Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Studies Are Not Ethical or Feasible

or

The “Animal Rule”

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Final Rule

New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

Federal Register 67: 37988-37998, 2002.

21 CFR 601.90 - 95 (biologics)

21 CFR 314.600 – 650 (drugs)

Not apply to devices

Not EUA

Not an Emergency Research IND

Not a Treatment IND

General Perspective and Take Home Message

- Animal rule represents a major departure in approvals
  - Least preferred route of approval
  - Used when all other means of approval are not acceptable
  - Regular clinical studies preferred despite the difficulties
    - Scattered clinical populations
    - Unpredictable and sporadic nature of event
  - A second preference is a clinical study using surrogate markers, e.g., ciprofloxacin for anthrax

General Perspective and Take Home Message

- Essentially, approval under the Animal Rule is based on a theory. This approach stands in stark contrast to the traditional regulatory perspective of the FDA and scientific experience on the use of animal models of disease.
- Examples,
  - **Animal models for the treatment of cancer or sepsis do not reliably predict clinical outcome**
  - **Clinical theories of efficacy without benefit of clinical trials maybe wrong no matter how compelling they seem**
    - **Steroids and brain trauma**
    - **Anti-arrhythmia and irreversible progression from benign to fatal**
- The Animal Rule is not a quick and easy pathway
  - **Deliberately rigorous and occurs within a framework ordinarily used for clinical studies plus additional burdens, e.g., establishing why something works**

Approval Based on Evidence of Effectiveness in Animals

- FDA may grant marketing approval…based on adequate and well-controlled animal studies…likely to produce clinical benefit
- May take into account other data, including human data
- …rely on evidence from…animals to provide substantial evidence of effectiveness

Background and Introduction

- Outright approval
  - Essentially adopts the same standards for clinically based approvals and applies them to laboratory based studies. Just as more than one clinical trial is the standard for demonstrating efficacy, testing in multiple species is the standard for the Animal Rule
  - Safety remains to be established through human experience
- Approvals - only pyridostigmine at this time; ciprofloxacin for anthrax was based on a surrogate marker

Final Rule – Requirements or 4 Pillars

- FDA will rely on animal efficacy data only where:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product
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

Final Rule – Requirements or 4 Pillars (continued)

FDA will rely on animal efficacy data only where:

3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity

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

Animal Rule – Application and Characteristics

- Applied to far ranging settings– infectious disease, chemical insults to the nervous system, radiation injury
- Emphasizes understanding of mechanisms of action for efficacy and toxicity
- Increased need for predictability of laboratory animal studies relative to clinical problems
- Focuses on differences between species in response
- Places premium on careful experimentation and model building

GLP

- Documentation and responsibilities: protocols, study reports, study directors, archiving, QA/C
- Verification of test system and test article under conditions of use – e.g., strength and stability, numbering of animals, chow
- Experimental conditions relating to animal use
- Non-GLP data may be excluded as information forming the basis of approval. May be used as supporting information
- GLP vs. non-GLP, no such thing as almost GLP
- Exemptions and deviations
- Agency discretion

Animal Rule and Some Products for Application to Counter Terrorism and Medical Products of Long Standing Interest such as Treating Radiation Injury

- Not a collection of studies which is consistent with or supports a proof-of-efficacy concept
- Some critical laboratory studies may be unusable and/or not repeatable – ethics, facilities, technique,
- Continuity of empirical data - consistency of the test article and its relationship to the product being approved

Substantial Evidence – the ‘Golden’ Standard

“Evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof”

Substantial Evidence

- Drawn from “adequate and well-controlled investigations”
- Conclusions reached fairly and responsibly by experts (FDA) that the therapeutic will have the effects as claimed under the conditions of use
- Effects are clinical significant and cannot be solely statistically in nature

Adequate and Well-controlled

- Suitable subjects – represent the population intended for use
- Minimizes potential for bias in study design by investigator
- Reduces confounding factors
- Permits quantitative evaluation
- Test article is standardized for identity, strength, purity, quality, and dosage form
- Uncontrolled studies are corroborative and supportive

Sec 601.90 (similarly for 314.600)

"…when results of those animal studies establish that product reasonably likely to provide clinical benefit in humans"

Often confused with an important pharmacodynamic measure, e.g., correction of neutropenia

Effective dose in humans based on

- Pharmacokinetics
- Pharmacodynamics

Approval Subject to Three Requirement

1. Postmarketing Studies

   To verify and describe the product's clinical benefit when feasible and ethical (i.e., use due diligence to prove effectiveness in a clinical situation). May not be feasible until the event arises

2. PM restrictions as need to assure safe use, commensurate with product specific safety concerns. For example, distribution may be restricted to certain facilities or health care providers with special training or experience

Approval Subject to Three Requirement

3. Labeling for recipients
   - Provided prior to use
   - Explain that product's approval based on efficacy studies conducted in animals alone
   - Indication(s)
   - Directions for use (dosage and administration)
   - Contraindications
   - Adverse Events
   - Other relevant information

Reasons to Withdraw Approval

- PM clinical study fails to verify benefit
- Applicant fails to perform PM study with due diligence
- Experience shows that PM restriction are inadequate to ensure safe use of the product
- Applicant fails to adhere to PM restrictions
- Promotional materials are false or misleading
- Other evidence demonstrates that product is not safe or effective

Pyridostigmine

- Pretreatment for use against nerve agents, GD (soman); carbamylation of AChE
- Useful only in conjunction with atropine
- Carbamylation of other ChE as well as AChE
- Two pivotal animal study
  - Multiple arm study with controls
  - Animals randomized to treatment
  - Investigators “blinded” to treatment
  - Mortality as outcome measure
- Also tested in several other species

Pyridostigmine

- Protective ratio varied among animals
- AChEI, the theoretical mechanism of action, was not always consistent with protective effect

Hypothetical Study of an Anti-Radiation Drug or Biological - The Claim - XYZ Increases Survival by Preventing Infection after ARS

Case A – A 3 arm study using either XYZ alone, XYZ in combination with antibiotics or no treatment was conducted. XYZ demonstrated the ability to correct neutropenia in ARS, but did not demonstrate by itself an increase in the amount of radiation causing death. But the combination arm with antibiotics demonstrated benefit. Is XYZ approvable as a stand alone for increasing survival after ARS?

What is the medical benefit of XYZ itself?

Improved survivability? – didn't show benefit alone

Perhaps the actual question was whether XYZ enhanced ability to ward off infection in conjunction with antibiotics.

If so - was the study designed properly and did the study demonstrate the effect?

Well - no, it lacked an antibiotic arm alone. Cannot determine enhancement by XYZ.

Hypothetical Study of an Anti-Radiation Drug or Biological - The Claim - ABC Increases Survival from Bleeding Disorders after ARS

Case B – Product ABC is thought to improve neutropenia and thrombocytopenia.

ABC is demonstrated to have a survival benefit in ARS and survival in the animal model was independent of improvement in neutropenia but strongly dependent on correction of platelet count

Human studies demonstrate ABC corrects neutropenia but does not effect thrombocytopenia

Is ABC approvable?

Conclusions – Animal Rule

- Animal rule represents a major departure in approvals
- Will represent a challenge to industry and government