Proposed Changes to (*in vitro*) Potency Testing Requirements for Batch Release of Veterinary Biologics in the United States

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Disclaimer

- These are proposals for discussion purposes only and are subject to review by the Office of General Counsel (OGC), the Agency and the Federal Register clearance process

A Thought

The tao that can be told
Is not the eternal Tao.
The name that can be named
Is not the eternal name

The unnamable is the eternally real.
Naming is the origin
Of all particular things.

Free from desire, you realize the mystery.
Caught in desire, you see only the manifestations.

Yet mystery and manifestations
arise from the same source.
This source is called darkness.

Darkness within darkness.
The gateway to all understanding

Tao Te Ching: Lao-tzu, translated by Stephen Mitchell, Harper & Row

A Second Opinion

"He who talks doesn't know,
He who knows doesn't talk"
"That is what Lao-tzu told us,
In a book of five thousand words.
If he was the one who knew,
How could he have been such a blabbermouth?"

Po Chu-I, poet and stand-up comedian, ibid

Introduction

- Current potency testing for U.S. Veterinary Biological Product is embodied in:
  - Title of the Code of Federal Regulations Section 113.8 (9CFR, 113.8)
  - Veterinary Services Memorandum 800.90
  - 9CFR Standard Requirements (SR)
  - Individual Firm Outlines of Production and Special Outlines

Task

- Clarify
- Facilitation 3R’s
- Revisit last set of changes to see if objectives were met
- Recommendations

Proposed changes (Summary)

- All potency assays covered by "Umbrella Potency Policy"
- Validated assays
- Direct antigen quantification
- Relative antigen quantification
- Qualified references with expiration dates and supporting stability data
- Quality assurance program for assays
- Potency references correlated to efficacy

Proposed changes (Summary)

- In-process potency testing + additional testing on finished product
- *in vitro* testing for reference requalification
- *in vitro* testing for stability of references and biological products
- 6 year dating on non-product references
- Elimination of repeat immunogenicity
- Potency testing of non-protective surrogate antigen or chemical moiety correlated to efficacy

Proposed changes-“Umbrella Potency Policy”

- Target and surrogate animal species
  - Vaccination-challenge
  - Vaccination-immune status evaluation (serology or CMI)
- Live agent quantification
  - For vectored products in conjunction w/expression assay
- *In vitro* relative potency evaluation
- *In vitro* direct quantification of antigen or active component
- Assays must be validated and qualified
  - Accuracy, precision, ruggedness, specificity, sensitivity, and dynamic range
  - Assay must be relevant

Proposed changes-“Umbrella Potency Policy” (cont’d)

- References qualified, expiration dating established by real time stability studies
- Quality assurance program implemented which can discriminate between valid tests and “no tests”
  - Require trend charts with ranges
    - Positive and negative controls
    - References
- Potency test correlated to efficacy
- Assays able to discriminate between satisfactory and marginally unsatisfactory serials (RP’s between 0.85 and 1.0) as part of validation process

Target and surrogate animal species: Vaccination-challenge

- Validated model
  - Qualified and clinically relevant
    - APHIS approved
    - Prospective data
    - Retrospective data
    - Literature references
- Validated challenge culture
  - APHIS approved
  - Prospective data
  - Retrospective data
  - Literature references

Target and surrogate animal species: Vaccination-immune status evaluation (serology for example)

- Validated relationship between immune status and efficacy
  - Prospective data
    - Dose titration studies
    - Passive immunization
  - Retrospective data
  - Literature references
- Validated assay
  - Elisa
  - Other immunoassays
  - Agent neutralization or -cidal assays
- Unexpired validated references

Live agent quantification

- Viral titer
  - Overage specified as plus $10^{1.2}$ added to the titer or equivalent of the approved efficacy trial serial
    - Overage a composite of:
      - $10^{0.5}$ for variation in production consistency (filling and manufacturing) and product stability
      - $10^{0.7}$ for test error
- Bacterial count
  - Overage specified as plus $10^{0.3}$ added to the titer or colony forming units or equivalent of the approved efficacy trial serial
- Other live agent
  - Specified in a filed Outline of Production or Special Outline or Standard Requirement

Live agent quantification (cont'd)

- All live agents
  - Stability must be verified by real time stability studies
  - Production consistency must be verified by APHIS approved studies
    - Overage may be reduced by demonstrating
      - Reduced test error
      - Production variation
      - Enhance real time stability
  - Validated assay

Live agent quantification (cont'd)

- Reference culture for growth promotion, culture characteristics and identity
- Potency release specifications, reference lot number, expiration date, and the approval date must be stated in a filed Outline of Production
- Procedures for conduct of the quantification may be detailed in the Outline of Production or a reference made to a filed Special Outline
- If bacterial or viral products are evaluated by methods other than $\log_{10}$ or organism count, an appropriate overage must be approved by APHIS and specified in the filed Outline of Production.

In vitro assays

- All *in vitro* assays
  - Qualified assay
    - Relevant to the material being assessed
    - Correlated to efficacy
      - Protective antigen
      - Non-protective surrogate antigen or entity

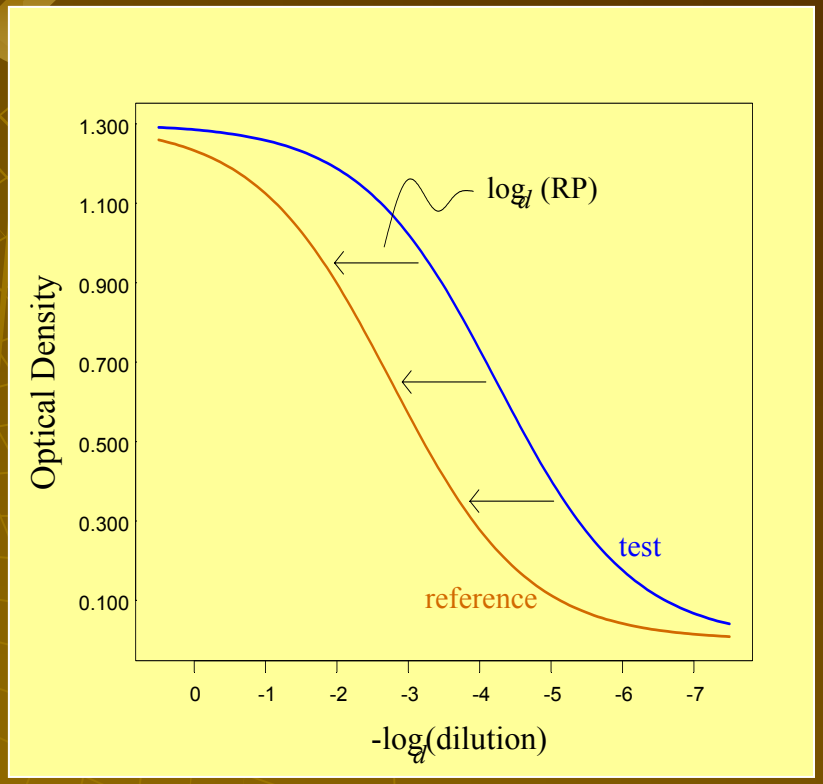
        Examples
        - Plasmid quantity and quality (DNA vaccines)
        - Immunomodulator (may be small molecule)
        - KDO as a measure of protective LPS
      - Must demonstrate ability to discriminate between efficacious and non-efficacious serials (between relative potency of 1.0 and 0.85, for example)
  - Validated assay

In vitro assays (cont'd)

- All *in vitro* assays
  - References must be unexpired, qualified, and have expiration dating established by real time stability studies
  - Quality assurance program implemented which can discriminate between valid tests and "no tests"
    - References
    - Positive and negative controls
    - Trend charts references and controls

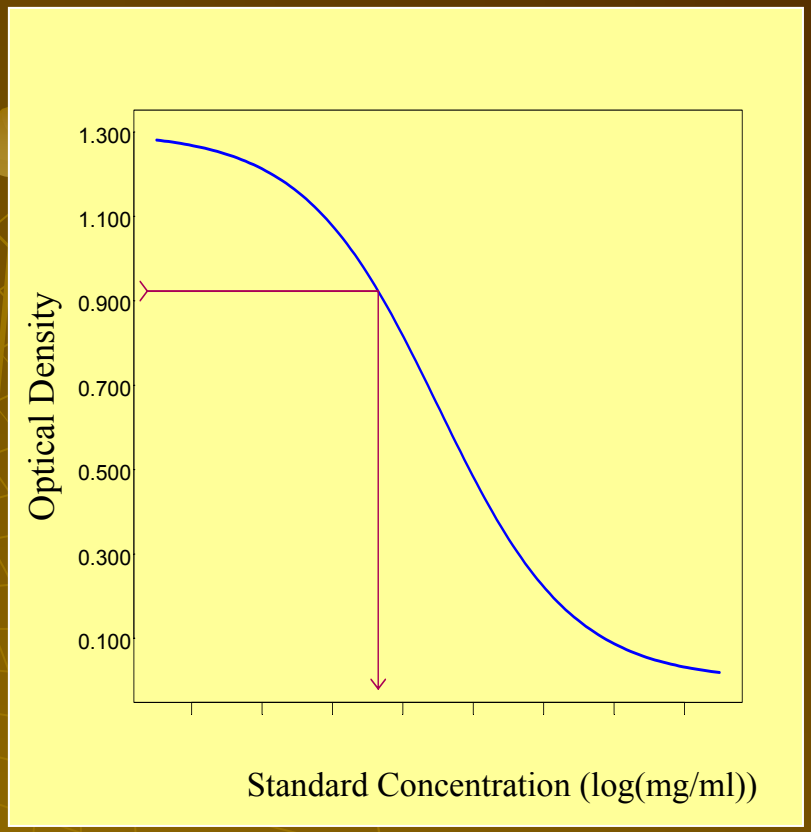
in vitro assays (cont'd)

- Relative antigen content (relative potency)
  - Evaluated by determination of the relative shift of parallel test and reference curves (typically estimated by a single relative potency parameter in nonlinear regression)



in vitro assays (cont'd)

- Direct antigen quantification
  - Evaluated by assessing the quantity of the antigen or entity of interest by interpolation on a standard curve against a reference or standards



All References

- **All references are initially qualified in animals**
- **Well characterized references may have stability established by *in vitro* assays subject to approval by APHIS**
- **Initial dating for product references is equal to product dating and subject to real time stability**
- **Non-product references may have an initial dating period of 6 years subject to verification by real time stability studies**

All References (cont'd)

- **Requalification of well characterized references may be established by *in vitro* testing subject to approval by APHIS**
- **Expiration date, lot number, approval date and test methods must be included in Section V. of the filed Outline of Production**
- **Subject to quality assurance monitoring**

Quality assurance monitoring

- Maintenance of QC charts or trend analysis
  - References and standards
  - Positive controls
  - Negative controls
- Demonstrate ability to discriminate between valid tests and invalid or "no tests"

In-process potency testing of inactivated products

- Potency test performed on bulk biologic product prior to final formulation
- Requires additional validated tests be performed on completed bulk or finished product (test panel)
- Test panel assesses qualitative and quantitative aspects of completed product
  - Test panel must evaluate parameters indicative of proper formulation, mixing, physical state and be acceptable to APHIS
  - Detailed or referenced in filed Outline of Production (detailed in filed Special Outlines)
  - Acceptance criteria for test panel must be stated in Section V. of the filed Outline of Production
  - Test panel outcome is part of serial release requirements and included on APHIS Form 2008
- Samples of bulk in-process material must be retained

Retest provisions

- **Stated in the filed Outline of Production**

New or Revised Definitions

- Potency
- Efficacy
- No-test
- Immune status evaluation
- Surrogate animal species
- Potency test
- Valid test
- Satisfactory
- Unsatisfactory
- Inconclusive
- Invalid test
- Retest
- Live vectored agent

Implementation

- New products must be in compliance if the Product License Application is submitted 6 months or more after the effective date of the final rule
- Currently licensed products will have 10 years from the effective date of the final rule with the exceptions below:
  - Currently licensed Products adding a new claim requiring an efficacy trial will be treated as a new product for each antigen affected
  - New products consisting of combinations of currently licensed products that require an efficacy trial for licensure will be treated as new products for each antigen requiring an efficacy trial

Anticipated detailed guidance documents

#	VSM temporary #	Content
1	800.aaa	Assay validation
2	800.bbb	In process potency testing
3	800.ccc	Live viral products
4	800.ddd	Live bacterial and other live products
5	800.eee	Retest provisions
6	800.fff	Efficacy defined
7	800.ggg	Stability of references and expiration dating of product
8	800.hhh	Reference qualification and requalification
9	800.iii	Host animal V-C
10	800.jjj	Surrogate animal V-C
11	800.kkk	Host animal serology
12	800.lll	Surrogate animal serology
13	800.mmm	Relative potency testing

Predicted Impact

- Stimulate development of *in vitro* assays for serial release
- Reduction in use of animals for testing
- Increase confidence in serial release tests
- Reduce costs to industry
  - Testing
  - Time

Acknowledgments

- TNTC of the Staff at CVB and members of AVBC and AHI