The FDA Animal Rule

ASM Biodefense and Emerging Diseases Meeting
February 10, 2016

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 and Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) partners

Background

- 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

- "Traditional" licensure/approval pathway involves testing safety and efficacy in human subjects

2001

2014

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

Presentation Objectives

- Describe Regulatory Mechanisms to Support Medical Countermeasure Approval/Licensure
  - "Animal Rule"
- Discuss Scientific Challenges
- Describe examples of products approved under the Animal Rule
- Highlight Additional Resources

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 or immune correlate data/information

-Other relevant data/information that allows selection of an effective dose in humans

Caveats

- The Animal Rule does not apply if licensure is possible based on other routes

- Use of Animal Rule does not preclude the requirement for human safety studies

- Subject to additional postmarketing data collection on safety and efficacy

- In assessing the adequacy of animal data, the FDA may take into account other available data, including human data

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
- Ensuring animal welfare
- 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

Products Approved Under the Animal Rule

- ## 2003 Pyridostigmine bromide
  - for use as a pretreatment for exposure to the chemical nerve agent Soman
  - Non-human primates, guinea pigs, and rodents

- ## 2006 Cyanokit (hyrdoxycabalomin)
  - for treatment of known or suspected cyanide poisoning
  - Dogs

- ## 2012 Levaquin (levofloxacin)
  - for prophylaxis and treatment of plague
  - Non-human primates

- ## 2012 Raxibacumab
  - for treatment of inhalational anthrax in combo with antibacterial drugs
  - Non-human primates and rabbits

Products Approved Under the Animal Rule (2)

- 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
    - Non-human primates and guinea pigs

- 2015 Ciprofloxacin
    - for the prophylaxis and treatment of plague
    - Non-human primates

- 2015 Moxifloxacin (Avelox)
    - for the prophylaxis and treatment of plague
    - Non-human primates

Products Approved Under the Animal Rule (3)

- ## 2015 Anthrax Immune Globulin Intravenous (Anthrasil)
  - for the treatment of inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs
  - Non-human primates and rabbits

- ## 2015 Filgrastim (Neupogen)
  - to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
  - Non-human primates

- ## 2015 Pegfilgrastim (Neulasta)
  - to treat adult and pediatric patients at risk of developing myelosuppression
  - Non-human primates

- ## 2015 Anthrax Vaccine Absorbed (BioThrax)
  - for use after known or suspected anthrax exposure
  - Non-human primates and rabbits

Resources: 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

- Final Guidance for Industry Product Development Under the Animal Rule
  - Issued October, 2015

- **http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm399217.html**

Resources (2)

- Product labels/Package inserts
- Summary basis for Regulatory Approval
- Approval memos (redacted)
- Advisory committee materials (if applicable)
- FDA website and staff
- Peer-reviewed literature
- Training courses

The University of Texas Medical Branch (UTMB)
Office of Regulated Nonclinical Studies Presents

Achieving Data Quality & Integrity in Maximum Containment Laboratories

April 25 - 29, 2016

National Institutes of Health
Natcher Conference Center, Bethesda, Maryland

For registration information email:
Diane.Garrett@fda.hhs.gov

Registration is open now
and ends **February 19, 2016**

Achieving Data Quality & Integrity in Maximum Containment Laboratories
April 25 - 29, 2016

- Cross-education of subject matter experts for advancement of medical countermeasures
- Problem-based learning to enhance data quality and integrity for studies conducted un- der high containment (BSL-3/4)
- Interactive lectures, practical approaches, case studies, online modules, expert panels and simulated BSL-3/4 laboratory exercises
- Course faculty from academia, business and industry, BSL-3/4 laboratories, and the National Interagency Confederation for Bio- logical Research (NICBR), including FDA and NIH
- Networking with sponsors, scientists, physicians, nurses, pathologists, veterinarians, quality assurance personnel, regulators, agency reviewers, and policy-makers

20

Conclusions

- There are challenges associated with MCM development
- The Animal Rule has created opportunities for the advancement of MCMs
- Since 2003, 11 products have been approved/licensed under the Animal Rule
  - Includes small molecule and biologic drug products and vaccines
  - A variety of animal models (small and large) have been used to support these approvals
- There are resources available to assist
  - Guidance documents
  - Approval memos and advisory committee materials
  - Training
  - FDA website and staff

Acknowledgments

OCET Leadership

RADM Carmen Maher
Assistant Commissioner
for Counterterrorism Policy (Acting)
Director, OCET (Acting)

Dr. Robert Fisher
Director, MCM Regulatory Science

FDA Center MCM Leadership

Dr. Rosemary Roberts (CDER); rosemary.roberts@fda.hhs.gov
Mr. David Rouse (CBER); david.rouse@fda.hhs.gov
Dr. Nicolette deVore (CBER); nicolette.devore@fda.hhs.gov

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

FDA Medical Countermeasures Initiative
Protecting National Health and Security

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

23