



# **USDA Perspective on 3R Implementation**

**Geetha B. Srinivas, D.V.M., Ph.D.  
Section Head, Virology & Molecular Biology  
Policy, Evaluation, and Licensing  
Center for Veterinary Biologics  
USDA APHIS  
Geetha.B.Srinivas@usda.gov**



# Objectives

- **Regulatory framework**
- **3R Enhancements: Manufacturer Initiated**
- **3R Enhancements: CVB Initiated**
  - **International Collaborations**
  - **Agency Led Projects**

# Regulatory Framework

- **Virus-Serum-Toxin Act (1913 & 1985)  
(21 U. S. Code, Sections 151-159)**
  
- **Title 9 Code of Federal Regulations  
(Parts 101-122)**
  
- **Veterinary Service Memoranda**
  
- **CVB Notices**



# Virus-Serum-Toxin Act

- Prohibits **W**orthless, **D**angerous, **C**ontaminated, or **H**armful (**W-D-C-H**) biologics
  
- 3R initiatives
  - Must meet the standards of the VSTA

# Outline of Production

- **Critical Elements –**
  - **Components of Biologics**
  - **Production Process**
  
- **Regulatory Flexibility-**
  - **Approved scientifically sound production changes allowed over time**
  
- **Final Product Testing**
  - **Foundation of market release**

# Final Product Testing

- **Potency**
  - **In vivo**
  - **In vitro**
  
- **Safety**
  - **Target Animal Batch Safety**
  - **Laboratory Animal Batch Safety**

# Animal Safety Batch Testing Exemptions

## International Collaboration

- **Designed for Target Animal Safety**
  - **Target Animal Safety Tests**
  - **Laboratory Animal Safety Tests**
  
- **Does it still provide the same need?**
  
- **VICH Guidance**



# VICH Considerations

- **Consistent, quality manufacturing processes as determined by a regulated authority**
  - **Seed lot manufacturing system**
  
- **Sufficient number of serials pass animal batch safety testing**
  
- **Pharmacovigilance Data**





# VICH Guidance

- **VICH GL50:** Harmonization of criteria to waive **target animal batch safety testing** for **inactivated** vaccines for veterinary use (2013)
  
- **VICH GL55:** Harmonization of criteria to waive **target animal batch safety testing** for **live** vaccines for veterinary use (2017)
  
- **VICH GL59:** Harmonization of criteria to waive **laboratory animal batch safety testing** for vaccines for veterinary use (2020)



# VSM 800.116

## Target Animal Safety Exemption

- Harmonize with VICH GL50 and GL55
- Evaluate final product testing results of 10 serials or 5 serials if 10 not manufactured in 3 years
- Evaluate manufacturing changes in Outline of Production
- Evaluate Pharmacovigilance data by firm submission of adverse event reports
- Exemption required license restriction to report adverse events



# **Draft Revision to Veterinary Services Memorandum 800.116**

- **Add laboratory animal batch safety exemption to harmonize with VICH GL59**
- **Pharmacovigilance data evaluated by CVB adverse event reporting system per Veterinary Services Memorandum 800.125**
  - **Effective February 27, 2021**
  - **Data available in CVB system**
  - **License restriction to report data not needed**

## **3R Initiatives: Manufacturer Initiated**

- **Limited Use**
  - **Confidential Business Information**
  
- **Veterinary Biologics Manufacturer Groups**
  - **AHI (Animal Health Institute)**
  - **AVBC (Association of Veterinary Biologics Companies)**

## **3R Initiatives: Manufacturer Initiated**

- **In vitro Potency Tests**
  - **VS Memorandum 800.112: Guidelines for Validation of *In Vitro* Potency Assays**
    - **Conceptualization**
    - **Development**
    - **Optimization**
    - **Verification**
    - **Monitoring**
  
- **Other enhancements**
  - **Reduction**
  - **Refinement**
    - **Analgesia**

## **3R Initiatives: CVB Initiated**

- **Industry-wide advantage**
- **International Collaborations**
- **Independent Research**

# CVB

## Independent Research

- **Information shared with industry**
  - **AHI, AVBC and other public meetings**
  - **Notices and Memorandums**
  - **Posting of testing methods on public website**
  
- **Reagents**
  - **Antibodies**  
*Leptospira, Clostridials, E. coli, etc*
  - **References**  
Rabies
  
- **Protocols and Supplemental Assay Methods**
  - **Publicly available through the CVB website**

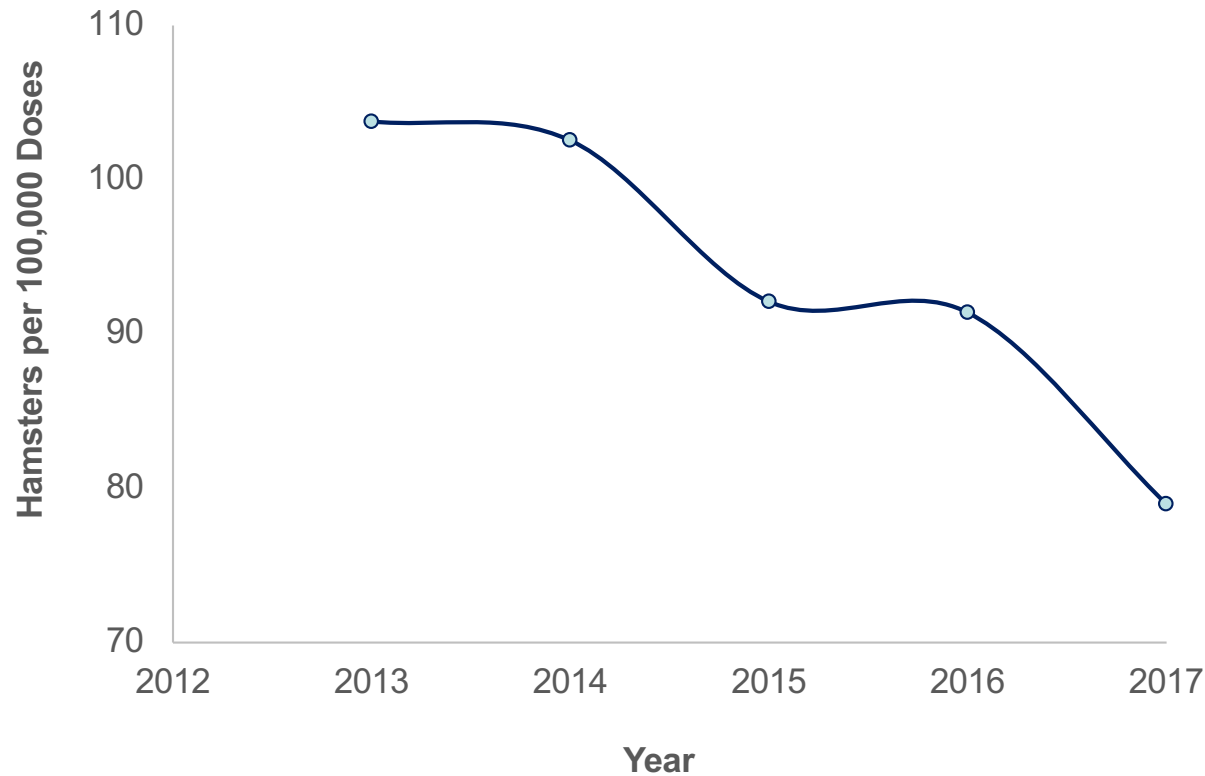
# **CVB Independent Research: Leptospira Regulatory Enhancements**

- **Replacement of codified hamster assays with ELISAs**
  - **Antibodies and References available**
  - **Product specific validation is required**
- **Exemption of back-titration hamsters from the codified assays**
  - **Notices 15-13 and 17-06**
- **Cryopreservation of virulent challenge**



# CVB Independent Research: **Leptospira 3R Implementation**

### Hamsters Per Doses Released



# CVB Independent Research: Cell Based Toxin-Antitoxin Assays

- **Potency test for Clostridium septicum Alpha antitoxin using a Cell Assay**
  - VERO Cells
  - [https://www.aphis.usda.gov/animal\\_health/vet\\_biology/publications/BBPRO1009.pdf](https://www.aphis.usda.gov/animal_health/vet_biology/publications/BBPRO1009.pdf)
  
- **Potency test for Clostridium perfringens Type D epsilon antitoxin using a Cell Assay**
  - MDCK Cells
  - [https://www.aphis.usda.gov/animal\\_health/vet\\_biology/publications/BBPRO1008.pdf](https://www.aphis.usda.gov/animal_health/vet_biology/publications/BBPRO1008.pdf)

Increasing amounts of toxin added to a standard and unknown antitoxin to determine the amount of antitoxin present by monitoring cell death

# Conclusions

- **Overview of CVB Regulatory Approach**
- **Manufacturer led 3R Initiatives**
- **International 3R Initiatives:**
  - **Animal Batch Safety Testing Exemptions**
- **CVB Independent Validation of 3R Initiatives**
  - **Reagents**
  - **Protocols**
  - **Memoranda and Notices**



United States Department of Agriculture

**Animal and Plant  
Health Inspection  
Service**

**Veterinary Services**

**Center for Veterinary  
Biologics**

**1920 Dayton Avenue  
PO Box 844  
Ames, IA USA  
50010**

**Phone: (515) 337-6100**

**Email:  
Geetha.B.Srinivas@usda.gov**

