Challenges in Approval of New Treatments in the Biodefense World

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Dr. Tracy MacGill
Office of Counterterrorism and Emerging Threats
Office of the Chief Scientist
Office of the Commissioner
U.S. FDA

U.S. Food and Drug Administration
Medical Countermeasures Initiative

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

The “Biodefense” Landscape

- 2001 “AmeriThrax”
  - 22 cases
  - 11 inhalational; 5 deaths
- (Re-) Emerging Diseases
  - Ebola (West Africa)
  - 8973 cases;4484 deaths (10/12/14)

MCM Development

- Critical need for MCM for chemical, biological, and radiological/nuclear (CBRN) threat agents
- Approved products with CBRN indications provide strategic advantages and improve public confidence

Presentation Objectives

- Discuss Regulatory Mechanisms to Support Product Approval/Licensure
  - "The Animal Rule"
- Describe Regulatory Mechanisms to Support Emergency Use
  - Emergency Use Authorization
- Describe Mechanisms to Support Product Development, Availability, and Use
  - The Medical Countermeasures Initiative (MCMi)

Challenges in MCM Development

- Section 505 (d) of the Federal Food, Drug, and Cosmetic Act (FD&C) requires a drug 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

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)
  - Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies is an established and relevant system
- 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

The Animal Rule Requirements (3)

21 C.F.R. § 314.610 (§ 601.91)

- Postmarketing Studies
  - "To verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are ethical and feasible."
  - "Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible."
- Information to be provided to patient recipients explaining that the approval is based on animal efficacy studies
- Approval with restrictions to ensure safe use
  - In cases where the drug product can be used safely only if distribution or use is restricted (e.g. certain facilities or practitioners, performance of specified medical procedures, recordkeeping requirements)

Potential 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
  - FDA-University of Texas Medical Branch (Galveston) “Achieving data quality and integrity in maximum containment laboratories” course
  - Sponsor should seek concurrence from FDA on the data quality and integrity plan prior to study initiation
- Ensuring animal welfare

Products Approved Under the Animal Rule

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

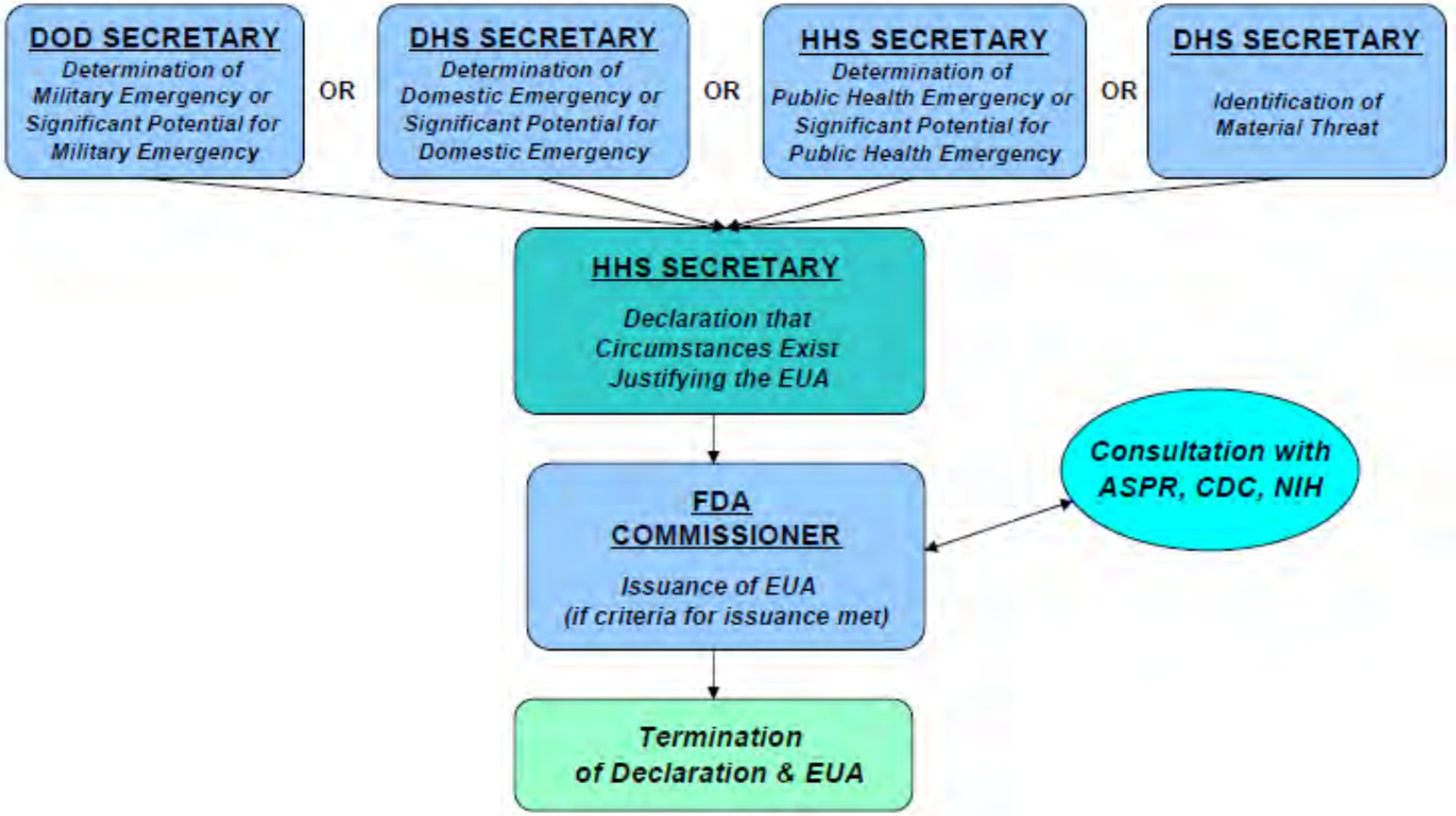
The Animal Rule: Guidance

- Original Draft Guidance Animal Models - Essential Elements to Address Efficacy Under the Animal Rule
- Revised Draft Guidance for Industry Product Development Under the Animal Rule
  - Issued May, 2014
  - Comment period has closed
- **http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.html**

Emergency Use Authorization (EUA)

- Section 564 of the FD&C Act was amended by Project BioShield Act (2004) to establish the EUA authority
- With this authority, FDA can authorize for use in CBRN emergencies the:
  - Use of unapproved MCMs
  - Unapproved use of approved MCMs
- Predicate determination (by DHS, DOD, or HHS Secretary) + HHS Secretary declaration that circumstances exist to justify EUA issuance
- Criteria for issuance:
  - Serious/life-threatening illness/condition caused by CBRN agent
  - Reasonable belief that the product may be effective
  - Product's known/potential benefits outweigh its known/potential risks
  - No adequate, approved, available alternative to the product
- Conditions of authorization specific to each EUA (e.g., clarification of roles, fact sheets for patients & health care providers, recordkeeping)

Brief Summary of Process for EUA Issuance
(FD&C Act § 564, as amended by PAHPRA)



Emergency Use Authorization (2)

- The Pandemic and All-Hazards and Preparedness Reauthorization Act (PAHPRA) 2013 further amended the FD&C Act and EUA authority
- Gives FDA clearer authority to issue EUAs before an emergency
  - Allows issuance of an EUA without declaring that an "emergency" exists (e.g., the EUA determination can be based on a "significant potential" for a public health emergency or on the identification of a material threat)
  - To allow for staging (moving product in interstate commerce), stockpiling, creating fact sheets, and rapid initial use
  - Criteria for issuance are the same whether the EUA is issued before or during an emergency
- Eliminates 1-year automatic expiration of the HHS declaration that supports EUA issuance
- Expands the time period for collection and analysis of data about an MCM's safety and clinical benefit beyond the effective period of the EUA
- Expressly permits FDA, when issuing an EUA for use of a diagnostic test, to categorize the test to allow it to be used at a point-of-care site

EUAs Issued

EUAs Issued by FDA			
Year	**MCM**	**Requester**	**Status**
Anthrax (*Bacillus anthracis*)			
2005	Anthrax Vaccine Adsorbed (AVA)	DoD	Terminated
2008	Doxycycline hyclate 100 mg oral tablets (in National Postal Model home & workplace kits)	HHS (ASPR/BARDA)	Amended in 2009, 2010, 2011 (2011 is current)
2011	All oral formulations of doxycycline (mass dispensing)	HHS (CDC)	Current*
2009 H1N1 Influenza Pandemic			
2009-2010	Antivirals (3)	HHS (CDC)	Terminated
	IVDs (18)	Various	
	Disposable N95 Respirators	HHS (CDC)	
Novel Influenza A (H7N9) Virus			
2013	CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel-Influenza A/H7 (Eurasian Lineage) Assay	HHS (CDC)	Current
2014	Lyra™ Influenza A Subtype H7N9 Assay	Quidel Corporation	Current
2014	A/H7N9 Influenza Rapid Test	Arbor Vita Corporation	Current
Middle East Respiratory Syndrome Coronavirus (MERS-CoV)			
2013 (reissued in 2014)	CDC Novel Coronavirus 2012 Real-time RT-PCR Assay	HHS (CDC)	Current
Ebola Virus			
2014 (*reissued*)	DoD EZ1 Real-time RT-PCR Assay	DoD	Current
2014	CDC Ebola VP40 rRT-PCR Assay	CDC	Current
2014	CDC Ebola NP rRT-PCR Assay	CDC	Current

* To be terminated after issuance of doxycycline emergency dispensing order, CGMP waiver, and CDC EUI (sec. 564A of the FD&C Act).

Additional information on current/terminated EUAs:
http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm

Emergency Use Authorities: Additional Information

- PAHPRA MCM Authorities: FDA Questions and Answers for Public Health Preparedness and Response Stakeholders (2014)
  - **http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM380269.pdf**

- FDA EUA Website (*official updates, current & terminated EUAs, questions & answers, guidance, etc*.)
  - **www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm**

- Emergency Use Authorization of Medical Products Guidance - Emergency Use Authorization of Medical Products (2007)
  - **Note: Under revision following the 2013 enactment of PAHPRA**
  - **http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm**

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
  - Modernizing the Legal, Regulatory, and Policy Framework

Advancing MCM Regulatory Science

- Goals:
  - Fostering MCM regulatory science initiatives to develop solutions to complex scientific regulatory problems.
  - Facilitating the incorporation of new, cutting-edge science into the regulatory review process.
  - Making product development more efficient and predictable.
- The program is being implemented through
  - Partnerships
  - Intramural research
  - Extramural research

MCMi Extramural Research

- Extramural research
  - Release of FDA Regulatory Science and Innovation BAA coincided with launch of extramural research program, providing a vehicle to support this research (FY2012)
  - The current solicitation (FDABAA-14-00120) is accepting applications until 2/20/2015
- FDA BAA topic area 7: Facilitate the Development of MCMs to Protect Against Threats to U.S. Global Health and Security
  - Proposed research projects should consider MCMi's goals of supporting MCM development, evaluation, and availability
  - Proposal evaluation conducted in coordination with PHEMCE partners

MCMi Extramural Research Projects

- Cross-species immune system reference, **Stanford University**, **FY2012**
- Organs-on-chips for radiation countermeasures, **the Wyss Institute at Harvard University**, **FY2013**
- Medical product center (CDER and CDRH) specific projects with **the Critical Path Institute** and **the University of Maryland**, **FY2013**
- Ensuring appropriate public use of medical countermeasures through effective emergency communication, **University of Pittsburgh Medical Center**, **FY2014**
- Bioquell HPV decontamination for reuse of N95 respirators, **Battelle Memorial Institute**, **FY2014**
- Optimizing respirator decontamination to ensure supplies for emergency preparedness, **Applied Research Associates**, **FY2014**
- Rapid assessment of acute illness and injury to enhance the U.S. response to public health emergencies, **U.S. Critical Illness and Injury Trials Group**, **FY2014**

Conclusions

- There are regulatory mechanisms for MCM approval/licensure and emergency use
  - The Animal Rule
  - Emergency Use Authorizations
- The MCMi provides a mechanism to support MCM development, evaluation, and availability
  - Regulatory review
  - Regulatory science (research $)
  - Legal, regulatory, and policy framework

Acknowledgments

Office Leadership

Luciana Borio, MD
Assistant Commissioner
for Counterterrorism Policy
Deputy Chief Scientist (Acting)
Director, OCET

CAPT Carmen Maher
Deputy Director, OCET

MCM Regulatory Policy

Elizabeth Sadove, JD
Brooke Courtney, JD, MPH

MCM Regulatory Science

CAPT Estella Jones
Pamela Chamberlain, DVM, PhD
Brenda Brooks
Susan Zhao, PhD
Kimberly Armstrong, PhD
Rakesh Raghuwanshi,MPH

Questions

- **For additional information please visit our website:**
  www.fda.gov/MedicalCountermeasures
  - **Includes links to**
    - ask questions? AskMCMi@fda.hhs.gov
    - Sign up for MCMi email updates

Twitter: @FDA_MCMi

Tracy MacGill, Ph.D.
tracy.macgill@fda.hhs.gov