

An Overview of the Regulations Commonly Known as the *Animal Rule*

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**DEPARTMENT OF HEALTH AND
HUMAN SERVICES**

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 98N-0237]

RIN 0910-AC05

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

AGENCY: Food and Drug Administration,
HHS.

ACTION: Final rule.

Animal Rule – Regulatory Citations

Drugs

- Subpart I – Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible
- 21 CFR Parts 314.600-650

Biological Products

- Subpart H – Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible
- 21 CFR Parts 601.90-95

The Animal Rule

Efficacy

- Efficacy is established based on adequate and well-controlled studies in animals
- “...when the results of those animal studies establish that the drug product *[or the biological product]* is reasonably likely to produce clinical benefit in humans.”

Quote from 21 CFR 314.610(a) for drugs and 21 CFR 601.91(a) for biological products

Safety

- Safety is evaluated “under the preexisting requirements for establishing the safety of new drug and biological products.”

Quote from See 67 FR 37988 at 37989, May 31, 2002

Scope of the Animal Rule

The Animal Rule can be used only when the following four circumstances are met:	
The product is intended to ameliorate or prevent a serious or life-threatening condition caused by exposure to a lethal or permanently disabling toxic chemical, biological, radiological or nuclear substance <i>[often referred to as a CBRN substance]</i>	✓
Human efficacy studies cannot be conducted because deliberate exposure of healthy volunteers to the substance would be unethical	✓
Field trials to study effectiveness of the product after an accidental or hostile exposure are not feasible	✓
The product cannot be approved or licensed for the proposed indication based on efficacy standards described in other parts of the regulations	✓

Animal Rule – Four Criteria

All four criteria must be met:

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

The Animal Rule – Three Additional Requirements

When a product is approved/licensed under the Animal Rule

Postmarketing studies to evaluate safety and clinical benefit if circumstances arise in which a study would be feasible and ethical
➔ A plan or approach to conducting such a study must be included with the marketing application

Approval with restrictions to ensure safe use, if needed

Information provided to patient recipients that explains that for ethical or feasibility reasons, the product's approval or licensure was based on efficacy studies conducted in animals alone

Origins of the Animal Rule

July 31, 1997

- FDA published a Request for Comments
- (62 FR 40996)

October 5, 1999

- FDA published the Proposed Rule
- (64 FR 53960)

May 31, 2002

- FDA published the Final Rule
- Effective July 1, 2002
- (67 FR 37988)

Animal Rule – Regulation Versus Guidance



Regulation – *The Animal Rule*

21 CFR 314.600-650 (for drugs) and 21 CFR 601.90-95 (for biologics)

- Standards for approval or licensure

Guidance – *Product Development Under the Animal Rule*

- Nonbinding recommendations; provides FDA's current thinking on the topic

Traditional Pathway Versus Animal Rule

Development Under a Traditional Pathway

- Chemistry, Manufacturing, and Controls
- Safety - Nonclinical
- Safety - Human
- PK - Human
- Efficacy - Human

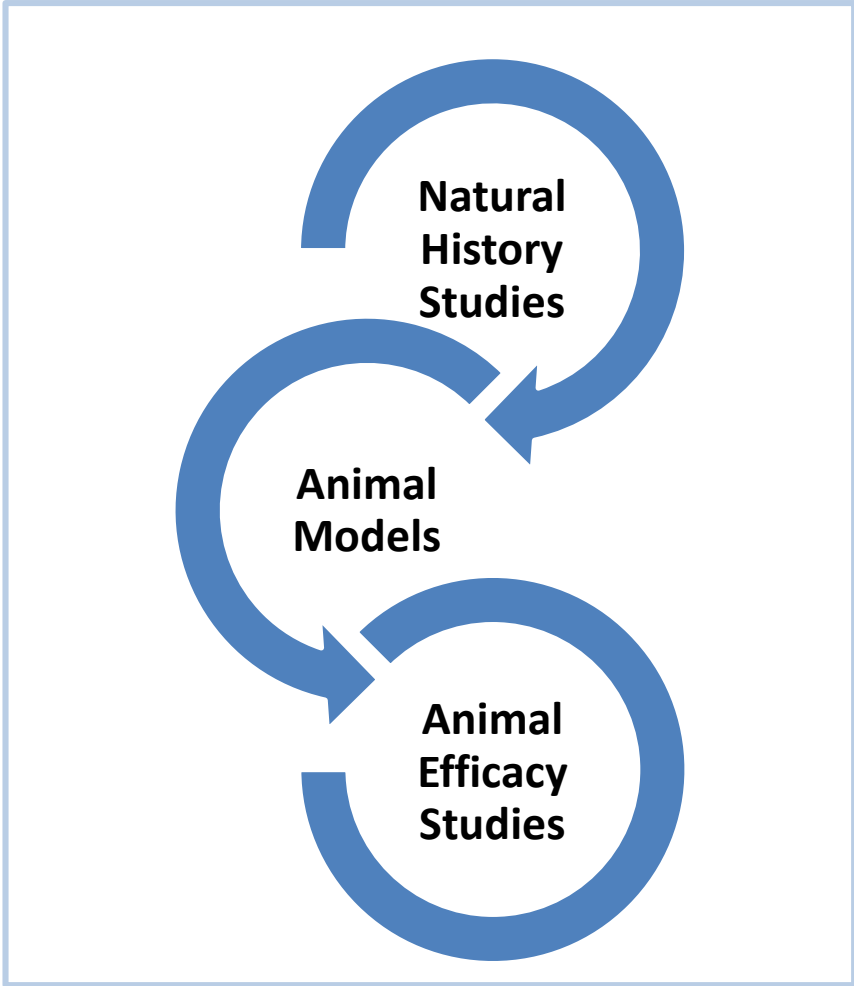
Development Under the Animal Rule

- Chemistry, Manufacturing, and Controls
- Safety - Nonclinical
- Safety - Human
- PK - Human
- Efficacy - Animal
 - Natural history studies
 - Adequate and well-controlled efficacy studies
 - PK/PD studies

Establishing Efficacy

Efficacy is established based on adequate and well-controlled studies in animals

- “...when the results of those animal studies establish that the drug product *[or the biological product]* is reasonably likely to produce clinical benefit in humans.”



Quoted from 21 CFR 314.610(a) for drugs; 21 CFR 601.91(a) for biologics

Key Points in Establishing Efficacy

Selection of Each Animal Model

Adequacy as a model of key elements of the human disease or condition

AND

Suitability with regard to the investigational drug or biological product

Design and Conduct of Efficacy Studies

The adequate and well-controlled animal efficacy studies substitute for human efficacy trials

From FDA's guidance *Product Development Under the Animal Rule* – sections V, VI, IX, and X

Animal Rule Approvals/Licensures

Soman Nerve Agent Poisoning – Lethal Effects

- Pyridostigmine bromide [30 mg tablet] (CDER, 2003)

Cyanide Poisoning

- Hydroxocobalamin injection, powder, lyophilized, for solution (CDER, 2006)

Plague – Pneumonic and Septicemic

- Levofloxacin [oral & injection] (CDER, 2012)
- Ciprofloxacin [oral & injection] (CDER, 2015)
- Moxifloxacin [oral & injection] (CDER, 2015)

Anthrax – Inhalational

- Raxibacumab injection (CDER, 2012)
- Anthrax Immune Globulin Intravenous (Human) (CBER, 2015)
- Anthrax Vaccine Adsorbed [injection]* (CBER, 2015)
- Obiltoxaximab [injection] (CDER, 2016)

Symptomatic Botulism

- Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) - (Equine) [injection] (CBER, 2013)

Hematopoietic Subsyndrome of Acute Radiation Syndrome

- Filgrastim [injection] (CDER, 2015)
- Pegfilgrastim [injection] (CDER, 2015)

Animal Rule Approvals/Licensures

More Than Two Species

- Soman Nerve Agent Poisoning – Lethal Effects
- Pyridostigmine bromide [30 mg tablet]

Two Species

- Anthrax – Inhalational
 - Raxibacumab injection
 - Anthrax Immune Globulin Intravenous (Human)
 - Anthrax Vaccine Adsorbed [injection]*
 - Obiltoxaximab [injection]
- Symptomatic Botulism
 - Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) - (Equine) [injection]

* only the post-exposure prophylaxis indication was an Animal Rule approval

One Species Plus Relevant Human Efficacy Data

- Cyanide Poisoning
 - Hydroxocobalamin injection, powder, lyophilized, for solution
- Plague – Pneumonic and Septicemic
 - Levofloxacin [oral & injection]
 - Ciprofloxacin [oral & injection]
 - Moxifloxacin [oral & injection]
- Hematopoietic Subsyndrome of Acute Radiation Syndrome
 - Filgrastim [injection]
 - Pegfilgrastim [injection]

Pediatric Dosing Information for Animal Rule Approvals/Licensures

Pediatric Dosing Information Included

- Levofloxacin [oral & injection] (*≥ six months of age*)
- Raxibacumab injection
- Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine) [injection]
- Ciprofloxacin [oral & injection]
- Anthrax Immune Globulin Intravenous (Human)
- Filgrastim [injection]
- Pegfilgrastim [injection]
- Obiltoxaximab [injection]

Pediatric Dosing Information Not Included

- Pyridostigmine bromide [30 mg tablet]
- Hydroxocobalamin injection, powder, lyophilized, for solution
- Moxifloxacin [oral & injection]
- Anthrax Vaccine Adsorbed [injection]*

Some Unique Considerations

Working with CBRN substances

- Limited number of laboratories capable of conducting animal studies with certain CBRN substances
- Significant challenges related to the specific CBRN substance

Establishing efficacy

- Appropriate animal models are needed for efficacy testing

Selecting human dose

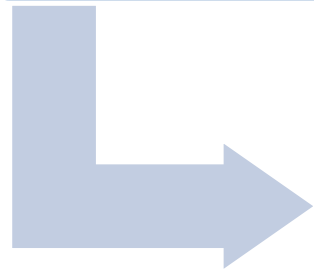
- Translating from animals to select an effective dose and regimen for humans
 - Developing a PK profile in sick or injured animals

Two Helpful Websites



Animal Rule Approvals

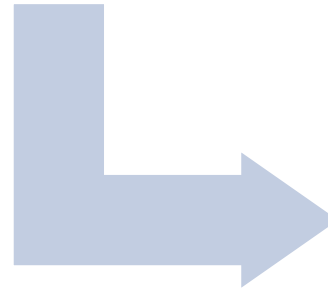
FDA.gov



Search on:
Animal Rule
Approvals

FDA's Medical Countermeasures Initiative (MCMi)

FDA.gov



Search on:
Medical
Countermeasures
Initiative

Medical Countermeasure Development - Contact Information for Questions

If you know the regulatory review division for your product

- Consult the review division

If you are unsure of the regulatory review division for your product

- Consult the CDER or CBER contacts
 - **CDER** - Rosemary Roberts, MD
 - 301-796-2210 or email: Rosemary.Roberts@FDA.HHS.gov
 - **CBER** - David Cho, PhD
 - 240-402-8036 or email: David.Cho@FDA.HHS.gov





BACKGROUND INFORMATION



A Critical Requirement of These Animal Studies

- Animal studies **must** comply with applicable laws and regulations as prescribed by the Animal Welfare Act and the Public Health Service Policy on Humane Care and Use of Laboratory Animals

Quoted from FDA's guidance *Product Development Under the Animal Rule* – section IV.B and Appendix A

Adequate Veterinary Care

Compliance with:

Animal Welfare Act

+

PHS Policy on Humane Care
and Use of Laboratory
Animals

+

General principles for the
care and use of animals in
biomedical research



**Ensures that adequate
veterinary care is provided,**
such that animals
experiencing more than
momentary or slight pain or
distress are provided relief
through appropriate
analgesia, treatment, or,
when prospectively defined
criteria are met, euthanasia*

*** Exceptions to this standard are
permitted only when scientifically
justified and approved by the IACUC**

From FDA's guidance *Product Development Under the Animal Rule* – Appendix B