FDA's Medical Countermeasures Initiative: Strengthening Regulatory Science to Support Development and Approval of Medical Countermeasures for Biological Threats

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Introduction

The U.S. Food and Drug Administration (FDA) plays a vital and active role in protecting the United States from chemical, biological, radiological, nuclear (CBRN), and emerging infectious disease threats (such as Zika virus, Ebola virus, and pandemic influenza). The FDA is responsible for assessing the safety and effectiveness of medical countermeasures (MCMs) – including diagnostic tests, drugs, and vaccines – that are needed to counter these threats. In addition, the FDA works closely with interagency partners and product developers to advance the development and availability of investigational MCMs. In 2010, the FDA established its Medical Countermeasures Initiative (MCMi) focusing increased resources on promoting the development of MCMs by establishing clear regulatory pathways for MCMs, instituting effective regulatory policies and mechanisms to facilitate timely access to available MCMs, and advancing MCM regulatory science to create the tools, standards, and approaches that support regulatory decision-making.

MCMi Regulatory Science Program

The MCMi Regulatory Science Program supports a robust intra- and extramural research portfolio focused on helping to translate cutting-edge science and technology into innovative, safe, and effective MCMs. The mission of the MCM regulatory science program is to foster MCM regulatory science initiatives to:

1. **Develop solutions to complex regulatory science problems,**
2. **Facilitate incorporation of cutting-edge science into the regulatory review process**
3. **Make product development more efficient and predictable.**

This program is being implemented through partnerships, and support of intra- and extramural research projects. The intramural research program, which began in 2011, has enhanced and expanded existing MCM research efforts at FDA. In 2012, the extramural program was initiated using the FDA Broad Agency Announcement (BAA) for Advanced Research and Development of Regulatory Science: FDABAA-18-00123N, Area 7.

MCMi Regulatory Science Priority Research Areas

- **Identifying, developing, and qualifying drug development tools, such as animal models and immune biomarkers, to assess safety and efficacy of MCMs**
- **Advancing broadly applicable, commercially ready tools, technologies, and platforms that can improve the manufacturing efficiency, consistency, and quality of MCMs**
- **Developing reference materials related to CBRN threat agents and emerging infectious diseases to facilitate development of MCMs**
- **Validating next-generation *in vitro* diagnostics platforms**
- **Developing and qualifying *in silico* predictive models (e.g., microphysiological systems) and *in vitro* assays to complement the use of *in vivo* animal models to assess safety and efficacy of MCMs**
- **Assessing the performance, design, and reuse of emergency medical equipment including PPE**

Medical Countermeasure Regulatory Science Research

Fostering innovation in the development of MCMs, including the use of novel technologies and platforms, by supporting both intramural and extramural regulatory science (Table 1).

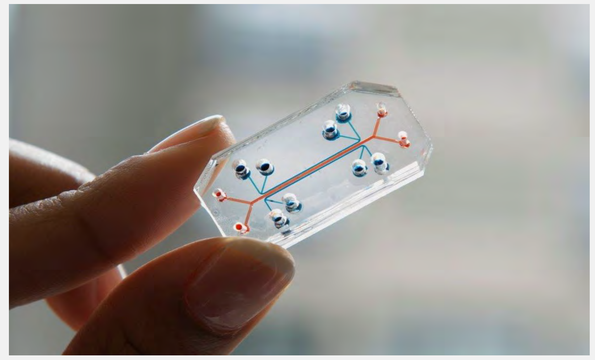
Table 1. MCMi Regulatory Science Research

Project Area	Project Title	Principal Investigator(s) Affiliation	Program
Animal models	Eye ZIKV infection: Development of a mouse model to correlate clinical imaging with immunohistochemistry and transcriptomics to evaluate safety and efficacy of therapeutics	Dr. Daniela Verthelyi FDA, Center for Drug Evaluation and Research (CDER)	Intramural
Assay development	Development of high-throughput micro-neutralization assays to assess neutralizing antibodies against Zika virus	Dr. Keith Peden FDA, Center for Biologics Evaluation and Research (CBER)	Intramural
	Sequencing using nanopore technology (Minion nanopore) for bacterial whole genome sequencing to support epidemiological investigations and fast virulence typing surveillance of *E. coli* and *C. botulinum*	Dr. Narjol Gonzalez-Escalona FDA, Center for Devices and Radiological Health (CDRH)	Intramural
Vaccines	Correlates of protection against Ebola virus predictive of vaccine efficacy in humans	Dr. Surrender Khurana FDA, CBER	Intramural
In silico predictive models	Organ-on-chips tools for testing radiation countermeasures	Dr. Donald Ingber Wyss Institute for Biologically Inspired Engineering at Harvard University	Extramural
Biomarkers (Immune Characterization)	Analysis of samples from Ebola survivors to better understand long-term sequalae of Ebola virus disease; and Ebola virus disease: Correlates of protection, biomarkers of disease outcome, and mutations with implications for efficacy of vaccines and therapeutics	Dr. Miles Carol Public Health England (PHE)	Extramural
	Sequelae and immunopathology of Ebola virus infections	Dr. Garry Nolan Stanford University	Extramural
	Spatio-temporal map of gene expression during lethal Ebola virus disease	Dr. Pardis Sabeti The Broad Institute	Extramural
Antibiotics and route of infection	Determination of the efficacy of antibiotics against melioidosis acquired by different routes	Dr. Michelle Nelson Defence Science and Technology Laboratory	Extramural
Sampling/pathogenesis	Analysis of samples from Ebola, Rift Valley fever, Crimean Congo hemorrhagic fever, Chikungunya, and Zika virus-infected individuals in Uganda, to establish a better understanding of microbial pathogenesis	Dr. Karen Martins United States Army Medical Research Institute for Infectious Diseases (USAMRIID)	Interagency
Personal protective equipment (PPE)	Research to mitigate a shortage of respiratory protection devices during public health emergencies	Brian Heimbuch Applied Research Associates	Extramural

MCMi Accomplishments

Since 2011, MCMi has supported 200+ intra- and extramural regulatory science projects to accelerate FDA's ability to perform science-based review of MCMs. Program accomplishments include:

- **Development of regulatory science research tools including a cross-species immune atlas database to better understand response to CBRN and emerging infectious disease agents in animal models and humans**
- **Development of a radiation organ-on-chip model with applications for MCM screening**
- **Development of ASTM E3135-18, the first consensus standard for ultraviolet surface decontamination, which could help mitigate PPE shortages during public health emergencies**
- **Publication (PHE): Transcriptomic signatures differentiate survival from fatal outcomes in humans infected with Ebola virus (https://www.ncbi.nlm.nih.gov/pubmed/28100256)**
- **Publication (FDA CBER): Human antibody repertoire after VSV-Ebola vaccination identifies novel targets and virus-neutralizing IgM antibodies (https://www.ncbi.nlm.nih.gov/pubmed/27798615)**



Under an MCMi project, Wyss Institute scientists are developing models of radiation damage in lung, gut, and bone marrow organs-on-chips and then using these models to test candidate MCMs to treat such damage. *(Image: Wyss Institute)*