Issue 3:
Policy Considerations for Different Product Types

Mark Zylstra
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Product-Specific Considerations,
- e.g. Viral Vaccines (live, killed, vectored)
- Bacterins
- Bacterial Extracts
- Toxoids
Critical Backdrops

• Why are we here?

• What are we trying to fix?

• What are the RISKS associated with
  – Current approach?
  – Proposed approach?
Regulatory Requirements

• 9 CFR 113.8

In vitro tests for serial release.
Live products

• 113.8 (a)(3)(i)

Potency for live products may be determined by \( \log_{10} \) virus titer or determining the live bacterial count based on the protective dose used in the Master Seed immunogenicity test plus an adequate overage for adverse conditions and test error.
Inactivated products

• 113.8 (a)(3)(ii)

Potency for inactivated products may be determined using tests for relative antigen content by comparing the antigen content of the test serial to a reference preparation using a parallel line immunoassay or equivalent method which measures linearity, specificity, and reproducibility in a manner acceptable to APHIS.
Live products

• 113.8 (a)(3)(i)

.......plus an adequate overage for adverse conditions and test error
Adequate overage for adverse conditions...

- Conditions within the manufacturing process
  - Recent important emphasis in process controls
    - Narrow process parameters
    - Narrow incubation and storage parameters
    - In-process testing/ monitoring
    - Greater documentation focus
    - Deviation investigation & Root Cause Analysis
    - Corrective and Preventive Action (CAPA) plans

- Collectively result in lesser overage requirement for adverse conditions
Adequate overage for adverse conditions...

- Conditions beyond the manufacturing process
  - Compliance with label instructions
    - Storage
    - Exposure to light
    - Reconstitution and mixing
    - Partial dosing
    - Extreme environmental conditions
  - Outside the consideration for overage for adverse conditions
Adequate overage for test error...

- Should be based on:
  - Assay type
  - Specific assay qualification study
  - Assay transfer validation study

- CVB focus on improvement of existing assays

- **Result:** lesser need for overage due to test error
Product-Specific Considerations,

- e.g.. Viral Vaccines (live, killed, vectored)
- Bacterins
- Bacterial Extracts
- Toxoids
Live viral vaccines

- Classical MLV Potency Test
- TCID$_{50}$ Assays
- Log$_{10}$
- Traditionally Accepted assay variability
  - 0.7 log$_{10}$
- Limited ability to decrease assay variability
- Less variability than animal models
Live Viral Vaccines

• Soooo.....

• Live virus titration assays may not be perfect, but they are one useful tool we have

• Their attributes and limitations should be considered in decisions about overages to account for adverse conditions and test error
Killed Viral Vaccines

- ELISA assays comparing test serial to qualified reference vaccine are most common
- Assay measures one or more relevant proteins
- Role of adjuvant is important for animal response
- Availability of viral antigen to the assay is key link to reference efficacy study
- Consistent extraction step part of validation
Killed Viral Vaccines

• ELISA assays recognized as more precise than TCID$_{50}$ assay
• Major area of regulatory focus
• Extensive interaction and input with industry led to rigorous acceptance criteria
• Complex assay qualification studies required
• Reference vaccine stability closely monitored
Killed Viral Vaccines

• Soooo.....

• Technical perspective: Little to no overage required for test error

• Regulatory perspective: 9 CFR 113.8 (a)(3)(ii) describes no requirement for overage due to adverse conditions and test error
Vectored Vaccines

- Dual-assay aspect makes this unique:
  1. Quantitate the vector by virus titration
  2. Determine portion of virions expressing target protein
     - Expression requirement/ ratio
     - e.g. immunofluorescent plaque assay
     - Possibly a QA type measurement
     - Parameters established during validation
  - Measurement used in the immunogenicity study
Vectored Vaccines

• Different MLV vectors may not always utilize host amplification
• Manufacturing methods may vary with vector backbone
• MLV regulations may or may not correlate well
Vectored Vaccines

• Conclusion:

Overage discussion should be product specific
Bacterins & Bacterial Extracts

• In vivo tests considered to be gold standard
  - e.g. hamster potency test for Lepto
  - guinea pig test for Clostridial bacterins

• Important opportunity for reduction of animal usage

• Living with a less precise in vivo assay

• Shouldn’t need burdensome requirements for in vitro assay
Bacterins & Bacterial Extracts

• Protein or lipid of relevance targeted for quantitation by:
  – ELISA
  – Immunoblot

• ELISA attributes previously discussed
Bacterins & Bacterial Extracts

- Bacterins may be more stable than MLV or ALC - potential preservative effect of inactivant
- Reduced overage required for stability loss
- Potential concerns with high protein/endotoxin levels
Toxoids

- e.g. Clostridial toxoids
- Lab animal model
  - in vivo tests outside scope of workshop
- Toxin neutralizing assay
  - expected to have similar variability to serum neutralization assays - $0.7 \log_{10}$
In-house release limit

• Common industry practice

• Built in overage at blending

• Insurance policy to ensure serials will pass
  – firm’s release testing
  – CVB’s release testing
  – through dating testing
Critical Backdrops

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Critical Backdrops

• Risks to increased antigen input:
  – Safety
  – Interference
  – Loss of solutions- present and future
  – Increased cost to consumers
Conclusions

• Throughout dating potency requirements should:
  – Have Minimum Protective Dose (MPD) as the basis
    - Mean potency of test lot at end of dating
Conclusions

- Throughout dating potency requirements should:
  - Have MPD as the basis
  - Be Data Driven
Conclusions

- Throughout dating potency requirements should:
  - Have MPD as the basis
  - Be data driven
  - MLV: Utilize harmonized approach
    - FDA
    - VICH
    - WHO
Conclusions

• Throughout dating potency requirements should:
  – Have MPD as the basis
  – Be data driven
  – MLV: Utilize harmonized standard
  – Inactivated products: No overage
    - Had been the CVB approach
    - No regulatory requirement for overage
    - No technical requirement for overage
Conclusions

• Throughout dating potency requirements should:
  – Have MPD as the basis
  – Be data driven
  – MLV: Utilize harmonized standard
  – Inactivated products- No overage
  – RISK BASED