

The “Animal Rule”: Use of animal models to study vaccines for filovirus infections

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Will cover the following issues...

- Background information on the “Animal Rule”
- What type of data the regulator is looking for
- Issues to consider when developing animal models (for both disease and efficacy)

The Rule was needed because..

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

- Epidemiology precludes “field trials”, the usual source of efficacy data, and
- Cannot conduct human challenge/protection studies.

The “Animal Rule”

“Approval of Biological Products (New Drugs) When Human Efficacy Studies Are Not Ethical or Feasible”

Note: “Animal Rule” is not the official name

Request For Comments: 62 FR 40996 (July 31, 1997)

Proposed Rule: 64 FR 53960 (Oct 5, 1999)

Final Rule: 67 FR 37988 (May 31, 2002)

Regulations: 21 CFR § 601.90-95 (biologicals)
21 CFR § 314.600-650 (drugs)

<http://www.gpoaccess.gov/cfr/index.html>

FDA may approve a product for which ...

- Human safety has been established, and
- “Animal Rule” requirements are met – based on adequate and well-controlled animal studies, the results of which establish that the product is reasonably likely to provide clinical benefit in humans.

Rely on evidence of effectiveness from animal studies only when:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.
 - Do we understand the pathogenesis/pathology of filoviruses reasonably well?
 - Do we understand the differences between Ebola and Marburg viruses? And between strains of each virus?
 - Do we understand how the vaccine “works”?

Rely on evidence of effectiveness from animal studies only when:

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].

Not the “Two Animal Rule”

- Which animal models (species & strains) are most relevant?
- Vaccine perspective: does the immune response in animals resemble that of humans?

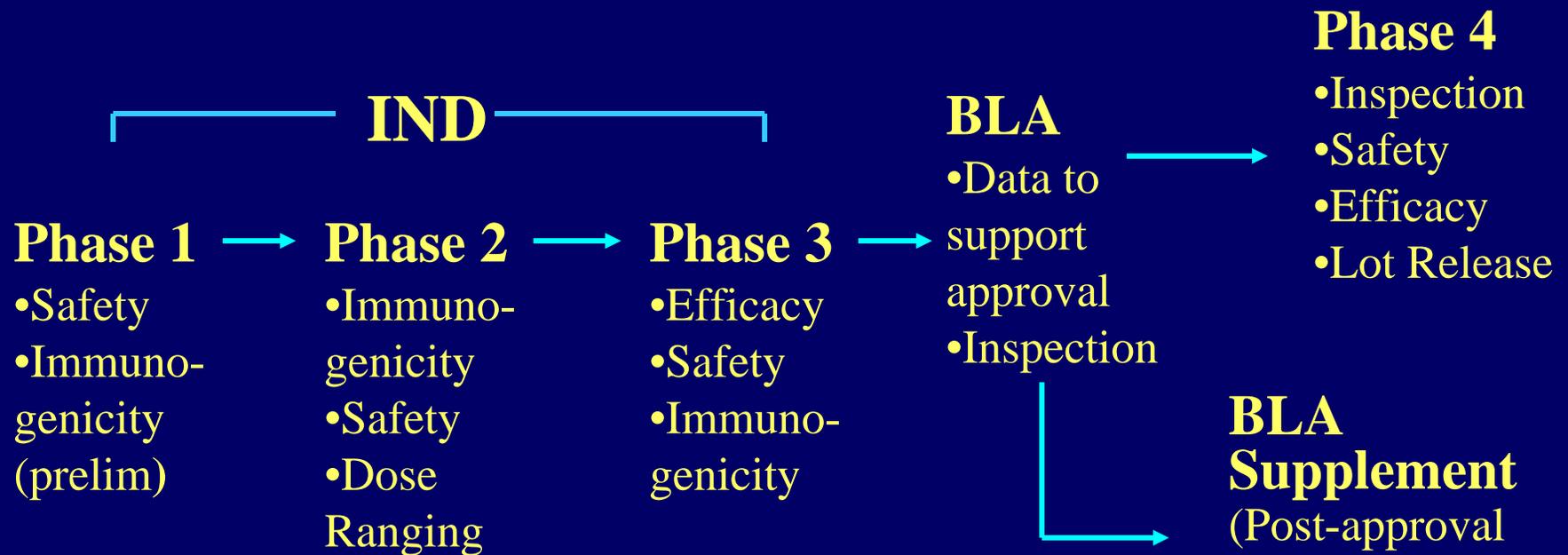
Rely on evidence of effectiveness from animal studies only when:

3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity (i.e.: model should cause death or major morbidity).
- Does the disease induced in animals resemble that seen in humans?

Rely on evidence of effectiveness from animal studies only when:

4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allows selection of an effective dose in humans.
- Vaccine perspective: what components of the immune response are important for protection and how can they best be measured?
 - Vaccine perspective: need to be able to bridge the immune response data from animals to humans.

Stages of Review and Regulation for a Conventional Vaccine



IND = Investigational New Drug Application
BLA = Biologics License Application

Animal Studies Should be Developed Along a Parallel Track to the Clinical Studies

“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 (challenge) Studies (GLP)
- Use final formulation
- Bridge animal & human immunogenicity data
- Prospective statistical plan
- Use validated assays, equipment, etc..

Meet with FDA on regular basis to discuss findings & future studies

Preclinical Pharm/Tox Animal Studies

Safety studies have little/nothing to do with the “Animal Rule” studies, and should be conducted prior to entry into Phase I.

Pharm/Tox Studies = Safety = pre Phase I

“Animal Rule” Studies = Efficacy = post Phase I

How are the animal models selected?

- Selection of species made on a case-by-case basis
 - Consult with outside “experts”
- Based on information in the literature
 - E.G.: Zaucha, GM, et. al., *The Pathology of Experimental Aerosolized Monkeypox Virus Infection in Cynomolgus Monkeys*, Lab Invest, 81 (12), p. 1581, 2001.
- Recommendations made at scientific meetings
 - E.G.: Anthrax (2002), Plague (2004), Filovirus (2007)
- Sponsor will need to justify choice of model to FDA

Some issues to be considered when developing an animal disease model

- Describe clinical characteristics of human disease; including symptoms, incubation period, progression and pathology (clinical, gross & histopathology).
- Describe usual outcome of untreated human cases.
- Does animal model mimic these human findings?
- How do different exposure routes impact the disease in animals? I.E.: if different from human exposure route, must justify why animal study was conducted that way.

Some issues to be considered when developing an animal disease model

- To what degree does the animal data compare with human data?
- Are there any clinical biomarkers that indicate pending onset of severe disease or death?
- How reproducible is the animal model?

Some issues to be considered when developing an animal efficacy model

- How does the timing of the intervention in the animal studies compare to what happens in the clinical setting?
- Are there concerns about immune response differences between species?
- How will the immune data be bridged to the human data?
- Is there a correlate of protection (i.e.: if this correlate is attained, will have protection)?

For example: Develop a detailed table describing the finding for each species – will help highlight gaps in knowledge

	Humans	Monkey (list each species of interest)	Rodents (list each species & strain of interest)
Clinical Disease			
Immunology			
Pathology			

Appropriate Facilities

- Select agent requirements
- Small and large animal model capability
- Experienced staff
- Validation experience
- BSL-3 or BSL-4 capability: only a handful of facilities in US that can conduct aerosol studies with infectious agents in NHP.
- GLP: very few facilities in the US can conduct infectious agent aerosol challenge studies in accordance with GLP requirements.

GLP & AWA Requirements

All studies subject to this Rule must be conducted in accordance with preexisting requirements under the Good Laboratory Practices (21 CFR § 58) regulations and the Animal Welfare Act (7 U.S.C. 2131).

21 CFR § 58 is being amended to reflect this requirement.

CBER: GLP expected for the definitive/pivotal animal studies – not necessary for the pilot studies. Also, if you want to describe an animal study in the label (package insert), then it should comply with GLP.

Assays & Immunology

- Considerable R&D may be necessary to develop and validate assays.
- Assay performance data:
 - Validation for both animal & human assays before pivotal/definitive study.
 - Goal should be a validated functional assay (or one that has been correlated to a functional assay).

By the time the definitive animal efficacy study is conducted, should be able to:

- Predict the outcome of negative controls when infected with a predetermined route, dose, and strain of the infectious agent.
- Preparation & administration of the infectious agent should be consistent with earlier studies that led to the design of the definitive study.
- Use validated assays to monitor the response and bridge data to humans. Non-validated assays will also be useful.
- Have a prospective statistical plan in place.

Potential misunderstandings

- If you can get FDA approval using another route – must use this alternative.
- Safety must still be demonstrated in human subjects enrolled in Phase I, II & III clinical trials.
- The Rule is not an Accelerated or Fast-Track approval.
- The Rule is not a short-cut to approval, in fact, may take longer.

The purpose of the “Animal Rule” is to develop a product for use in humans, not animals.

Summary

- Route of exposure important – should mimic what is expected during an attack or outbreak.
- Consider “life-history” type studies to learn more about the disease in each species.
- Will probably not have “everything” in one animal model – justification to develop more than one model.
- Need to address/fill the gaps of knowledge.

Summary

- The “Animal Rule” is new to both industry and the FDA – collaboration is essential for success.
- Early and frequent communication with the FDA works best.
- Expect interactions with FDA Advisory Committees:
 - In some cases, prior to animal efficacy trials, for concurrence with concepts.
 - Following Agency’s BLA review, prior to approval.

Acknowledgements

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- Barbara Styr, CDER/OND



I've heard this talk
30x already, BUT,
I'm still awake 😊

Thank you – Questions?

Animals Study Design Challenges

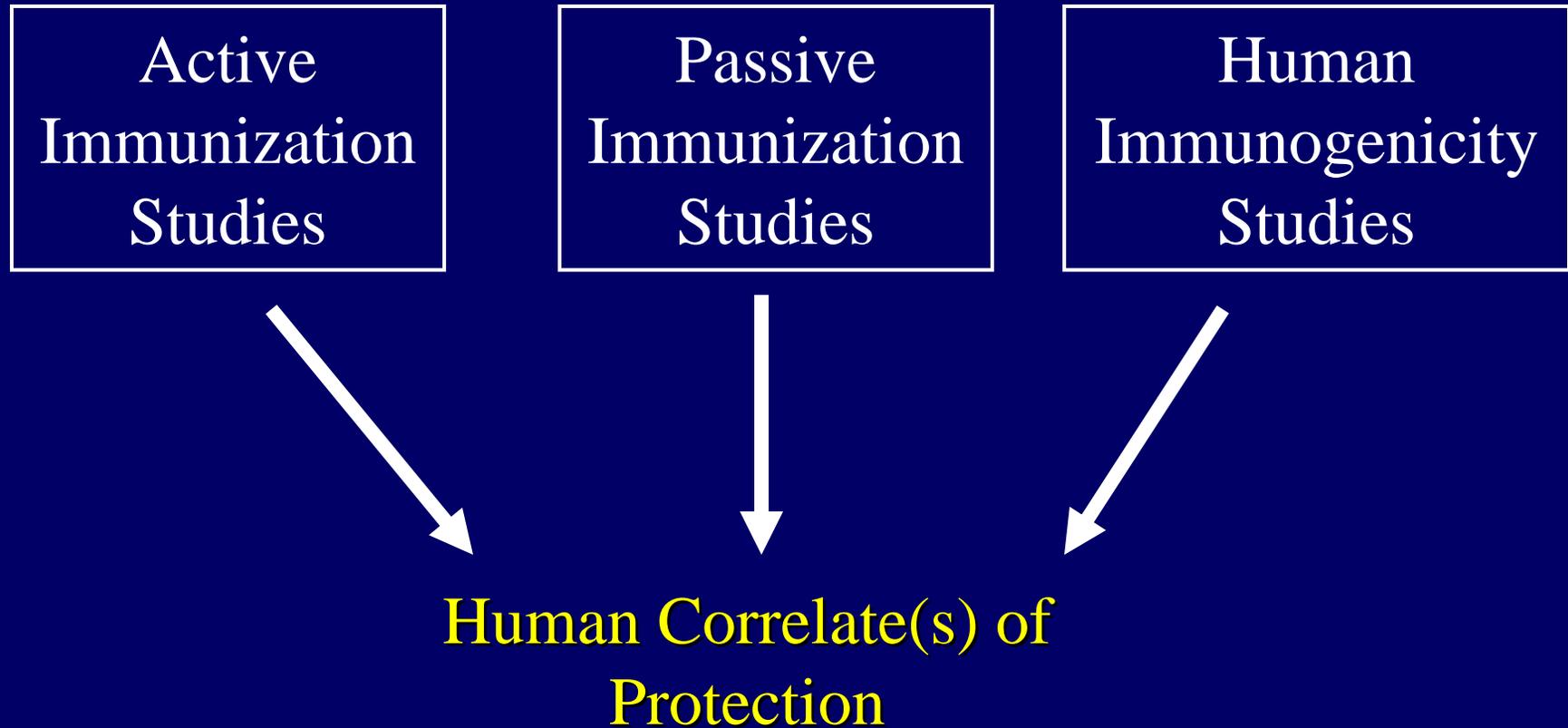
- The label indication. Pre-exposure/post exposure? Immune status of subject?
- Route of exposure. Mimic human exposure routes.
- Endpoints of animal studies. IACUC
- Appropriate challenge dose. Challenge route, species of animal and strain of infectious agent.
- Statistical considerations. Rodents/Rabbit vs. NHP
- Protection against multiple infectious agent strains. If more than one strain – which strains should be tested?

KEEP VARIABLES BETWEEN STUDIES TO A
MINIMUM

Example of studies that may needed

- Active immunization studies in animals
- Passive immunization studies in animals
- Human Immunogenicity Studies
- Human Safety Studies

Three Pronged Approach



What immunological assays? Goal should be a validated functional assay (or one that has been correlated to a functional assay).