CVB Regulatory Perspective - *3R Implementation & Example*





Angela Walker, D.V.M., Ph.D.
Center for Veterinary Biologics

Email: Angela.M.Walker@usda.gov

Center for Veterinary Biologics

APHIS
VS Veterinary Services
Safeguarding Animal Health
NCAH National Centers for Animal Health

Regulatory Authority

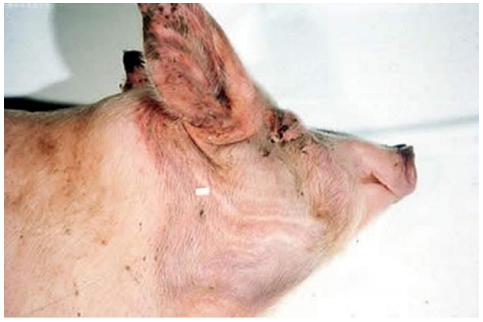
Virus-Serum-Toxin Act

- **Title 9 of the Code of Federal Regulation (9 CFR)**
  - Section 113.5: General Testing-Product released only after testing to establish pure, safe, potent and efficacious veterinary biologic
- **Veterinary Services Memorandum**
- **Center for Veterinary Biologics Notices**
- **Other Guidance Documents: Supplemental Assay Methods, Testing Protocols, Reagent Data Sheets**
  - https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics
- **Product Specific: Outline of Production**
  - Section V (Final Product Testing Requirements)

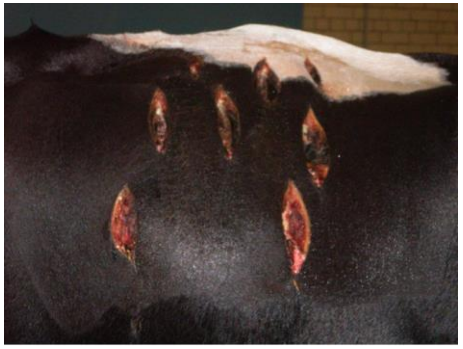
Importance of Animal Welfare

- **CVB supports implementation of 3RS in release testing.**

- **The goal of potency testing is to protect the animals in the field. All new assays must provide the same confidence as those currently approved in order to prevent their suffering.**



C. septicum: Courtesy of the Department of Pathobiology, University of Guelph.



C. novyi: Courtesy of Dr. Henry Stämpfli..

https://www.merckvetmanual.com/generalized-conditions/clostridial-diseases/malignant-edema

VSM 800.112 “Guidelines for Validation of *In Vitro* Potency Assays”

Validation provides evidence the assay does what it is intended to do for assays .

- **VSM 800.112 divides the validation process into several phases:**
  - **Conceptualization**
  - **Development**
  - **Optimization**
  - **Verification**
  - **Monitoring**

Protocols and Reagents

❖ Supplemental Assay Methods (SAMs)

- SAMs 624 – 627 posted on public website

❖ Monoclonal Antibodies

- *L. canicola* = 4DB-001
- *L. grippotyphosa* = LGF02-002
- *L. icterohaemorrhagiae* = 294-004
- *L. pomona* = 2D7

❖ Polyclonal Antibodies

Communication

- **International Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing: State of the Science and the Way Forward**
  - Vaccine manufacturers encouraged to initiate or continue product-specific validation with ELISAs
  - The CVB encouraged to re-examine the necessity of back-titration animals in the hamster challenge assay
  - International harmonization of alternative potency methods was recommended by all

- **Focus workshops on *Leptospira* vaccine potency testing at AHI and AVBC meetings**

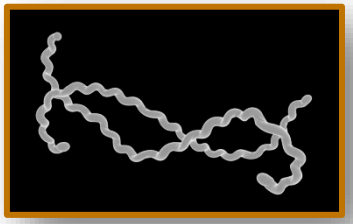
9 CFR Potency Tests for Leptospira Potency Tests

❖ Overview

Vaccinate

Wait

14 - 18 days



Challenge w/Leptospira

Observe

14 days

Count survivors

❖ Animal Numbers

Vaccinates	Challenge Controls	Concurrent Challenge (LD50 Titration)
10	10	20

Codified Potency Tests for Leptospira Bacterins

- **Vaccine Disposition**
  - Satisfactory: 80% Vaccinates Survive

- **Validity Requirements**
  - 80% Death in Challenge Controls
  - LD50:10 – 10,000

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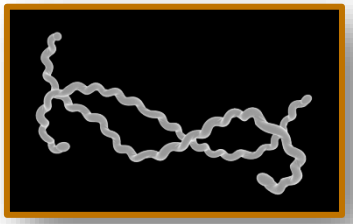

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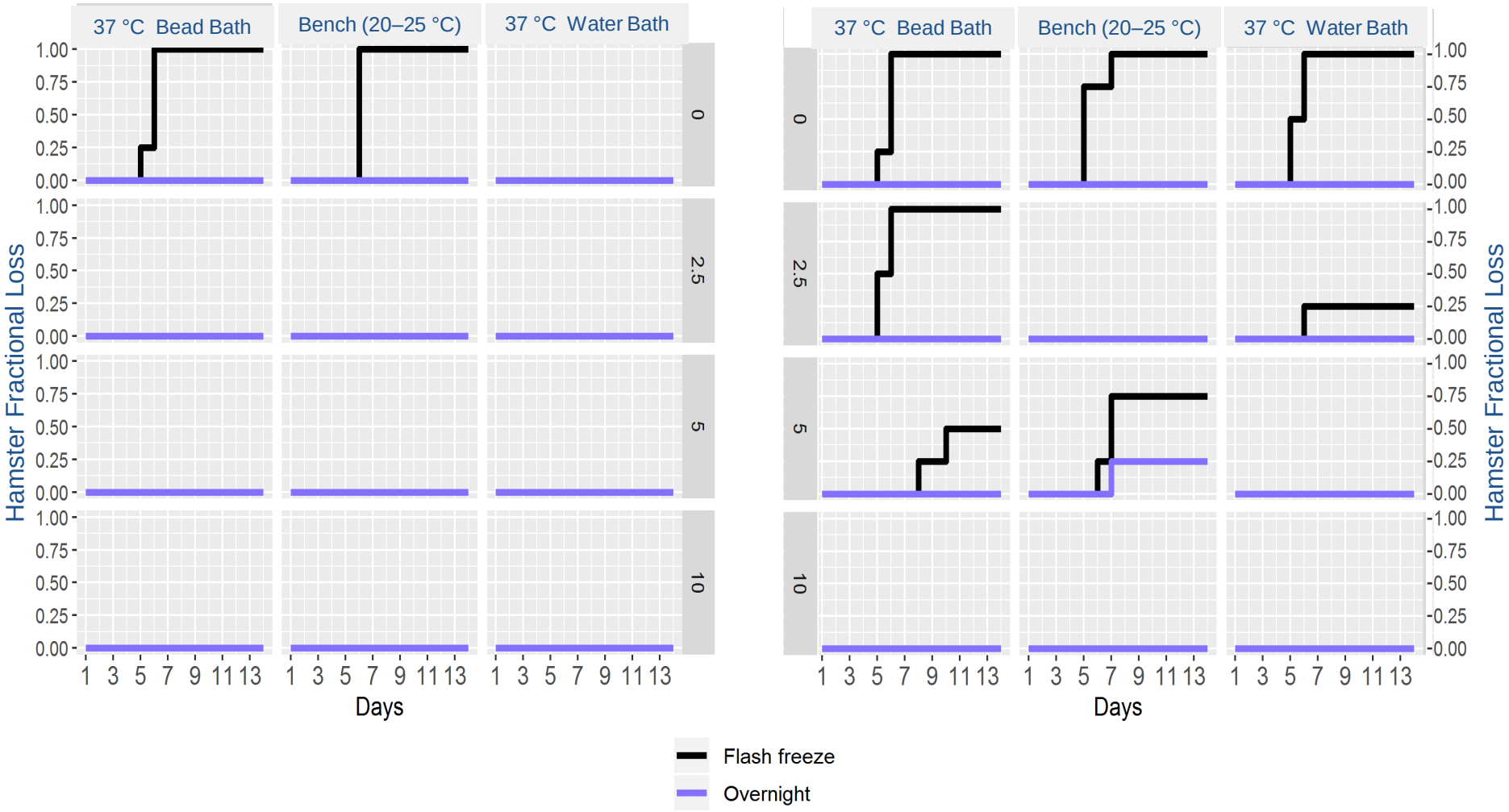
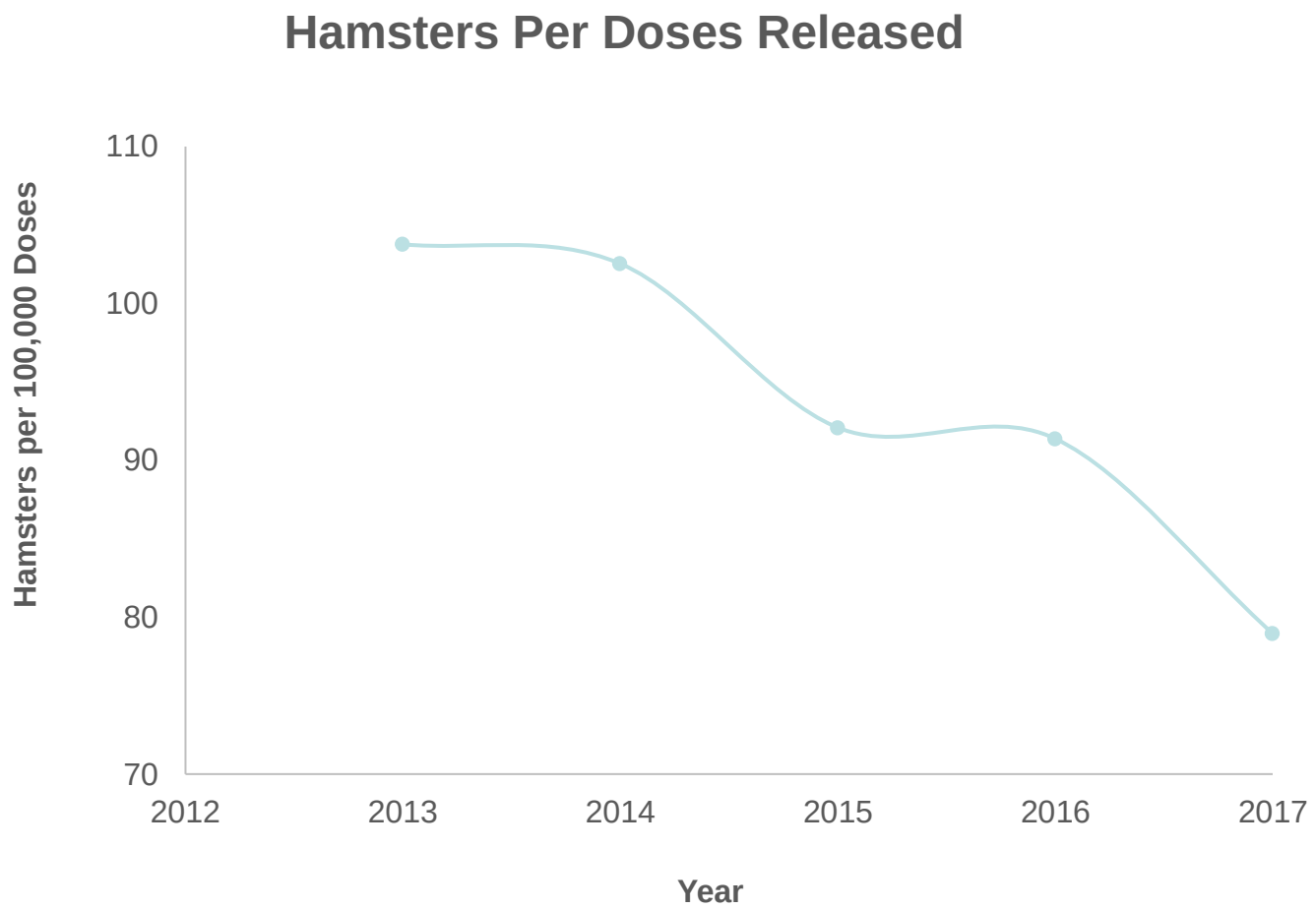
Grippotyphosa



9 CFR Potency Testing: Hamster Use

- Validate ELISAs for serial release
- Published two notices exempting back-titration hamsters from the codified assays: Notice 15-13 and 17-06
- Long-term maintenance of virulent challenge



United States Department of Agriculture

National Centers for Animal Health, Ames, Iowa, USA