

## ABSTRACT

FDA's 'Animal Rule' (AR, October 2015) provides a regulatory pathway for approval of human pharmaceuticals when it is neither ethical nor feasible to perform human efficacy trials. In such situations, and with FDA concurrence, the Agency will accept 'Clinical Trials' in animals to demonstrate the efficacy of drugs for human use. The uniqueness of these AR studies, coupled with their dissimilarities to toxicology studies for which SEND is designed, pose challenges for data standardization, including: 1) establishing a trial design model that permits protocol-specified cohort selection for analyses; 2) the central importance of creating analysis datasets; and 3) providing the data in a form ready for assessment by scientists and regulatory reviewers, as in pivotal human trials. These and other AR data standardization challenges are being addressed by a CDISC/CPATH/FDA initiative to develop a suitable standard for AR studies along with an Implementation Guide (IG).

## 1. WHAT is FDA's ANIMAL RULE?

- Animal Rule (AR) Regulations: 21 CFR 314.600 through 314.650 for drugs; 21 CFR 601.90 through 601.95 for biological products
- The AR states, "For drugs developed to ameliorate or prevent serious or life-threatening conditions caused by exposures to lethal or permanently disabling toxic substances, when human efficacy studies are not ethical and field trials are not feasible, FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans."
- Sponsors need to obtain FDA concurrence to use the AR pathway, and discussions with the Agency are recommended, starting in the early stages of AR drug development and continuing throughout the development program.
- Drugs evaluated for efficacy under the AR should undergo traditional toxicology and nonclinical safety testing in animals. PK and safety assessments should be conducted in healthy human volunteers, if possible.

### Product Development Under the Animal Rule Guidance for Industry

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

## 2. RECENT ANIMAL RULE APPROVALS

| Treatment          | Indication                                                |
|--------------------|-----------------------------------------------------------|
| Ryanodex®          | Malignant hyperthermia                                    |
| Levaquin®          | Plague                                                    |
| Levaquin®          | Inhalational anthrax                                      |
| Avelox®            | Plague                                                    |
| Biothrax®          | Inhalational anthrax: post-exposure prophylaxis (vaccine) |
| Anthim®            | Inhalational anthrax                                      |
| Raxibacumab®       | Treatment and prophylaxis of inhalational anthrax         |
| Botulism Antitoxin | Botulism                                                  |

## 3. HOW DO ANIMAL RULE STUDIES DIFFER FROM TOXICOLOGY STUDIES?

Animal efficacy studies conducted under the AR substitute for efficacy trials in humans. Most such studies involve exposure of animals to a toxic substance, such as an infectious agent, and treatment with a drug or biologic.

### 3.1 STATISTICS

**3.1.1 Statistical Analysis of Efficacy** is a critical requirement of the AR and a central feature of AR studies. The statistical analysis plan should be prospectively designed. Some sponsors follow Good Clinical Practice (GCP) regulations for data analysis (described in E9: Statistical Principles for Clinical Trials, 1998, ICH, FDA), as guidelines for applicable statistical procedures for efficacy are not part of GLP regulations.

**3.1.2 Multiple Study Populations:** Statistical analysis for efficacy can involve multiple overlapping study populations, as is the case for clinical trials. These populations can include a full analysis set (generally all animals randomized to the study); a per protocol set (subjects whose treatment complied with the protocol); a safety set (all subjects that received the test article).

**3.1.3 Analysis Datasets** are generated as part of statistical analysis of an AR study. Some sponsors choose to generate all tables and listings for the final report from these analysis datasets.

## 3. HOW DO ANIMAL RULE STUDIES DIFFER FROM TOXICOLOGY STUDIES? (continued)

### 3.2 STUDY DESIGN and STUDY CONDUCT

**3.2.1 Exposure to lethal or disabling toxin (challenge agent),** such as an infectious agent (Anthrax) or extreme heat, must be quantified on a by-animal basis. In terms of target dose and actual dose, along with time from exposure to disease or injury onset. The delivery method needs to be described.

**3.2.2 Blinding of study personnel and sponsor** to treatment and treatment group to avoid introducing bias.

**3.2.3 Prespecified criteria required by Animal Rule:**

- Study inclusion/exclusion criteria
- Trigger for intervention / treatment
- Supportive care (if appropriate)
- Euthanasia

**3.2.4 Parameters evaluated** in AR studies often differ from those in toxicology studies based on the need to monitor the onset and progression of pathophysiology in ways that are relevant to the medical management of humans.

**3.2.5 Specialized facilities for conduct of AR studies:** Many AR studies need to be conducted in Biosafety Level 3 or 4 laboratories for safety reasons based on the virulent nature of infectious agents under study.

**3.2.6 Electronic Data Capture in AR studies:** LIMS designed for toxicology studies may not be equipped for the type and diversity of electronic data capture needed for AR studies, resulting in manual data collection for some parameters.

### 3.3 REPORTS

**3.3.1 Final Study Reports** for AR studies are more similar to clinical study reports than to toxicology study reports. Some sponsors choose to have final reports for AR studies follow GCPs (described in E3: Structure and Content of Clinical Study Reports, 1995; ICH) and generate all tables in the final report from analysis datasets.

### 3.4 DIVERSITY

**3.4.1 Scientific Diversity in animal models, study designs, challenge agents** across AR programs

**3.4.2 Regulatory diversity:** some sponsors follow GCPs & AR for statistics & reporting, which are more specific than the AR & GLPs; others follow AR & GLPs.,

## 4. Standardization of AR Studies: What are the Challenges?

### DATA ANALYSIS

|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Analysis Data Sets | <ul style="list-style-type: none"><li>A standard for analysis datasets is not available for use with SEND and would be helpful in recreating the Sponsor's analysis.</li><li>An analysis standard is important for those AR studies that generate report tables and listings for efficacy and safety from analysis datasets.</li></ul>                                                                                                                                              |
| Trial Domains      | <ul style="list-style-type: none"><li>The SEND TX domain does not allow for protocol-specified cohort selection needed for efficacy and safety analyses, for multiple analysis populations (Section 3.1.2 of this poster); potential genotypic dissimilarity of subjects; other unique study design features.</li><li>SEND Trial Domains do not allow for inclusion &amp; exclusion criteria &amp; other prespecifications required by AR (Section 3.2.3 of this poster).</li></ul> |

### DATA CAPTURE

|                        |                                                                                                                                                                                                                                                  |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Exposure (EX) domain   | <ul style="list-style-type: none"><li>Targeted &amp; actual exposure to challenge agent must be quantified for for each subject as required by AR, in addition to test article exposure. SEND does not cover challenge agent exposure.</li></ul> |
| Microscopy (MI) domain | <ul style="list-style-type: none"><li>Different types of examinations are done on tissues post necropsy in AR, and many are qualitative.</li></ul>                                                                                               |
| Lab Tests (LB) Domain  | <ul style="list-style-type: none"><li>Cannot specify data for microorganisms in culture, a critical feature of many drugs studied under AR.</li></ul>                                                                                            |

## CONCLUSION

We believe AR studies can be standardized using a combination of SEND, SDTM, ADaM, and custom domains. The use of custom domains and variables, along with a decision tree, was presented in a poster at the 2015 PhUSE CSS by the Nonclinical Standards Roadmap Team (Frausing, et al: [http://www.phusewiki.org/wiki/images/3/3a/How\\_to\\_build\\_a\\_custom\\_domain.pdf](http://www.phusewiki.org/wiki/images/3/3a/How_to_build_a_custom_domain.pdf)). Some AR studies that follow GCPs are candidates for discussing their standardization using SDTM and ADaM with the relevant FDA review division. Development of an Implementation Guide (IG) for AR studies is planned by the CDISC/CPATH/FDA initiative.