

FDA

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MEDICAL COUNTERMEASURES INITIATIVE

# Challenges in the Development of Medical Countermeasures

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*Biology of Anthrax*

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# Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily represent those of the U.S. Food and Drug Administration nor should they be interpreted as official Agency policy

# Affiliation

- Office of Counterterrorism and Emerging Threats (OCET) is in the Office of the Chief Scientist under the Office of the Commissioner
- Mission of OCET
  - Facilitate the development and availability of safe and effective public health emergency medical countermeasures (MCMs)
  - Identify and resolve complex scientific and regulatory challenges facing MCM development, approval, availability, and security
  - Coordinate the Medical Countermeasures Initiative (MCMi)
    - Working closely with other FDA Offices and the Medical Product Centers

# Background

- Critical need for MCMs for chemical, biological, and radiological/nuclear (CBRN) agents and emerging/re-emerging infectious diseases
- Approved/licensed products provide strategic advantages and improve public confidence
- “Traditional” approval/licensure pathway involves testing safety and efficacy in human subjects

2001



2014



# Challenges for MCM Development

- The Federal Food, Drug, and Cosmetic Act (FD&C) requires human drug and biological products to be safe under conditions of use, and effective as demonstrated by “substantial evidence”
- “Substantial evidence” means adequate and controlled investigations, including well-controlled clinical trials
- Natural or accidental exposures to threat agents are rare
- It would be unethical to intentionally expose human volunteers to potential threat agents



# Presentation Objectives

- Describe Regulatory Mechanisms to Support MCM Approval/Licensure
  - “The Animal Rule”
  - Examples of products approved/licensed under the Animal Rule
- Discuss Scientific Challenges and Resources
- Describe the Medical Countermeasures Initiative (MCMi)
- Highlight MCMi Regulatory Science Research Program

# The Animal Rule

- “New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible”
  - 21 CFR 314 Subpart I (drugs) and 21 CFR part 601 Subpart H (biologics)
  - May 31, 2002 (67 FR 37988)
- Allows for the use of adequate and well-controlled animal studies as evidence of effectiveness for approval

# The Animal Rule (2)

- Study considerations
  - Conducted in a manner that ensures **data quality** (accordance with protocol, SOPs, and research standards) and **integrity** (assurance raw data and documentation)
- Must be in compliance with applicable laws and regulations governing the care and use of laboratory animals
  - The Animal Welfare Act-7 U.S. C. 2131
  - Public Health Service Policy on the Care and Use of Laboratory Animals



# The Animal Rule (3)

- Safety must still be established through the traditional pathway
  - Non-clinical studies (animals)
  - Clinical studies (human volunteers)
- Utilized only when efficacy evaluations are not feasible or ethical under any other FDA regulation
- In assessing the adequacy of animal data, the FDA may take into account other available data, including human data
- Evidence of effectiveness from animal studies will only be considered when specific criteria are met

# The Animal Rule: Requirements

- 1) The pathophysiological mechanism of the toxicity of the agent, and the mechanism by which the product prevents or substantially reduces that toxicity, must be reasonably well-understood
- 2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans

**-Unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans**

# The Animal Rule Requirements (2)

- 3) The animal study endpoint is clearly related to the desired benefit in humans
  - Enhancement of survival
  - Prevention of major morbidity
  
- 4) Data allow selection of an effective dose in humans
  - Kinetic and pharmacodynamic data/information
  - Other relevant data/information that allows selection of an effective dose in humans
  
- There are additional requirements to conduct post marketing studies to assess clinical benefit when ethical and feasible, for patient information, and approval/licensure with restrictions to may be necessary for safe use

# Products Approved under the Animal Rule



- 2003 Pyridostigmine bromide
  - For use as pretreatment for exposure to chemical nerve agent Soman
- 2006 Cyanokit (hydroxocobalamin)
  - For treatment of known or suspected cyanide poisoning
- 2012 Levoquin (levofloxacin)
  - For prophylaxis and treatment of plague
- 2012 Raxibacumab for anthrax
  - For treatment of inhalational anthrax in combo with antibacterial drugs
- 2013 Botulism antitoxin (Equine), Heptavalent (A, B, C, D, E, F, G)
  - For treatment of patients showing signs of botulism following documented or suspected exposure to botulinum neurotoxin
- 2015 Ciprofloxacin for plague
  - For the prophylaxis and treatment of plague

# Products Approved under the Animal Rule (2)



- 2015 Anthrasil (Anthrax Immune Globulin Intravenous, Human)
  - For treatment of inhalational anthrax
- 2015 Neupogen (Filgrastim) for H-ARS
  - To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
- 2015 Avelox (Moxifloxacin) for plague
  - For prophylaxis and treatment of plague
- 2015 Neulasta (Pegfilgrastim) for H-ARS
  - To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
- 2015 Biothrax (Anthrax Vaccine Absorbed)
  - To prevent disease following suspected or confirmed exposure to *Bacillus anthracis*
- 2016 Anthim (Obiltoxaximab)
  - To treat inhalational anthrax in combination with appropriate antibacterial drugs and to prevent inhalational anthrax when alternative therapies are not available or not appropriate



# Potential Scientific Challenges of Product Development Under the Animal Rule

- Need for characterized animal models of the human condition
  - Species availability
  - Species susceptibility
  - Similarity to disease in humans
- Collection of data to enable “dose” extrapolation
  - Need for bridging studies
- Achieving data quality and integrity in containment environment
  - Sponsor should seek concurrence from FDA on the data quality and integrity plan prior to study initiation
- Ensuring animal welfare



# Resources: Animal Rule Guidance

- **Product Development Under the Animal Rule Guidance for Industry (October, 2015)**
- **New Sections:**
  - Regulatory Considerations
  - Animal studies- General Expectations
  - Considerations for Preventative Vaccines and Cellular and Gene Therapies
  - Checklist of Elements for an Adequate and Well-Controlled Animal Efficacy Study Protocol
  - General Principles for the Care and Use of Animals in Biomedical Research
  - Types of Animal Care Interventions
  - General Expectations for Natural History Studies
- **Enhanced Sections:**
  - The Animal Rule
  - Essential Elements of an Animal Model
  - Design Consideration for the Adequate and Well-Controlled Efficacy Studies in Animals
  - Human Safety Information

# Additional Resources

- Qualification of Drug Development Tools Guidance for Industry and FDA Staff (January, 2014)
  - Animal Model Qualification
- Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax (Draft) Guidance for Industry (February, 2016)
- Information from previously approved/licensed MCMs
  - Product labels/Package inserts
  - Summary basis for Regulatory Approval
  - Approval memos (redacted)
  - Advisory committee materials (if applicable)
- FDA website and staff
- Training courses
  - “UTMB/FDA Achieving Data Quality & Integrity in Maximum Containment Laboratories” Course (April, 2017)





# FDA Medical Countermeasures Initiative (MCMi)

- MCMi was launched in 2010 in response to comprehensive year-long review of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)
- PHEMCE coordinates CBRN and Emerging Infectious Disease preparedness efforts
  - Partnership of BARDA, CDC, FDA, NIH, DHS, DoD, VA, USDA
  - Led by HHS Office of the Assistant Secretary for Preparedness and Health (ASPR)
- Objective: Facilitate MCM development, evaluation, and availability by
  - Enhancing the Regulatory Review Process
  - **Advancing MCM Regulatory Science**
    - Mission is to develop the tools, standards, and approaches to assess medical safety, quality, and performance of MCMs.
  - Modernizing the Legal, Regulatory, and Policy Framework

# MCMi Anthrax-focused Intramural Research



## Developing a New Animal Model and Novel Biomarkers for Anthrax Infection: a Basis for Enhancing the Regulatory Review of Medical Counter-Measures

- Goal: to develop a murine model of gastrointestinal (GI) anthrax to characterize mechanisms toxin-mediated effects on the GI other epithelial barriers that contribute to mortality during toxemia. The project will also enhance understanding of mechanisms of action of MCMs targeting anthrax toxins and the identification of physiologically relevant biomarkers to facilitate development of potency assays.
- Publications:
  - Huang B, Xie T, Rostein D, Fang H, and **Frucht DM**. (2015) Passive Immunotherapy Protects against Enteric Invasion and Lethal Sepsis in a Murine Model of Gastrointestinal Anthrax. **Toxins** 7: 3960-76.
  - Tao Xie, Chen Sun, Kadriye Uslu, Roger D. Auth, Hui Fang, Weiming Ouyang, and **David M. Frucht**. (2013) A New Murine Model for Gastrointestinal Anthrax Infection. **PLoS One** 8(6):e66943.

PI: CAPT David Frucht, CBER, [David.Frucht@fda.hhs.gov](mailto:David.Frucht@fda.hhs.gov)

# MCMi Anthrax-focused Intramural Research (2)



## Improving Anthrax Vaccine Stability

- Goal: To further understand the underlying causes of rPA instability and develop strategies for improving rPA vaccine stability that will continue to facilitate the development of next generation anthrax vaccines
- Publications:
  - Verma, A., Ngundi, M.M., and Burns, D.L. Mechanistic analysis of the effect of deamidation on the immunogenicity of anthrax protective antigen. Clin. Vaccine Immunol. 23: 396-402 (2016).

PI: Dr. Drusilla Burns, CBER, [David.Frucht@fda.hhs.gov](mailto:David.Frucht@fda.hhs.gov)

# MCMi Anthrax-focused Extramural Research

FDA

## Cross-species immune system reference (Stanford University)



- Goal: To use mass cytometry to conduct the first single-cell comprehensive cross-species (human, murine, NHP x 3 species) analyses of immune system function by measuring responses to CBRN relevant stimuli (including *Bacillus anthracis*)
- Accomplishments:
- Analyzing almost 1 billion cells from more than 200 donors under approximately 16 conditions, for a total of 3,136 samples.
- Discovery of a large number of differences between the studied species, including in responses to anthrax.
- Creating a reference database listing the cross-reactivity of more than 300 antibodies in five species in five blood cell types.
- **Open-access web resource:**  
<https://immuneatlas.org>



PI: Garry Nolan ([gnolan@stanford.edu](mailto:gnolan@stanford.edu))  
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# Conclusions

- There are challenges associated with MCM development
- The Animal Rule has created opportunities for the advancement of MCMs
  - Since 2003, 12 products have been approved/licensed under the Animal Rule
- MCMi is facilitating MCM development
  - MCMi Regulatory Science research program is addressing scientific gaps
- There are resources to assist with meeting challenges of MCM development
  - Guidance documents
  - Information from Information from previously approved/licensed MCMs
  - FDA website and staff

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# Questions

- For additional information please visit our website:  
[www.fda.gov/MedicalCountermeasures](http://www.fda.gov/MedicalCountermeasures)
  - Includes links to
    - ask questions? [@AskMCMi@fda.hhs.gov](https://twitter.com/AskMCMi)
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