e.g., Federal partners, academia, Institute of Medicine (IOM)) to tackle specific scientific and technical challenges and continued its critical biosecurity activities, including planning and participating in exercises with international partners.

[6] As of this writing, the Pandemic and All-Hazards Preparedness Reauthorization Act of 2011 [HR 2405 and S1855] is still pending before Congress.

In support of all these efforts, FDA continued its rigorous professional development program to make sure FDA staff acquire and maintain expertise in key medical countermeasure-related areas, including staying up to date on critical situational information such as CBRN threat assessments. FDA also expanded its MCMi web site to make relevant resources available to medical countermeasure developers, public health practitioners, and researchers engaged in biodefense and emerging disease activities.[7] In addition, FDA was able to approve a number of medical products to counter CBRN agents and emerging infectious disease threats. The following sections provide additional detail on activities and achievements.

Approving Medical Countermeasures

FDA continued to review marketing applications for medical countermeasures against CBRN agents and influenza (including situations relevant to potential pandemics) and approve or clear those that met standards for safety and efficacy. For example, in FY 2012 FDA:

- Approved Levaquin (levofloxacin) for the treatment of plague, including pneumonic and septicemic plague, due to *Yersinia pestis* and prophylaxis for plague in adults and pediatric patients 6 months of age and older. This product was approved under the Animal Rule.[8]
- Cleared nine influenza diagnostic 510(k) submissions and granted Clinical Laboratory Improvement Amendments (CLIA) waivers for three influenza devices.

Promoting Availability of Medical Countermeasures

FDA continued to work with Enterprise partners to ensure that the nation is as prepared as possible to deploy medical countermeasures from the Strategic National Stockpile in the event of a public health emergency. For example, FDA worked with the Centers for Disease Control and Prevention (CDC) and the Biomedical Advanced Research and Development Authority (BARDA) to develop pre-Emergency Use Authorization (EUA) packages for countermeasures held in the Strategic National Stockpile, including to facilitate their use in at-risk individuals such as pediatrics and pregnant women.[9] FDA also completed the review of the pre-EUA package for

[7] FDA has implemented an electronic notification system and encourages signing up at the MCMi web site to receive electronic notifications.

[8] The Animal Rule states that in selected circumstances, 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).

[9] FDA has developed a pre-EUA submission process by which FDA works with product sponsors or government agencies, such as CDC, to develop pre-EUA packages that can form the basis of an EUA request and issuance during a declared emergency. Pre-EUA packages contain data and information about the safety and efficacy of a 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 in advance of an emergency and assist in the development of conditions of authorization, fact sheets, and other documentation needed for an EUA. This advance work ensures that the information is adequate for a potential

the Modified Vaccinia Ankara (MVA) smallpox vaccine, which was developed and stockpiled for at-risk individuals of all ages (e.g., persons with HIV infection or atopic dermatitis, children, pregnant women, nursing mothers). In addition, FDA completed final reviews for six high-priority pre-EUA packages for diagnostic devices for use by the Department of Defense (DoD) to detect possible biothreats and worked with CDC to develop a robust pre-EUA package for a medical product held in the Strategic National Stockpile to be used in response to a radiation/nuclear event.

Enhancing FDA's Product Review and Approval Processes for the Highest Priority Medical Countermeasures and Related Technologies

Under MCMi, FDA is focused on clarifying regulatory requirements to optimize product review pathways for drugs, vaccines, diagnostic devices, and other equipment that will be needed to counter the effects of a CBRN agent or emerging infectious disease threat and to enable the surveillance of these products for safety and performance during such an event. To evaluate its review approach and track progress in key high-priority areas, FDA created five action teams that are identifying hurdles and gaps, exploring possible solutions to targeted problems, identifying and developing best review practices, and fostering the implementation of new and innovative review approaches.

Key Achievements in High-Priority Topic Areas

Next Generation In Vitro Diagnostic Tests

During FY 2012, FDA worked to develop standards for evaluating multiplex, in vitro diagnostic tests (tests that can identify multiple agents). Achievements include:

- Published a concept paper on novel regulatory approaches for multiplex diagnostic tests.
- Held a workshop on October 13, 2011, on advancing regulatory science for highly multiplexed microbiology/medical countermeasure devices
- Published draft guidance on standards for evaluating new multiplex diagnostic tests based on the concept paper and the workshop
- Worked with the Defense Threat Reduction Agency (DTRA) and the National Center for Biotechnology Information (NCBI), to establish a publicly available reference database that will be critical to developers seeking to validate their candidate multiplex in vitro diagnostic tests
- Completed reviews of six pre-EUA submissions for diagnostics for the DoD
- Developed legislative proposals in collaboration with HHS that would enhance the rapid availability of point-of-care diagnostics under an EUA

EUA and will significantly reduce the time needed during an emergency to review the submission and issue an authorization where appropriate.

Radiation Injury

Medical products are needed to improve survival and mitigate and treat injuries from radiological/nuclear events and their delayed effects including acute radiation syndrome (ARS). Also needed are decorporation or blocking agents to reduce internal contamination from exposure to radionuclides and biodosimetry devices that can be used in a radiological/nuclear event to assess exposure to radiation and facilitate response activities. FDA is clarifying the regulatory requirements for the products that have been most challenging to develop along existing pathways. FY 2012 achievements include:

- Held workshops in September 2012 on
  - Regulatory science considerations for medical countermeasure radiation biodosimetry devices — FDA is developing guidance on how to establish the performance of radiation biodosimetry devices
  - Medical countermeasures for burn mass casualty incidents
- Worked with CDC to develop a robust pre-EUA package[10] for a product in the Strategic National Stockpile that helps stimulate the production of white blood cells and could reduce the consequences of ARS as a result of exposure to radiation. The pre-EUA package will reduce the time needed during an emergency to authorize the use of this product under an EUA, thus greatly increasing preparedness.
- Provided technical and regulatory guidance to developers whose products are in early development and who are receiving funding from BARDA
- Established a scientific forum with National Institutes of Health (NIH) to address issues related to animal models, efficacy protocols, and regulatory issues

Warfighter Trauma

FDA is working to facilitate development and evaluation of candidate medical countermeasures and related technologies to support the warfighter. FY 2012 achievements include:

- Held workshop on September 6-7, 2012, on the risks and benefits of hydroxyethyl starch solutions[11]
- Facilitated the expedited review of DoD's submission of an expanded access protocol for a freeze dried plasma. The approved protocol enables the product to be used to support deployed troops.
- Through a collaboration with the US Army Medical Materiel Development Activity (USAMMDA), began work to identify specific needs, challenges, and opportunities

[10] See footnote 8 for discussion of pre-EUA.

[11] Hydroxyethyl starch (HES) solutions are synthetic colloids administered intravenously to patients to maintain or expand plasma volume when clinically indicated. HES solutions are indicated for the treatment of hypovolemia (low blood volume) that may result from trauma, sepsis, burns, or anaphylaxis.

related to development and/or availability of medical countermeasures for the warfighter. This effort involves a number of DoD programs engaged in the research and development of countermeasures and related technologies.

- Provided assistance to DoD on potential approaches for addressing the unique challenges in conducting studies or making available MCMs for the warfighter.

Surveillance

FDA is partnering with CDC and HHS to develop an action plan for the development of systems that can be used to monitor the safety and performance of medical countermeasures during public health emergencies. FY 2012 achievements include:

- Initiated an action team in April 2012, co-chaired by FDA and CDC, to develop an action plan for intra-event surveillance of the use, safety, and performance of medical countermeasures.
- Performed an assessment of existing CDC and FDA surveillance systems; identified capabilities and limitations of current systems (e.g., to assess safety and performance), and presented the summary of findings to HHS as part of the action plan described below.
- Garnered stakeholder input on intra-event surveillance needs through IOM's Forum on Medical and Public Health Preparedness for Catastrophic Events, which held a session on intra-event medical product surveillance at FDA's request. This event was a forum for multiple stakeholders from the Federal, State, and local levels, as well as the private sector and academia, to contribute their ideas to this effort.
- Developed an action plan for presentation to and approval by the Enterprise in fall 2012 that explained findings and proposed next steps for developing a national capability for intra-event surveillance to monitor the safety and performance of medical countermeasures during a public health emergency.

Pediatric and Maternal Populations

FDA is working to identify and address the needs of at-risk populations – with a special focus on pediatric and maternal populations – to ensure that safe and effective medical products are available for these groups should a public health emergency occur. For example, many of the medical products currently in the Strategic National Stockpile do not have approved indications for children, and there are often large data gaps for their use in pregnant women. FY 2012 achievements in this area include:

- Completed an assessment of the Strategic National Stockpile to identify data gaps that could inhibit the effective use of stockpiled medical countermeasures in children and other at-risk individuals. FDA is working with Enterprise partners to fill those data gaps.
- Held a workshop on February 15-16, 2012, on ethical and regulatory challenges in the development of medical countermeasures for pediatrics

- Held a workshop on April 30 – May 1, 2012, on scientific issues related to selecting animal models for use in evaluating medical influenza countermeasures (anti-influenza drugs) that may be given during pregnancy
- Worked with BARDA to help ensure that, whenever appropriate, medical product development contracts consider plans for pediatric dosing
- Began working with the Enterprise's Pediatric/Obstetrics Integrated Program Team (IPT)[12] — FDA is providing technical and regulatory assistance on identified FDA-related issues

Building the Necessary Science Base for the Regulatory Review of Medical Countermeasures

During FY 2012 FDA expanded its intramural medical countermeasure regulatory science program. Since the program began, FDA scientists have proposed more than 100 innovative regulatory science research projects for funding in areas related to medical countermeasure development. During FY 2012, FDA funded 46 regulatory science proposals, after review and approval by the Regulatory Science Steering Committee, fostering research in the following high-priority areas:

- Animal model development and qualification
- Identification and qualification of biomarkers for safety and efficacy
- Use of protein engineering to stabilize vaccine proteins
- Immune responses, including identification of correlates of protection
- Methods to assess product quality and related product release assays
- Risk communication to improve public health outcomes
- Validation of next-generation in vitro diagnostics platforms
- Assessing performance of emergency medical equipment
- Real-time tracking and evaluation of the safety and efficacy of medical countermeasures during a public health emergency

Highlights of activities and achievements:

- Held multiple workshops and meetings:
  - December 14-15, 2011, Antiviral Drugs Advisory Committee meeting on pathways for the development of drugs intended to treat variola virus infection (smallpox) in the event of an outbreak

[12] This IPT was established by the Enterprise to support and assist with strategies for identifying, developing, acquiring, deploying, and using high priority MCMs for children and pregnant women in public health emergencies. For more information on Enterprise IPTs see the 2102 Enterprise Strategy available at http://www.phe.gov/Preparedness/mcm/phemce/Documents/2012-PHEMCE-Strategy.pdf.

- April 2, 2012, joint meeting of the Anti-Infective Drugs and Nonprescription Drugs Advisory Committees on the types of consumer studies needed to assess proper use of a MedKit containing doxycycline to be taken in the event of anthrax exposure
- April 3-4, 2012, Anti-Infective Drugs Advisory Committees meeting on the development of an animal model of pneumonic plague and on data provided to support the safety and efficacy of ciprofloxacin and levofloxacin for the treatment of pneumonic plague in humans
- June 19-20, 2012, joint FDA/National Institute of Allergy and Infectious Diseases (NIAID) workshop on universal influenza vaccines
- July 24, 2012, workshop on the use of computer simulation of the US blood supply in support of planning for emergency preparedness
- August 23, 2012, workshop on the use of influenza disease models for quantitative benefit–risk evaluation of vaccines
- September 17-18, 2012, multiagency-sponsored meeting on animal model development

- In January 2012, FDA presented on regulatory pathways supporting development and approval of vaccines formulated with novel adjuvants at Phacilitate's North American 2012 Vaccine Forum
- FDA launched an animal model qualification program, which will enable the product-neutral evaluation of animal models and provide a more timely determination that a particular model is appropriate for the demonstration of efficacy to support approval of classes of products for specific indications.
- FDA held a 2-day MCMi Regulatory Science Symposium on June 5 -6, 2012 to present regulatory science projects underway at FDA and with leaders and partners in the field.
- FDA completed a portfolio review and gap analysis of the intramural regulatory science program related to medical countermeasures to guide future investments.
- FDA issued a broad agency announcement (BAA) on May 23, 2012 to solicit proposals from external organizations for the extramural component of the medical countermeasures regulatory science program. FDA is reviewing proposals received under the BAA and to date has funded one proposal. An innovative solicitation vehicle, the BAA remains open until May 23, 2013.
- FDA established scientific partnerships with the NIH, the Defense Advanced Research Projects Agency (DARPA), Defense Threat Reduction Agency (DTRA), and the National Interagency Confederation for Biological Research (NICBR).[13]

[13] In September 2012, FDA became a member of the NICBR, located at Fort Detrick and the Federal National Laboratory for Cancer Research in Maryland. NICBR is a collaboration of Federal agencies involved in medical research and advanced biotechnology. Their goals are to enhance public health, medical research, and biotechnology development by coordinating and synchronizing scientific interactions in areas of mutual interest.

- FDA and the University of Texas Medical Branch, Galveston National Laboratory are collaborating to establish good laboratory practices (GLP)-equivalent standards for ensuring the integrity of data from studies conducted in a biosafety level (BSL) 4 high-containment environment. A training program will be held on those standards in the spring of 2013.
- In FY 2012, 28 peer-reviewed articles were published in well-respected scientific journals based on MCMi-funded regulatory science research.

Modernizing and Optimizing the Statutory, Regulatory, and Policy Framework to Foster Development and Availability of Medical Countermeasures and Help Ensure an Effective Public Health Response

FDA's MCMi legal/policy team continues to identify and address areas where changes to existing statutes, regulations, and policies could enhance the nation's capabilities to prepare for and respond to a public health emergency involving a CBRN agent or infectious disease threat, like pandemic influenza. Achievements in this area support activities and facilitate achievements under the other two MCMi key goals. For example, collaborations established with other agencies and organizations like CDC, ASPR, BARDA, DoD, the Department of Homeland Security (DHS), and IOM greatly enhance deliberations and coordination of other activities and goals. In addition to these efforts, FDA is working closely with State and local partners to strengthen their medical countermeasure response capacity — especially important during a public health emergency. Key activities and accomplishments are noted here:

- On February 6, 2012, FDA issued a final rule, Exceptions or Alternatives to Labeling Requirements for Products Held by the Strategic National Stockpile.
- FDA developed proposals to clarify or augment certain statutory provisions related to FDA's emergency authorities as part of reauthorization process for the Pandemic and All-Hazards Preparedness Act (PAHPA). If implemented, the proposals will not only enable pre-event planning and positioning of medical products, but also facilitate efficient and rapid deployment of such products in the case of a CBRN-related emergency. Key proposals will accomplish the following:
  - Enhance statutory clarity and flexibility related to FDA's ability to issue EUAs, including before a CBRN or infectious disease event or outbreak to enable countermeasure staging, stockpiling, and rapid initial use.
  - Clarify authority with respect in vitro diagnostic devices to explicitly allow FDA to temporarily classify the complexity of a device when issuing an EUA for purposes of identifying which laboratories may appropriately use the device.
  - Streamline existing mechanisms to enable preparedness and response activities related to FDA-approved products without having to issue an EUA. For example, medical products could be dispensed with emergency use instructions, instead of with *individual* prescriptions — which would be very difficult to do during an emergency; certain requirements could be waived related to manufacturing and labels; and public health authorities could pre-position medical countermeasures.

- Address statutory uncertainties related to the extension of the shelf-life for stockpiled medical countermeasures for CBRN emergency uses.

- FDA provided extensive technical assistance to HHS and Congress as part of the PAHPA reauthorization effort to codify activities already being implemented under the MCMi with the goal of providing the highest quality and most timely guidance possible to stakeholders engaged in development of medical countermeasures.

- FDA also provided technical assistance to legislators to ensure that legislative approaches related to targeted plans for assisting stakeholders engaged in medical countermeasure development allow sufficient flexibility to address the unique scientific challenges posed by some medical products, without diverting resources from other critical efforts.

- During FY 2012, FDA entered into collaborations using memoranda of understanding (MOUs) in support of MCMi. FDA signed an MOU with ASPR to promote FDA-ASPR-BARDA collaboration and enhanced information sharing. FDA also updated an MOU with DARPA to support innovation in the development of medical products, including for medical countermeasures, and new technologies that can advance regulatory science.

- FDA worked with State and local public health authorities and responders to support preparedness and response capabilities at the state and community levels, including responding to numerous EUA-related inquiries and participating in multiple national-level workshops, meetings, and webinars on legal preparedness and FDA's role in distributing and dispensing medical countermeasures. For example:

  - February 2012: FDA participated in a workshop on Federal roles and in a town hall meeting on Federal issues and updates (National Association of County & City Health Officials Public Health Preparedness Summit 2012: Regroup, Refocus, Refresh: Sustaining Preparedness in an Economic Crisis, Anaheim, CA)

  - March 2012: FDA presented on Recent Developments in FDA's Emergency Authority for Medical Countermeasures (Public Health Law Webinar Series, Network for Public Health Law, the American Society of Law, Medicine, and Ethics, and the Public Health Law Research Program) and developed follow-up questions and answers.

  - June 2012: FDA presented on Public Health Law for Medical Countermeasure Distribution and Dispensing (CDC's Strategic National Stockpile Second Wednesday Webinars)

  - June 2012: FDA presented on Ensuring Local Preparedness and Response: Managing Bioterrorism and Pandemics at the State Level (2012 Biosecurity Conference, Boston, MA)

  - July 2012: FDA joined the planning committee for the National Association of County & City Health Officials' annual Public Health Preparedness Summit 2013 (and plans to participate in a summit workshop on the impact of the reauthorization of PAHPA

  - October 2012: FDA presented on Federal legal authorities for distributing and dispensing (2012 Public Health Law Conference, Atlanta, GA)

- FDA authored a chapter in the Food and Drug Law Institute book, *Food and Drug Law and Regulation* (2d ed.), entitled "Medical Countermeasures: Emergency Preparedness and Response Roles and Authorities."
- FDA joined the IOM's Forum on Medical and Public Health Preparedness for Catastrophic Events. This forum was established by IOM to provide national leadership in coordinating the ongoing efforts among members from Federal, State, and local government; business; and professional associations (e.g., the American Medical Association) to develop sustainable partnerships between the public and private sector so that communities are adequately prepared for natural or human-made catastrophic events.
- When presented with legal, regulatory, and policy challenges associated with the development, distribution, administration, stockpiling, or use of specific medical countermeasures, FDA worked with appropriate partners to develop and propose new approaches for addressing these challenges. Specific examples of areas where FDA provided policy assistance to relevant partners include the following:
  - First responders' ready access to and use of medical countermeasures (e.g., MedKits)
  - Issues related to countermeasure development that are unique to the warfighter
  - Issues related to expiration dating that are unique to medical countermeasures
  - Approaches to data collection during a public health emergency
  - Issues relating to international sharing of MCMs during foreign, domestic, or global health emergencies

Professional Development Activities

To make sure that FDA staff remain up to date on the cutting-edge science supporting development of medical countermeasures and receive the relevant situational information about potential CBRN threats, FDA established a targeted professional development program.

The following is a snapshot of the professional development activities tailored to those FDA scientists and reviewers who are involved with medical countermeasure development and approval.[14]

- **MCMi Lectures:** These lectures, presented by highly respected leaders in their fields, broaden the understanding for FDA staff of the policies, procedures, and US governmental and public health response framework for addressing CBRN and emerging infectious disease threats. Examples of topics include:
  - Importance of life sciences in national security

[14] Whenever feasible, FDA offers continuing education credits to physicians, nurses, pharmacists, and veterinarians who attend these professional development activities.

  - CBRN portfolio of medical countermeasures
  - Pathogenesis and targets for vaccines and therapeutics
  - Smallpox: past, present, future issues

- **Foundations for Pre-Clinical Review lecture series:** This is a monthly lecture series on pre-clinical scientific and technical issues related to countermeasure development under the Animal Rule. Invited speakers include both internal and external experts in the field and target FDA scientists and reviewers. Examples of presentations include:
  - New methods in telemetry
  - Toxicology testing for vaccines
  - Translational biomarkers
- **MCMi Hot Topics:** These are timely, scientific briefings on topics of interest to FDA scientists involved in the review of medical product applications. Subject matter experts from Federal agencies, academia, and regulated industry are invited to speak on scientific issues related to development of medical countermeasures. Examples of topics include:
  - Allosteric monoclonal antibodies
  - Vaccine manufacture issues, with local site visit
  - Biosimilars
- **Threat briefings:** Invited experts from DHS and the intelligence community bring FDA scientists and reviewers with security clearances the latest scientific and technical information on biosecurity issues.
- **Conference support:** During the year, MCMi supported attendance of FDA scientists and reviewers at scientific and training conferences (e.g., the American Society for Microbiology Biodefense and Emerging Diseases Research meeting, the Biodefense Vaccines and Therapeutics and Biosecurity workshop).
- **Georgetown University Certificate Program** on Biohazardous Threat Agents and Emerging Infectious Diseases. This 12-credit, on-line, graduate level certificate program is available to select FDA staff who are involved in MCMi activities need a more in-depth understanding of 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.
- **High-containment research training:** FDA and NIH have launched a training program for FDA staff in high and maximum biocontainment security level (BSL)-4 laboratory facilities. In a related project, FDA and the University of Texas Medical Branch, Galveston National Laboratory are collaborating to develop GLP-equivalent standards to ensure data integrity in BSL-4 laboratory facilities. A training program on these standards is also being developed. The training program, which will launch in spring 2013, will be open to all interested parties.

Next Steps

Reducing regulatory uncertainties associated with medical countermeasure development — which largely stem from gaps in scientific knowledge — is one of the most important challenges to the development and regulatory assessment of medical countermeasures. Reducing regulatory science uncertainties is also one of the most important challenges that the U.S. government must continue to address to successfully sustain and increase the engagement of countermeasure developers. FDA's expanded engagement in the Enterprise under the MCMi is among the most significant improvements to emerge from the Secretary's 2010 Enterprise Review. MCMi has brought additional resources to FDA and has enabled FDA to build on substantive efforts to foster the development of medical countermeasures. With this increased engagement, FDA has already been able to help resolve many of the regulatory uncertainties associated with countermeasure development so that development programs can move forward.

FDA's MCMi is a long-term initiative that will continue to build on existing programs while identifying new areas of focus. Plans are already underway for FY 2013 and beyond including:

- Issuing revised draft guidance on developing products under the Animal Rule in FY 2013.
- Furthering efforts to seek out opportunities for partnering in existing priority areas and any new areas as they are identified. Such collaboration remains the cornerstone of the initiative..Proposals to the BAA may offer new opportunities for collaborative research.
- Continuing to bring to bring all available expertise to bear on the challenges and gaps of medical countermeasure development and evaluation including through a combination of in-house regulatory science research, collaborative activities, competitive funding of external regulatory science research, and engagement of the external community through workshops and meetings. Workshops and meetings will play a key role — such as the workshop on the development of medical countermeasures for *Burkholderia* that was held in November 2012. Additional meetings and training on good laboratory practice, including in the BSL-4 environment, are planned for late 2012 and 2013.
- Continuing to explore new, innovative approaches to the regulatory review processes to improve development timelines and success rates and continuing to work closely with Enterprise partners to facilitate the development of high-priority medical countermeasures and related technologies such as advanced development and manufacturing capabilities.
- With passage of the PAHPA reauthorization legislation, providing guidance to stakeholders and implement FDA-related statutory changes to optimize our country's ability to efficiently and effectively prepare for and respond to CBRN agents or emerging infectious diseases. FDA will make sure the implementation process is as transparent as possible through the MCMi web page.
- Maintaining the MCMi targeted professional development program.

FDA anticipates consistent and continuous resources to support MCMi. The coming year should show substantial progress in the regulatory science program, with funding awarded to new intra- and extramural research projects. FDA will continue to work closely with our partners and with current and prospective sponsors as they invest in the development of these critical medical products. In support of their efforts, FDA will continue to bring cutting edge regulatory science and innovative approaches to medical product development and evaluation, to improve FDA's regulatory processes, and to make sure the medical products that will be needed in the event of a public health emergency are not only readily available, but also safe and effective.

Acronyms

ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BAA	Broad Agency Announcement
CBRN	Chemical, biological, radiological, and nuclear
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
DHS	Department of Homeland Security
DARPA	Defense Advanced Research Projects Agency
DoD	Department of Defense
DTRA	Defense Threat Reduction Agency
Enterprise	Public Health Emergency Medical Countermeasures Enterprise
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HHS	Health and Human Services
IOM	Institute of Medicine
MCMi	Medical Countermeasures initiative
MOU	Memorandum of Understanding
NCBI	National Center for Biotechnology Information
NICBR	National Interagency Confederation for Biological Research
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCET	Office of Counterterrorism and Emerging Threats
PAHPA	Pandemic and All Hazards Preparedness Act
USAMMDA	US Army Medical Materiel Development Activity