Vaccine Development and the FDA Approval Process

Southern Research Institute

Michael G. Murray, Ph. D.

This presentation introduces the basic tenets of the US Food and Drug Administration (FDA) Animal Rule and includes considerations for developing an animal efficacy study leading to a successful FDA submission. During the last 15 years the emergence of terrorism in the US, has led to increased funding and interest in developing medical countermeasures (MCM's) to prevent or treat serious clinical events involving bio-treat agents such as those that cause anthrax, smallpox, botulism, plague and tularemia. However, development of MCM's presents many unique scientific and ethical challenges. In most cases it would not be scientifically feasible or medically ethical to conduct a human clinical trial for development of a MCM for anthrax or small pox or plague. So, in response to this dilemma, the FDA issued regulations to allow for the approval of drugs and biological products based on efficacy studies conducted in animals when human studies would be unethical or not feasible. The regulation is intended to facilitate the approval process for products intended for human use when treating diseases caused by chemical, biological, nuclear, radiological agents (CBRN) that have potential to harm a high percentage of the US human population. Today's presentation will be limited to a discussion of the Animal Rule in the context of a human infectious disease – smallpox.

M E M O

Presentation Outline

- Introduction
  - Who we are
  - What is our experience
- Understanding the Animal Rule
  - What is the Animal Rule?
  - When does it apply?
  - What does it require?
  - Considerations for developing an animal efficacy study leading to a successful FDA submission
  - Describe an example Case Study

SOUTHERN RESEARCH INSTITUTE

US Food and Drug Administration (FDA)

- Centers for Biologics Evaluation and Research (CBER)
  - Vaccines
  - Biological products
- Centers for Drug Evaluation and Research (CDER)
  - Drugs

Responsible for ensuring the safety and efficacy of drugs, vaccines and biological products

- Non-clinical testing
- Human Clinical Trial

SOUTHERN RESEARCH INSTITUTE

The Animal Rule What is it?

- Federal regulations
  - CFR 314.600 for drugs
  - CFR 601.90 for biological
- Allows FDA approval products for human use based on efficacy data generated in animals instead of a human clinical trial
- Applies to products used to prevent the harmful effects of chemical, Biological, radiological or nuclear (CBRN) substances
- Guidance for Industry
  - www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078923.pdf

www.fda.gov
Searchable for animal rule

SOUTHERN RESEARCH INSTITUTE

The Animal Rule
What is it?

- Federal regulations
  - CFR 314.600 for drugs
  - CFR 601.90 for biological
- Allows FDA approval products for human use based on efficacy data generated in animals instead of a human clinical trial
- Applies to products used to prevent the harmful effects of chemical, Biological, radiological or nuclear (CBRN) substances
- Guidance for Industry
  - www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078923.pdf

www.fda.gov
Searchable for animal rule

SOUTHERN RESEARCH INSTITUTE

The Animal Rule
What it is not.

- Does not provide a simplified or expedited path to develop therapeutics
  - In vitro activity evaluations (efficacy, cytotoxicity etc.)
  - Mechanism of action determination
  - Preclinical pharmacology and toxicology studies for early product development are required
  - Pharmacokinetic analysis in uninfected animals and humans
  - Pharmacokinetic interactions with products likely to be used in combination with the product in development
  - Determination of synergy or antagonism with products likely to be used in combination with the product in development

SOUTHERN RESEARCH INSTITUTE

The Animal Rule
What does it require?

- Pathophysiological mechanism of the disease is reasonably well understood and it is reduced or prevention by the product
- The effect is demonstrate in more than one animal species expected to respond that is predictive for humans
- The animal efficacy study endpoints are clearly related to the desired benefit in humans
- The data generated in the animal study and the human studies allows selection of an effective dose in humans

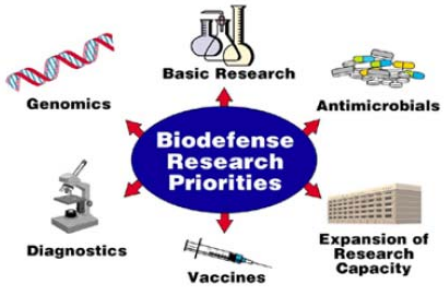
SOUTHERN RESEARCH INSTITUTE

Outline

- Historical background
- Considerations for Animal Model development
- Review of Regulatory Path
- Orthopoxvirus Animal Models
  - Monkeypox vs. Smallpox
- Case study – demonstrate utility

SOUTHERN RESEARCH INSTITUTE

NIAID'S STRATEGIC PLAN FOR BIODEFENSE



SOUTHERN RESEARCH INSTITUTE

IN VITRO AND ANIMAL MODELS FOR EMERGING INFECTIOUS DISEASES AND BIODEFENSE PROGRAM

- Established in 2003
- Multi-$Million Contracts awarded to 10 institutions including Southern Research, Contract N01-AI-30063
- Objectives:

  To Support the Development, Validation and Use of Various Small and NHP Models to Screen and Test Efficacy of New Products Against Category A- C Agents.

  e.g. Diagnostics, Therapeutics, Vaccines, Immunotherapies

SOUTHERN RESEARCH INSTITUTE

EXAMPLES OF ANIMAL MODELS

- Smallpox: Monkeypox NHP & Dormice; Vaccinia, Cowpox, Ectromelia Mouse; Rabbitpox
- Tularemia: Rodent and NHP
- Anthrax: Rodent & NHP
- VEE/WEE: Guinea Pig and Mouse Model
- West Nile: Mouse
- Plague: Mouse and NHP
- Influenza – Mouse, Ferret and NHP

SOUTHERN RESEARCH INSTITUTE

Considerations for Animal Model Development & Utility

- Species – mouse, rabbits, guinea pigs, NHP plus other
- Challenge Virus – different for each species
- Standardized Challenge Dose – optimal for reproducibility
- Route of Challenge – Parenteral vs Respiratory (IN, IT, aerosol)
- Clinical Endpoints – needs to mimic human disease
- Pivotal IND-enabling Studies under GLP 21 CFR part 58 requiring validated assays and associated equipment
- Robust statistical plan

SOUTHERN RESEARCH INSTITUTE

ROLE of ANIMAL MODEL "ANIMAL RULE"

Approval of Biological Products:

- *In some cases, human efficacy trials may not be feasible or ethical*

FDA may approve a product if:

- *"Animal Rule" requirements are met based on adequate and well-controlled animal studies*
- *Data from animal studies demonstrate that the product is reasonably likely to provide clinical benefit in humans*

SOUTHERN RESEARCH INSTITUTE

"ANIMAL RULE" APPLICABLE TO:

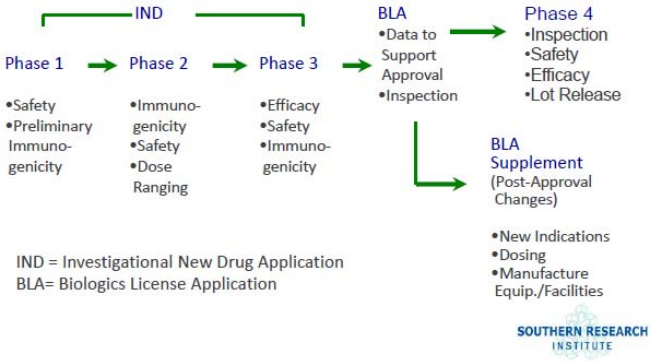
Development and procurement of MCM (Therapeutics and Vaccines) for:

- Smallpox: Modified Vaccinia Ankara (MVA), ST-246 & CMX001
- Anthrax: Recombinant Protective Antigen (rPA), antibiotics, monoclonals
- Plague: Subunit Vaccine based on F1 and V
- Tularemia: *F. tularensis* Live Vaccine Strain (LVS)

SOUTHERN RESEARCH INSTITUTE

REVIEW AND REGULATORY PATH FOR A CONVENTIONAL VACCINE

Vaccines: Goal is to develop a regimen that elicits protection immunity and is safe.



IND = Investigational New Drug Application
BLA= Biologics License Application

SOUTHERN RESEARCH INSTITUTE

PARALLEL ANIMAL STUDIES

Bridging Animal Data to Humans

- Pre-IND & "Phase I"
  - Model Development
  - Proof of Concept
  - Early Immunogenicity
- "Phase II"
  - Immunogenicity, Develop Bridging Data
  - Dose Ranging & Vaccine Schedule
  - Preliminary Challenge Studies
  - Continue to Develop Efficacy Studies
  - Develop Validated Assays, Equipment, etc.
- "Phase III"
  - Definitive or Pivotal Efficacy Studies (GLP)
  - Use Final Formulation
  - Bridge Animal & Human Immunogenicity Data
  - Statistical Plan
  - Use Validated Assays, Equipment, etc.

SOUTHERN RESEARCH INSTITUTE

ORTHOPOXVIRUS ANIMAL MODELS FOR SMALLPOX"

Established Models:

- NHP Variola
- NHP Monkeypox
- Marmoset Monkeypox
- Rabbitpox
- Dormice & CAST/EiJ mouse Monkeypox
- Vaccinia
- Cowpox
- Ectromelia Mouse

Tenet 2: The effect is demonstrate in more than one animal species expected to respond that is predictive for humans.

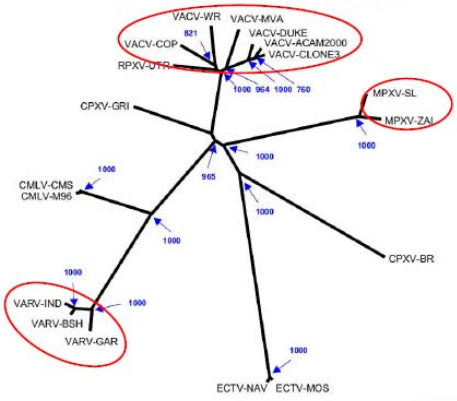
SOUTHERN RESEARCH INSTITUTE

Genus Orthopoxviruses

- Members: variola, monkeypox, vaccinia, cowpox, ectromelia, rabbitpox, camelpox, racoonpox, taterapox, buffalopox
- Similar morphologically
- Immunological related and confer protection against other members of genus

SOUTHERN RESEARCH INSTITUTE

Orthopoxvirus phylogeny



SOUTHERN RESEARCH INSTITUTE

Virology Journal 2006, 3:88

Characteristics of Orthopoxviruses

- Large dsDNA genome
- Encode ~ 200 proteins: RNA & DNA synthesis, immune evasion
- Replicate in the cytoplasm
- 2 infectious forms of virus:
- Intracellular mature virus (IMV), the majority of infectious progeny, very stable
- Extracellular enveloped virus (EEV), important for virus dissemination

SOUTHERN RESEARCH INSTITUTE

"MONKEYPOX NHP MODEL FOR SMALLPOX"

UTILITY FOR PRECLINICAL VACCINE DEVELOPMENT

SOUTHERN RESEARCH INSTITUTE

Comparison of Smallpox & Monkepox

Smallpox	Human Monkeypox
Variola	Monkeypox virus
Genus Orthopoxvirus	Genus Orthopoxvirus
~ 30 – 40% mortality	~ 1 – 10% mortality
Human-specific	Humans, monkeys, rodents
Eradicated	Africa – few hundred cases/year

SOUTHERN RESEARCH INSTITUTE

Monkeypox NHP Model Recapitulates Features of Human Smallpox

Breman and Henderson, 2002 NEJM, 346.

SOUTHERN RESEARCH INSTITUTE

DISEASE ENDPOINTS

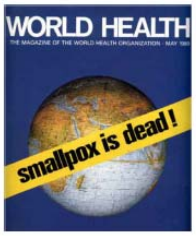
Severe disease is characterized by animals displaying the following disease endpoints after challenge with MPXV via parenteral or respiratory route:

- Pyrexia, Anorexia, and Weight Loss
- Lethargy, Depression, Rough coat, Edema
- Viremia: 6 to 8 logs at Euthanasia
- Development of pock lesions
- Coughing, Nasal discharge, Dyspnea
- Lung involvement & Respiratory Distress following exposure via respiratory routes
- Moribundity

Tenet 1: Pathophysiological mechanism of the disease is reasonably well understood and it is reduced or prevention by the product.

SOUTHERN RESEARCH INSTITUTE

CASE STUDY



The World Health Organization (WHO) Smallpox Eradication Program initiated in 1966 resulted in the disappearance of the disease, and the last reported case was in Somalia, 1977. In 1980, the WHO officially declared the eradication of smallpox.

- Resulted in cessation of routine vaccination
- Population immunity declined
- Concern of deliberate release of variola virus

SOUTHERN RESEARCH INSTITUTE

CASE STUDY cont'd

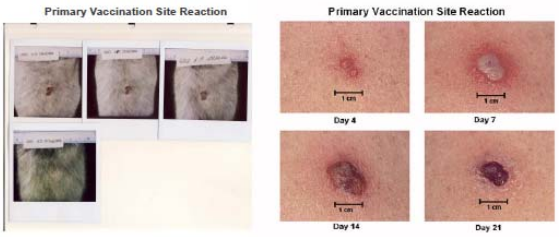
- Concerns with adverse side-effects may preclude large scale redeployment of the current smallpox vaccine (live VACV). Therefore, the development and evaluation of safer live vaccines is needed.
- MVA: derived by >500 passages of the parent virus in chicken embryo fibroblast cells resulted in deletion/mutations that severely restrict the replication and virulence of the vaccine. MVA provides a single round "pseudo live" immunization.

"A SINGLE VACCINATION WITH DRYVAX AND MVA CONFERS PROTECTION AGAINST LETHAL MONKEYPOX CHALLENGE VIA INTRAVENOUS ROUTE"

SOUTHERN RESEARCH INSTITUTE

Dryvax Elicits a Vaccine "Take" in Non-human Primates

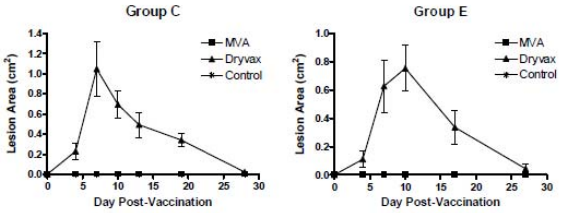
A. Macaque　　B. Human



Primary vaccination site reaction in NHP similar to human

SOUTHERN RESEARCH INSTITUTE

LESION SIZE AT VACCINATION SITE

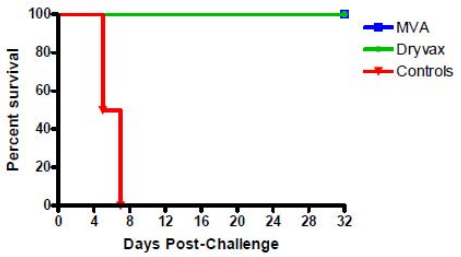


Tenet 3: The animal efficacy study endpoints are clearly related to the desired benefit in humans.

SOUTHERN RESEARCH INSTITUTE

Dryvax and MVA Vaccine Confer Protection against lethal Monkeypox Disease

Intravenous Challenge Model
($5x10^7$ PFU/mL)



Tenet 3: The animal efficacy study endpoints are clearly related to the desired benefit in humans.

SOUTHERN RESEARCH INSTITUTE

Further Demonstration of Vaccine Protection in the NHP Monkeypox Model

Gordon SN, Cecchinato V, Andresen V, Heraud JM, Hryniewicz A, Parks RW, Venzon D, Chung HK, Karpova T, McNally J, Silvera P, Reimann KA, Matsui H, Kanehara T, Shinmura Y, Yokote H, Franchini G. Smallpox vaccine safety is dependent on T cells and not B cells. J Infect Dis. 2011 Apr 15;203(8):1043-53.

Hirao LA, Draghia-Akli R, Prigge JT, Yang M, Satishchandran A, Wu L, Hammarlund E, Khan AS, Babas T, Rhodes L, Silvera P, Slifka M, Sardesai NY, Weiner DB. Multivalent smallpox DNA vaccine delivered by intradermal electroporation drives protective immunity in nonhuman primates against lethal monkeypox challenge. J Infect Dis. 2011 Jan 1;203(1):95-102.

Zielinski RJ, Smedley JV, Perera PY, Silvera PM, Waldmann TA, Capala J, Perera LP. Smallpox vaccine with integrated IL-15 demonstrates enhanced in vivo viral clearance in immunodeficient mice and confers long term protection against a lethal monkeypox challenge in cynomolgus monkeys. Vaccine. 2010 Oct 8;28(43):7081-91.

Buchman GW, Cohen ME, Xiao Y, Richardson-Harman N, Silvera P, DeTolla LJ, Davis HL, Eisenberg RJ, Cohen GH, Isaacs SN. A protein-based smallpox vaccine protects non-human primates from a lethal monkeypox virus challenge. Vaccine. 2010 Sep 14;28(40):6627-36.

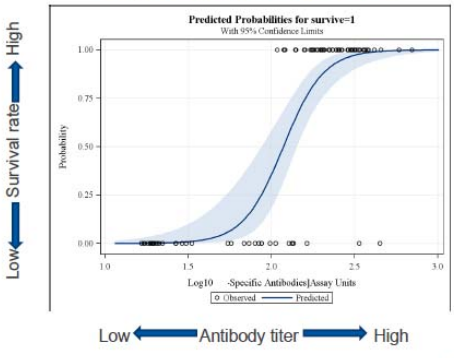
Hooper JW, Ferro AM, Golden JW, Silvera P, Dudek J, Alterson K, Custer M, Rivers B, Morris J, Owens G, Smith JF, Kamrud KI. Molecular smallpox vaccine delivered by alphavirus replicons elicits protective immunity in mice and non-human primates. Vaccine. 2009 Dec 11;28(2):494-511.

Tenet 3: The animal efficacy study endpoints are clearly related to the desired benefit in humans.

SOUTHERN RESEARCH INSTITUTE

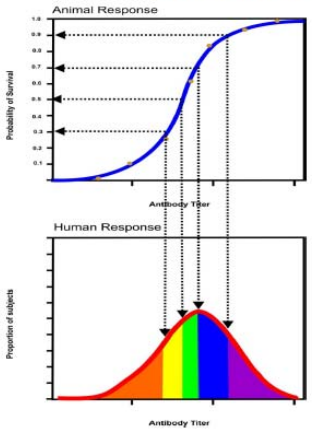
Defining Immune Correlates of Protection

Logistic Regression Model



SOUTHERN RESEARCH INSTITUTE

Bridging to Human Data



Tenet 4: The data generated in the animal study and the human studies allows selection of an effective dose in humans

SOUTHERN RESEARCH INSTITUTE

SUMMARY

1. Several animal models are in place to support preclinical development and evaluation of new vaccines and therapeutics for Biodefense.
2. The FDA “Animal Rule” requires the utility of appropriate and standardized animal models.
3. Pivotal IND-enabling efficacy studies must be conducted in compliance with GLP 21 CFR part 58.
4. The NHP Monkeypox Model is appropriate for the development of MCMs for biodefense and emerging pathogens.

SOUTHERN RESEARCH INSTITUTE

M E M O