U.S. FDA Regulatory Perspective on Postmarketing Requirements Under the Animal Rule

Susan McDermott, MD
Lead Medical Officer
Counter-Terrorism and Emergency Coordination Staff
Office of the Center Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Non-Clinical Data for Regulatory Decision-Making on the Efficacy of Medical Countermeasures
European Medicines Agency
Hybrid workshop
24-25 Nov. 2025

FDA supports the 3Rs

FDA endorses the principles of replacement, reduction, and refinement of the use of animals in biomedical research.

Financial disclosures

I do not have any relevant financial disclosures for this presentation and attest that the clinical recommendations are evidence-based and free of commercial bias.

The Animal Rule

Drugs

Subpart I –

Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

21 CFR Parts 314.600-650

Biologics

Subpart H –

Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible

21 CFR Parts 601.90-95

Federal Register Vol. 67, No. 105, 37988-37998, May 31, 2002

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

The Animal Rule

Scope: The Animal Rule can be used only when all of these 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 (CBRN) substance	Definitive human efficacy studies cannot be conducted because deliberate exposure of healthy volunteers to the lethal or permanently disabling toxic CBRN substance would be unethical	Field trials to study effectiveness of the product after an accidental or hostile exposure to the CBRN substance have not been feasible	The product cannot be approved or licensed for the proposed indication based on efficacy standards described in other parts of the regulations

The product has been studied for safety

From 21 CFR 314.600 for drugs; 21 CFR 601.90 for biologics

The Animal Rule

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

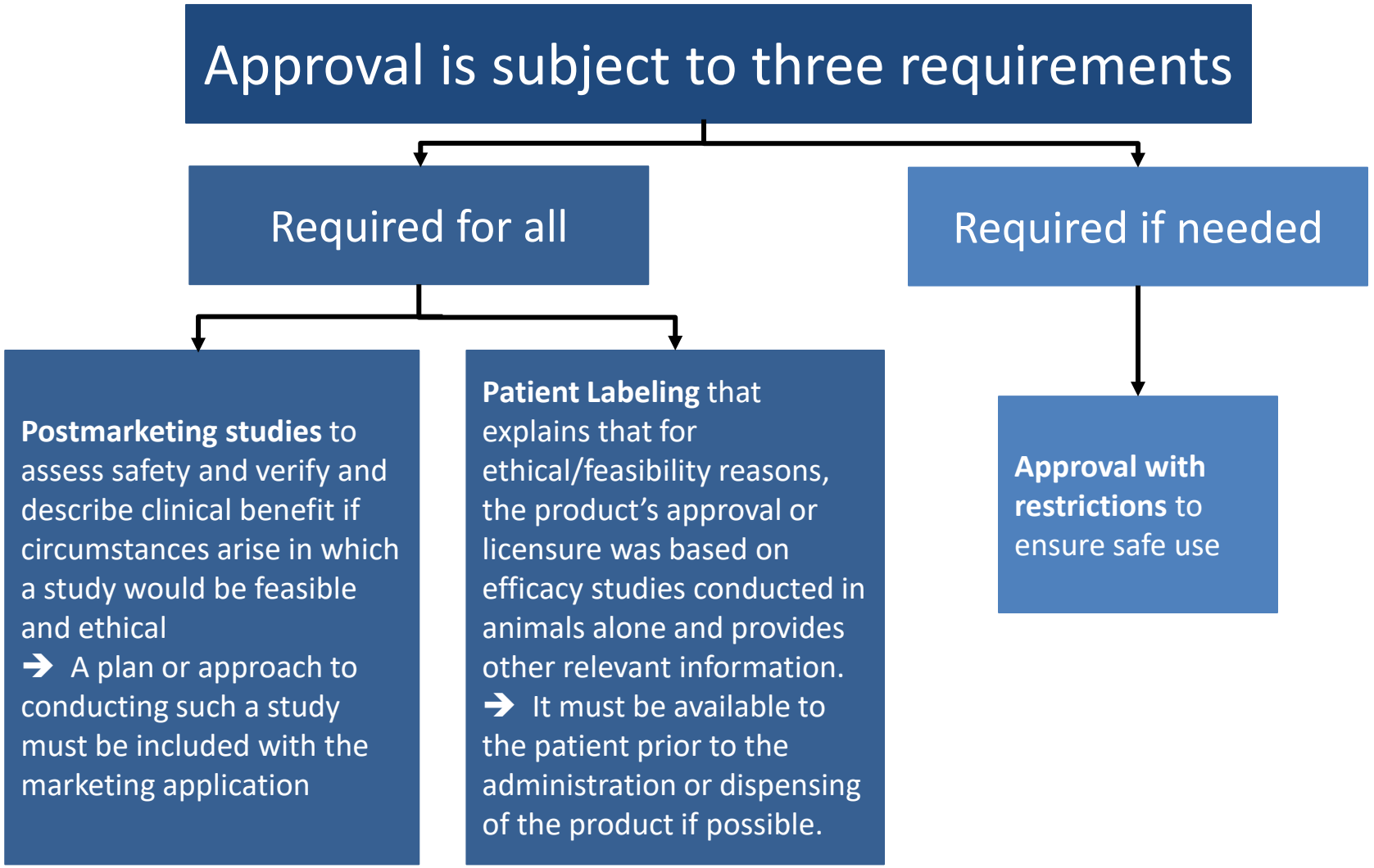
All four criteria must be met

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

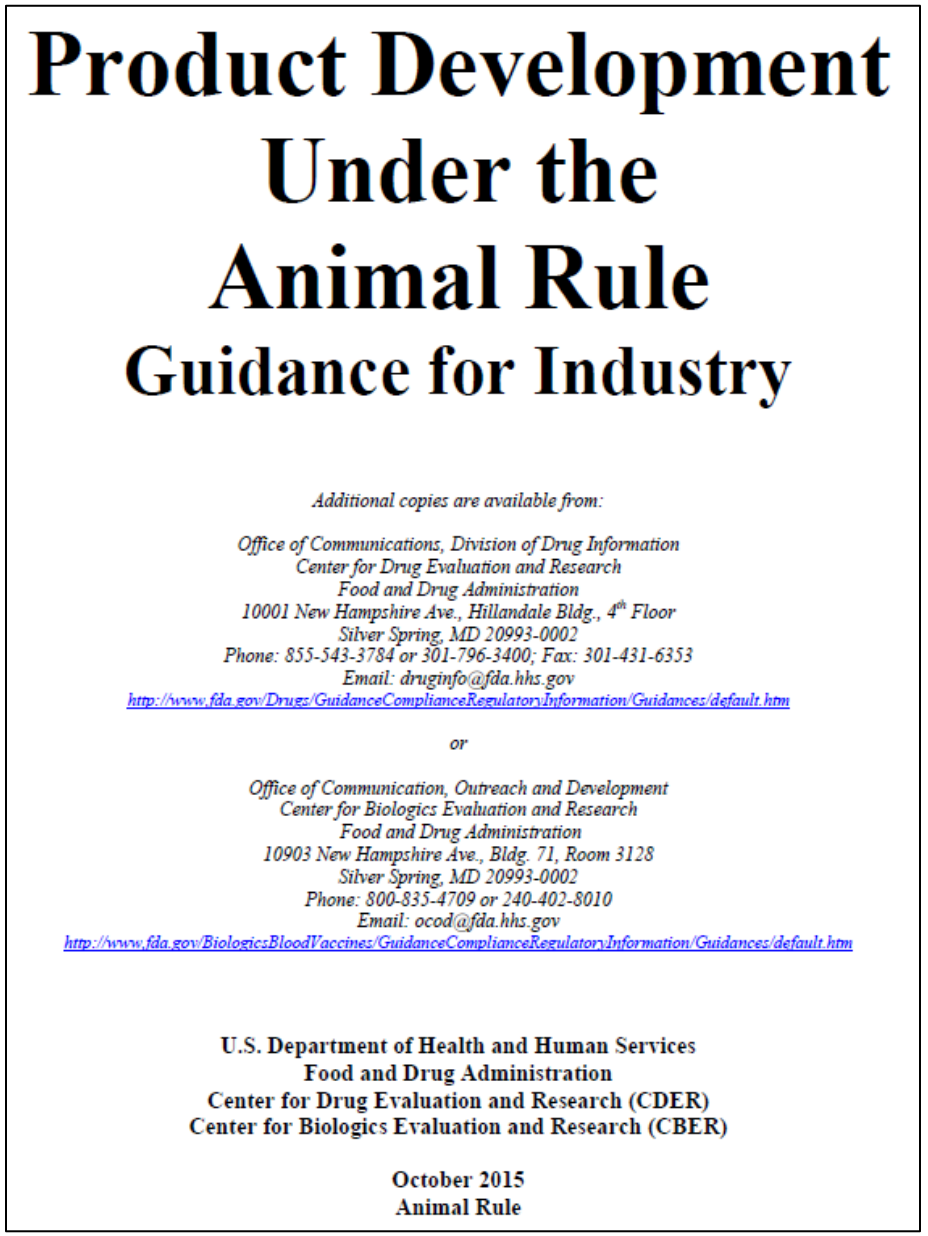
4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

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

The Animal Rule



From 21 CFR 314.610(b) for drugs; 21 CFR 601.91(b) for biologics



Product Development Under the Animal Rule

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2015
Animal Rule

See: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-development-under-animal-rule

Animal Rule approvals/licensures

Soman Nerve Agent Poisoning – Prophylaxis Against Lethal Effects

- PYRIDOSTIGMINE BROMIDE (pyridostigmine bromide tablet (30 mg)) (CDER, 2003)
- PYRIDOSTIGMINE BROMIDE (pyridostigmine bromide extended-release tablets (105 mg)) (CDER, 2024)

Anthrax – Inhalational

- RAXIBACUMAB (raxibacumab injection) (CDER, 2012)
- ANTHRASIL (Anthrax Immune Globulin Intravenous (Human)) (CBER, 2015)
- BIOTHRAX (Anthrax Vaccine Adsorbed) (CBER, 2015)
  - Only the post-exposure prophylaxis indication was an Animal Rule approval
- ANTHIM (obiltoxaximab injection) (CDER, 2016)
- CYFENDUS (Anthrax Vaccine Adsorbed, Adjuvanted) suspension for intramuscular injection (CBER, 2023)

Cyanide Poisoning

- CYANOKIT (hydroxocobalamin injection, powder, lyophilized, for solution) (CDER, 2006)

Symptomatic Botulism

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

Hematopoietic Syndrome of Acute Radiation Syndrome

- NEUPOGEN (filgrastim injection) (CDER, 2015)
- NEULASTA (pegfilgrastim injection) (CDER, 2015)
- LEUKINE (sargramostim solution and lyophilized powder, for injection) (CDER, 2018)
- NPLATE (romiplostim for injection for subcutaneous use) (CDER, 2021)

Plague – Including Pneumonic and Septicemic Plague

- LEVAQUIN (levofloxacin tablet, oral solution & injection) (CDER, 2012)
- CIPRO (ciprofloxacin hydrochloride tablet & oral suspension, ciprofloxacin IV infusion) (CDER, 2015)
- AVELOX (moxifloxacin hydrochloride tablet & moxifloxacin injection) (CDER, 2015)

Smallpox Disease

- TPOXX (tecovirimat)
  - TPOXX (tecovirimat capsule for oral use) (CDER, 2018)
    - TPOXX (tecovirimat capsule for oral use) (*expanded patient population*) (CDER, 2022)
  - TPOXX (tecovirimat injection for intravenous use) (CDER, 2022)
- TEMBEXA (brincidofovir oral suspension & tablet) (CDER, 2021)

For more information see FDA's Animal Rule Information webpage and FDA's Animal Rule Approvals webpage.

Postmarketing Requirements and Commitments

- Postmarketing *requirements* (PMRs) include studies and clinical trials that sponsors are ***required*** to conduct under one or more statutes or regulations.
- Postmarketing *commitments* (PMCs) are studies or clinical trials that a sponsor has agreed to conduct, but that are ***not required*** by a statute or regulation.
- FDA has created a searchable database of information on postmarketing studies and clinical trials for drugs and biologics
  - PMCs containing proprietary information are not included in the database

See https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarketing-requirements-and-commitments-introduction

Animal Rule Postmarketing Studies Requirement

21 CFR 314.610(b)(1)

(b) Approval under this subpart will be subject to three requirements:

(1) Postmarketing studies. The applicant must conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible….

Animal Rule Postmarketing Studies Requirement

- The Animal Rule regulations do not indicate what types of studies (e.g., controlled trials, observational studies) are acceptable to fulfill the requirement
- Different approaches have been proposed

Acceptability of Sponsor's Postmarketing Plan or Approach

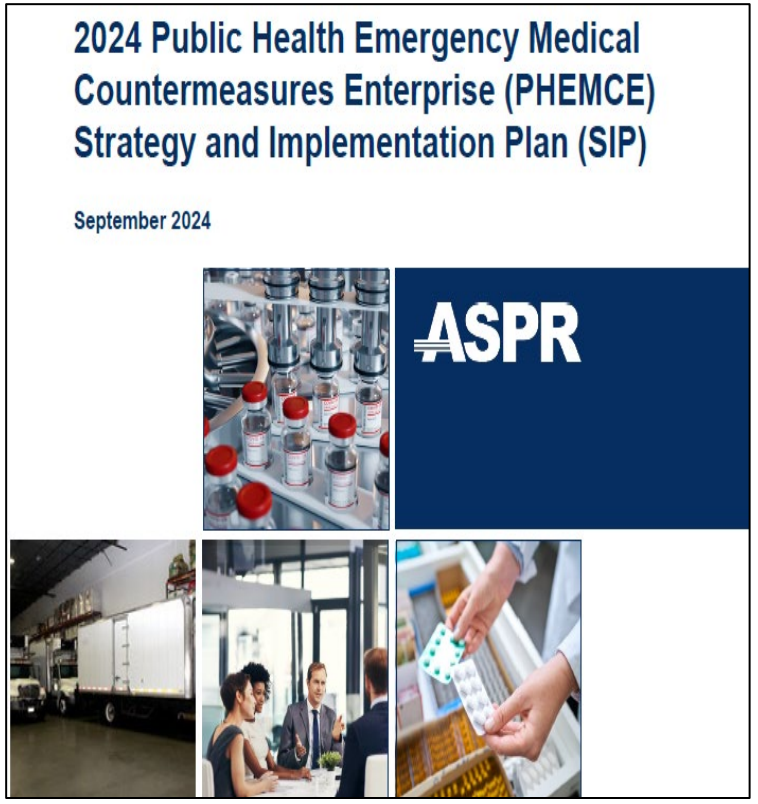
- There is no standardized postmarketing protocol for products approved under the Animal Rule
  - Acceptability is contextually/situationally determined for each product
- Regulatory review of the marketing application, including the postmarketing plan or approach, is conducted at the level of the product review division, with other FDA experts consulted as needed
  - In CDER, application review is based on the MCM's proposed indication

Postmarketing Data Collection During an Exigency

- Multiple potential challenges
  - Type of threat agent (e.g., destruction related to an explosive device), location of the exigency (e.g., rural area vs large metropolitan area), and the number of people affected
- If an exigency occurs, product sponsors will ideally collaborate with US government to collect necessary study data
- Lessons learned during the COVID-19 pandemic
  - Reagan-Udall Foundation: COVID-19 Clinical Evaluation of Therapeutics
- Increased use of real-world data in regulatory submissions
  - FDA Real World Evidence

Medical Countermeasure Preparedness

- Coordinated effort within the federal government
- Shared goal of having approved or licensed MCMs available
- Close collaboration between agencies



https://aspr.hhs.gov/PHEMCE/2024-PHEMCE-SIP/Pages/default.aspx


FDA
U.S. FOOD & DRUG
ADMINISTRATION