UTILIZATION OF THE BARDA NON-CLINICAL STUDIES NETWORK TO FACILITATE EFFICACY EVALUATION OF SMALLPOX COUNTERMEASURES

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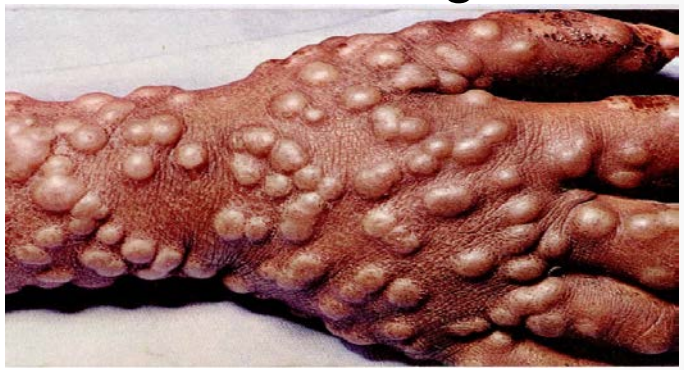
Resilient People. Healthy Communities. A Nation Prepared.

Outline

- Why is BARDA concerned about smallpox?
- How is BARDA addressing the threat of smallpox?
- How are drugs evaluated and approved to treat smallpox infections?
- How is BARDA supporting the development of smallpox drugs?
- What impact has the BARDA Nonclinical Studies Network had on the development of smallpox drugs and preparing the nation for a smallpox outbreak?

Why is BARDA Concerned About Smallpox?

- Smallpox is caused by the variola virus and is spread by close human contact resulting in:
  - Primary viremia
  - Prodrome
  - Viral dissemination
  - Secondary viremia
  - Lesions
  - Death (often due to systemic organ failure or septic shock)



- Mortality rate > 30% and responsible for more deaths than any other infectious disease (> 500 million deaths in 20th century alone).

How is BARDA Addressing the Threat of Smallpox?

- Though smallpox was eradicated in 1980 and natural re-emergence of smallpox is unlikely, a deliberate release would constitute an international public health emergency.
- BARDA is supporting the development of multiple smallpox MCMs:
  - Tecovirimat (SIGA Technologies)
  - Brincidofovir (Chimerix)
- Given the lack of natural disease and the high mortality rates, smallpox antiviral drugs must be evaluated for efficacy in animals under the FDA Animal Rule.

FDA Animal Rule

- The FDA Animal Rule allows for the approval of MCMs for the treatment of life-threatening conditions due to a CBRN exposure based on the results from animal efficacy studies when human efficacy trials are not feasible or ethical.
  - The mechanism of action of both the CBRN agent and the MCM are well understood.
  - The effect of the MCM is demonstrated in one or two animal species that are predictive of the human response.
  - The animal study endpoint (i.e. mortality) is clearly related to the desired benefit in humans.
  - The MCM behaves the same in both humans and the chosen animal model.

The Need for Alternative Models of Human Smallpox

- There are no accepted animal models for human smallpox virus
  - Host range of variola is restricted to humans
  - NHP models of variola infection require high challenge dose (> 10^9 pfu)
  - Variable mortality rates are observed
- FDA and the scientific community agreed these were poor models that did not recapitulate the early stages of disease and were unlikely to provide ability to predict the efficacy of countermeasures against smallpox.

The Need for New Animal Models of Smallpox

- In 2011, the FDA, USG, drug developers, and members of the scientific community met to explore alternative models. The FDA provided the following guidance:
  - "Based on feedback from the Advisory Committee and additional discussions within CDER, we recommend that you perform adequate and well-controlled studies in models of orthopoxvirus infection in two animal species which include assessments of dose-exposure-response. During the Advisory Committee, the rabbit/rabbitpox model or mouse/ectromelia model were discussed as possible options to consider."
- This represented an opportunity for BARDA to use the BARDA Non-Clinical Studies Network (NSN) to develop models that would benefit for both USG and sponsors.

The Benefits of a Single Developer of Animal Models

- The development of a single model by BARDA (instead of each developer trying to develop their own model) has many advantages:
  - Avoids duplication of efforts
  - Saves the USG money
  - Reduces the number of animals sacrificed to develop the model
  - Ensures standardization for drug evaluation and allows “head-to-head” comparisons
  - Develops “drug independent” models for universal efficacy evaluation of potential medical countermeasures
  - Makes the reagents and models available to other product developers

The BARDA Nonclinical Studies Network

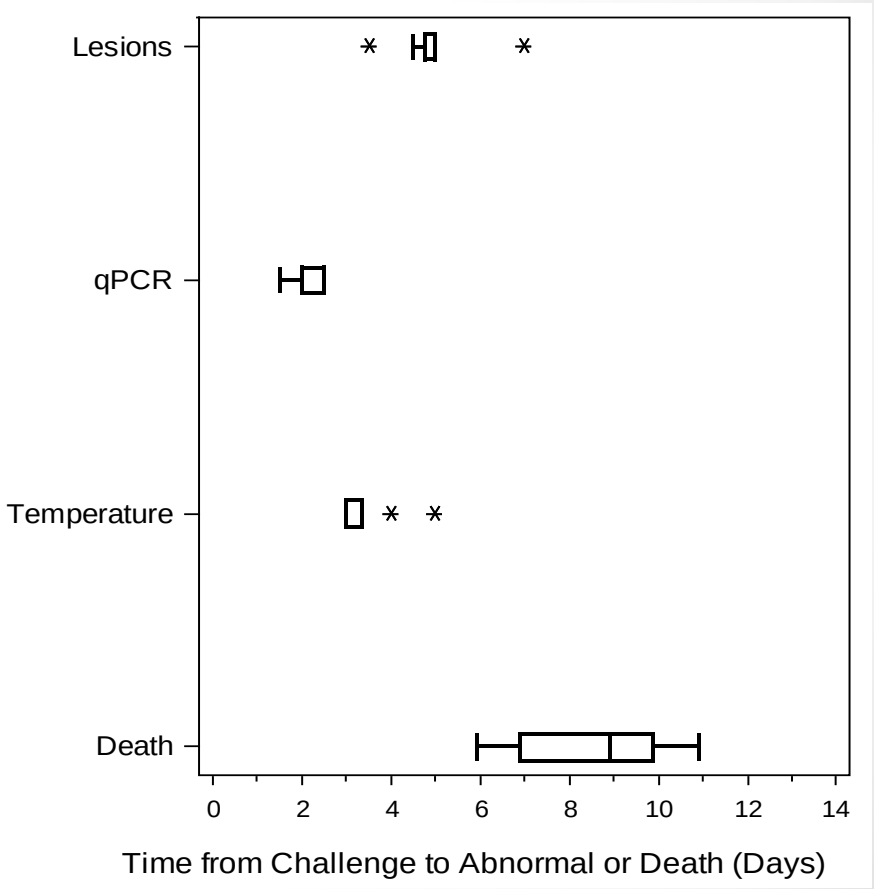
- Under the BARDA NSN, BARDA solicited competitive bids from network members to:
  - Generate standard challenge reagents of RPXV and ECTV
  - Perform the necessary studies for model characterization (natural history, serial sacrifice)
  - Identify biomarkers and clinical signs that sponsors can propose as triggers for medical intervention
  - Perform these activities while maintaining an active dialogue with the FDA to ensure effort is correctly directed

FDA's Role in Developing Smallpox Animal Models

- This has been a collaborative effort between BARDA, CROs and CDER's Division of Antiviral Products under PreIND 118,305 in which CDER has provided critical feedback regarding:
  - Design of study protocols
  - Generation and characterization of the challenge agent
  - Determination of an appropriate challenge dose
  - Animal weight and age for use in challenge studies
  - Mortality endpoints
  - Euthanasia criteria
  - Clinical triggers for initiating treatment

The Rabbitpox Model of Human Smallpox

- Generated and thoroughly characterized RPXV reagents.
- Demonstrated that the stages of RPXV disease in infected animals were similar (though compressed) to those observed in humans infected with smallpox.
- Identified reproducible clinical signs that could serve as triggers for initiating treatment.



The Ectromelia Model of Human Smallpox

- Though multiple ectromelia models have been developed and published, the FDA signaled a preference for a respiratory challenge model resulting in high mortality at a low challenge dose.
- Two CROs developed ectromelia models in Balb/c mice and C57/Bl6 mice.
- Analysis of data during model development led FDA to indicate clear preference for the Balb/C model.

The Impact of the BARDA Non-Clinical Studies Network

- BARDA and its CROs developed reproducible animal models of human smallpox in mice and rabbits that could be used to evaluate the efficacy of smallpox MCMs.
- FDA informed product developers that the rabbitpox model and the parameters of the ectromelia model may be used to perform pivotal studies in support of the efficacy evaluation of smallpox MCMs.
- The two product developers are currently using the models to conduct pivotal studies under the Animal Rule.

The Impact of the BARDA Non-Clinical Studies Network

- BARDA was able to use the Non-Clinical Studies Network to:
  - Develop a product independent animal model of human smallpox in two species
  - Avoid duplication of effort among sponsors and USG agencies
  - And save the Government time and money

Thank You!