

# Challenges Facing Sponsors Seeking Licensure of Vaccines Using the Animal Rule

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## Introduction

No vaccine has yet been licensed using the Animal Rule, a set of regulations which permits the assessment of vaccine efficacy in animals in cases where human trials are not feasible or ethical. This regulatory approach still requires Sponsors to meet the manufacturing, quality, preclinical and clinical standards required under more traditional pathways to licensure. Licensure using animal models still poses the risk that the vaccine(s) may not work as intended in humans, thus efficacy testing using the Animal Rule could present a more complicated path to licensure than the more traditional route of efficacy testing in humans. It is particularly challenging to develop and refine relevant animal models that mimic human disease, to demonstrate vaccine efficacy and amelioration of disease using animal challenge models and to bridge the animal responses to human immune responses to predict clinical benefit. Defining the required level and mechanism of protection, the onset and duration of immunity, and identifying the immune response(s) and assays that correlate with protection (especially when the mechanisms of protection are not clearly identified) must be addressed in product development plans so that the regulatory, clinical and nonclinical strategies effectively advance the product. Validation of assays, processes and animal model components will be necessary. The most significant challenge is bridging the animal and human responses following vaccination in a way that demonstrates sufficient similarity to support the claim that the vaccine is likely to provide clinical benefit in humans. As deviations from product development plans result in significant cost and schedule ramifications, frequent communication with the FDA regarding study designs and strategy is essential for success. This presentation will address these challenges and review efforts by Alliance members and individuals from government to further dialogue and identify pathways forward.

## The Alliance for Biosecurity

The Alliance for Biosecurity works to promote a stronger, more effective partnership between government and the BioPharma industry to better develop critically needed medical countermeasures. The Alliance also seeks to usher in a new era in the prevention and treatment of severe infectious diseases that present global security challenges. This new era will be characterized by the capacity to rapidly develop, produce and stockpile medical countermeasures for the country. The Center for Biosecurity and BioPharma members of the Alliance are striving to create a long-term national security vision for achieving and sustaining defenses against a range of current and future biothreats.

## What is the Animal Rule?

- An opportunity to license unique products that would otherwise remain in regulatory limbo with no clear pathway for approval.
- The FDA will consider the animal data to support licensure of a product only when the following conditions are met:
  - 1) The pathophysiological mechanism of toxicity and the prevention or substantial reduction of this toxicity by the vaccine are reasonably well understood in the animal models.
  - 2) The effect is demonstrated in a single sufficiently well-characterized animal model for predicting the response in humans, or independent substantiation of the effect in multiple animal species.
  - 3) The animal study endpoint clearly relates to the desired benefit in humans.
  - 4) The kinetics and pharmacodynamics of the product in animals and humans allows for selection of an effective human dose.
- Sponsors are expected to demonstrate that the effect of the product in animals is reasonably likely to predict clinical benefit in humans.
- Animal Rule approval is subject to requirements (e.g., post-marketing studies, restrictions on use, specialized information package for recipients and termination of requirements).
- Nonclinical studies adhere to the Animal Welfare Act (7 U.S.C. 2131 et seq.).

## What the Animal Rule is Not!

- Does not apply to products when approval can be based on a demonstration of efficacy as described in other regulations such as 21 CFR 601.41
- Does not address evaluation of safety as safety must be demonstrated in human volunteers in clinical trials (i.e., Phase 1, 2 and 3).
- Does not equal a short cut to approval.

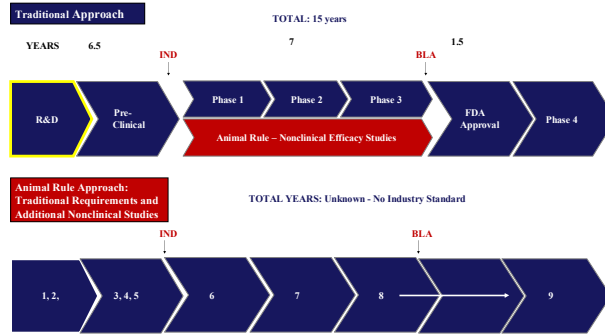
Table 1 Addressing Animal Rule Requirements in Nonclinical Studies

Requirement	Study Design
Label indication	<ul style="list-style-type: none"> <li>• Identify animal models that are susceptible to pathogen by the route of exposure intended for the label indication</li> </ul>
Understand the disease	<ul style="list-style-type: none"> <li>• Determine the lethal or effective dose for 50% of animals (LD<sub>50</sub> ED<sub>50</sub>)</li> <li>• Establish natural history and disease progression in animal models</li> </ul>
Demonstrate efficacy in one or more species which react as humans would with similar endpoint	<ul style="list-style-type: none"> <li>• Test article administration combined with an active challenge</li> <li>• Evaluate immune response</li> <li>• Establish assays to be used to investigate correlates of protection</li> </ul>
Select effective human dosage	<ul style="list-style-type: none"> <li>• Demonstrate efficacy in animal challenge studies</li> <li>• Evaluate dosage in clinical trials and link to correlate of protection</li> </ul>

Table 2 Considerations in Animal Model Selection

Issue	Considerations
Species	<ul style="list-style-type: none"> <li>• Disease in the animal model has to compare to human disease and pathogenesis</li> <li>• Availability of sufficient animals</li> <li>• May need multiple animal models to satisfy Animal Rule requirements</li> </ul>
Correlate of Protection	<ul style="list-style-type: none"> <li>• What mechanisms of protection have been identified for the pathogen?</li> <li>• Need an assay that measures relevant immune responses in animals and humans</li> <li>• Is assay species-neutral to facilitate comparisons between species?</li> <li>• Will have to be able to predict clinical benefit</li> </ul>
Study Design	<ul style="list-style-type: none"> <li>• What is the intended label indication?</li> <li>• Is the challenge material characterized and have the route and dosage been determined?</li> <li>• What are the endpoints of the study?</li> <li>• What manipulations are required?</li> <li>• Is the vaccine available and released for use?</li> <li>• What are the statistical considerations?</li> <li>• Draft FDA Guidance: "Animal Models — Essential Elements to Address Efficacy Under the Animal Rule."</li> </ul>
Facility	<ul style="list-style-type: none"> <li>• Is there adequate space and appropriate equipment for the study?</li> <li>• When can the facility perform the study (queue)?</li> <li>• What is the biosafety containment level?</li> </ul>

Figure 1 Product Development Timelines for Traditional vs. Animal Rule Licensure Pathways



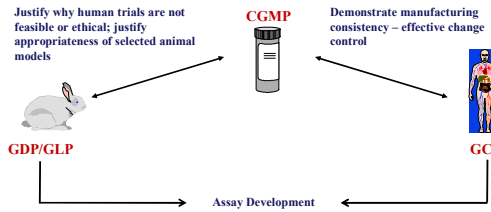
## HHS Technology Readiness Levels for Medical Countermeasures Products



Figure 2 The Challenges of Balancing Manufacturing Development, Animal Model Development and Clinical Trials

Successful bridging of animal responses to human responses to predict clinical benefit from pivotal animal studies is critical to licensure using the Animal Rule. Consideration should be given to identifying species-neutral assays for comparison of data across species, and to functional assays for predicting clinical benefit. Considerations should also be given to harmonizing vaccine lot, blood draws and functional assays between clinical and nonclinical studies with the goal of demonstrating relevant responses in animals and clinical samples.

- The goals of integrating studies include:
- Bridging nonclinical to clinical immune response to vaccination
  - Defining a correlate of protection
  - Supporting selection of an effective dose for pivotal studies



CGMP, Current Good Manufacturing Practices; GDP, Good Documentation Practices; GLP, Good Laboratory Practices; GCP, Good Clinical Practices

Figure 3 Integration of Development Processes

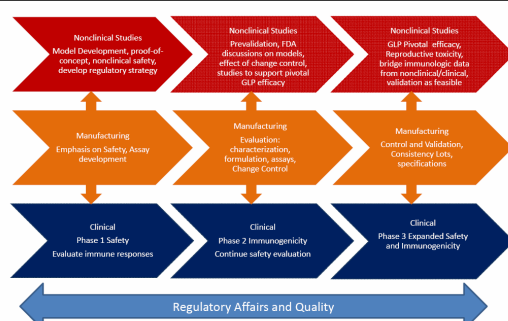
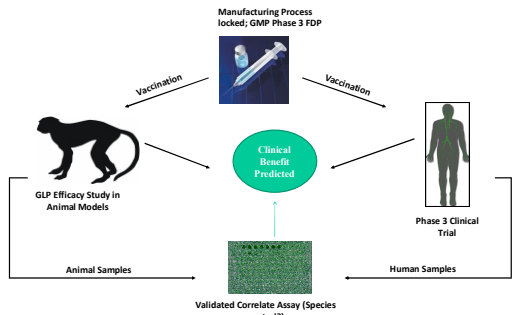


Figure 4 The Hardest Challenge: Bridging the Protective Immune Response



## Alliance Activities

Much can and should be done by public and private partners in advance of a bioterrorist attack or natural pandemic to minimize illness and death, as well as catastrophic social, economic and political disruption. The Alliance pursues opportunities to partner with government and other stakeholders to develop new solutions aimed at greatly enhancing our country's ability to defend itself against biothreats.

- Sample Alliance activities include:
- Educating members of Congress and other government stakeholders about biosecurity and drug development issues.
  - Promoting the goals of the Biodefense Advanced Research and Development Authority (BARDA) within HHS.
  - Publishing in Nature Biotechnology an article about the challenges of animal model development under the FDA's Animal Efficacy Rule and presenting proposed solutions.
  - Pursuing a public-private collaboration on animal model development issues.
  - Members of the Alliance and experts from NIAID, USAMRIID, DTRA, and BARDA have been working together to develop a joint database of natural history and control data for Animal Models relevant to therapeutic countermeasures. The purpose of the database is to share data, increase scientific understanding, accelerate development of needed countermeasures, and decrease overall use of animals.
  - Providing venues for stakeholder dialogue about key biosecurity policy issues.
  - Developing and presenting consensus policy proposals to government.

## Alliance for Biosecurity Members

- MEMBERS**
- Bavarian Nordic
  - Center for Biosecurity of UPMC
  - Cangene Corporation
  - DOR BioPharma, Inc.
  - DynPort Vaccine Company LLC, A CSC Company
  - Elusys Therapeutics, Inc.
  - Emergent BioSolutions
  - Hematech, Inc., a subsidiary of Kyowa Kirin
  - Human Genome Sciences, Inc.
  - NanoViricides, Inc.
  - Pfizer Inc.
  - PharmAthene
  - SIGA Technologies
  - Unither Virology LLC, a subsidiary of United Therapeutics
- ASSOCIATE MEMBERS**
- Battelle Biomedical Research Center
  - Lovelace Respiratory Research Institute

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## References

- 21 CFR 601.91 Subpart H, "Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible"
- Draft FDA Guidance: "Animal Models — Essential Elements to Address Efficacy Under the Animal Rule"
- Gronvall et al. The FDA animal efficacy rule and biodefense. Nat. Biotech. 2007 Oct; 25: 1084-1087.