USDA Perspective on 3R Implementation

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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 **Worthless, Dangerous, Contaminated, or Harmful (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
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

Year

Hamsters per 100,000 Doses

2012 2013 2014 2015 2016 2017
CVB Independent Research: Cell Based Toxin-Antitoxin Assays

- Potency test for Clostridium septicum Alpha antitoxin using a Cell Assay
  - VERO Cells

- Potency test for Clostridium perfringens Type D epsilon antitoxin using a Cell Assay
  - MDCK Cells

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
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