Synopsis of Issues Concerning 9 CFR 113.8 and VSM 800.90

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Flow of Presentation

- Impetus
- Chronology of Potency Testing Policies
- Development of a Potency Testing Policy

Impetus for Potency Testing Policy Review

- Commitment to reduction of animal use
- Improve quality of testing and testing regulations
- Utilize evolving technology

A Chronology of *In Vitro* and Potency Policy

1960-1970's

- All vaccines required vaccination & challenge of target or surrogate laboratory animals for serial release.
  - Most lab animal test models were not correlated to target animal protection (efficacy).
  - All animals were sacrificed at the end of the test

- Potency testing of live vaccines (virus) were replaced by quantification of live organisms (titration).
  - Major step toward reducing animal use and 1st example of *in vitro* potency testing.
  - Master Seed Lot Principle was introduced.
    - Requalification of the M.S. in host animals in 3 yrs
      - If satisfactory, then no additional requalification was required.

A Chronology of *In Vitro* and Potency Policy

1980's - Present

- 9 CFR 113.8 changed from "Virus titration in lieu of animal test for immunogenicity" to "*In vitro* tests …".
  - Opened the door to *in vitro* testing and expanded to live vaccines including viral and bacterial
- Minor revisions to 113.8 in 1991 to allow for organizational structure.
- In 1997, 9 CFR 113.8 was revised to include information on potency testing by relative antigen content as outlined in VSM 800.90.
  - VSM 800.90 intended as a guidance document and not a regulation
- NVSL/CVB RelPot computer program was developed
- Redefined "death" to reduce pain and suffering (9 CFR 117.4)

Impact of Current Regulations on Animal Usage

Type of Vaccine	No. ML P.C.	Total P.C.	% ML
Vaccines & Viruses	417	626	67
Bacterins & Bacterial Extracts	0	179	0
Vaccines w/ Bacterin-Toxoids	0	70	0
Toxoids	0	15	0
FFM	78	171	46
Total	**639**	**1314**	**47**

Current Status of Potency Testing Policy

- Single approved test particular to each licensed product
  - *In vivo* host animal vaccination-challenge
  - Host or surrogate lab animal serology
  - *In vitro* testing
    - Requires qualification of references in host animals
    - Others do not require references unless specified in 9 CFR or Outline of Production

Development of a Potency Testing Policy

TASKS:

- Review 9 CFR 113.8 and VSM 800.90
- Gather feedback from program and stakeholders
- Make recommendations to program and Directors
- Draft documents for discussion regarding changes in potency testing and reference qualification

What is “potency”?
What is “efficacy”?

Citations

- "Relative strength of a biological product as determined by test methods or procedures…." (9 CFR 101.5)
- Program definition: "…pure, safe, potent, and efficacious…to prevent preparation, sale, barter, exchange, or shipment…of worthless, contaminated, dangerous, or harmful virus, serum, toxin, or analagous product…" (VSTA).
- Master Reference is a reference whose potency is correlated, directly or indirectly, to host animal immunogenicity." (VSM 800.90 III.A.1.)
- Immunogenicity = the "ability of a biological product to elicit an immune response in animals as determined by test methods or procedures acceptable to APHIS." (9CFR 101.5(r)).
- "Potency assays measure the quantity of specific antigenic material present and compare that quantity to the dose shown to be efficacious." (*Vet Micro*, 1993 **37**:202).
- Efficacy = "specific ability or capacity of the biological product to effect the result for which it is offered when used under the conditions recommended by the manufacturer." (*Vet Micro*, 1993 **37**:202).

Potency: The quantity or relative strength of the active material that is required to produce the effect for which the product is licensed.

Efficacy: A measure of the expected direct effect of a product on a treated individual relative to non-treatment when used under the conditions recommended by the manufacturer.

Disclaimer: Definitions are for the purpose of discussion only. For current definitions, see 9 CFR

Development of a Potency Testing Policy

FINDINGS:

- "Umbrella" policy
- Common rules for all references and all assays
- Encourage movement away from animal testing
  - Utilize novel and emerging technologies whenever possible

Development of a Potency Testing Policy

FINDINGS (cont'd):

- Regulations and guidance documents have evolved along different paths over time
- Need for Regulations and guidance documents that are amenable to changing knowledge of animal health, disease, and technology
- Need consistent definitions for terms
- More specifics on how to do and come into compliance with requirements and recommendations
  - Utilize novel and emerging technologies whenever possible

Development of a Potency Testing Policy

FINDINGS (cont'd):

- Need consistency in the Regulations and guidance documents in order to alleviate misunderstandings by industry and CVB staff
- Regulations and guidance documents permit alternative *in vitro* testing but they are rarely used
- Some products have migrated to *in vitro* tests but the majority have not
- Products with Standard Requirements have been slow to change to *in vitro*
- Common features among all potency tests

Recommendations

- Look at all potency tests no just *in vitro*
- Provide incentives to firms to switch to *in vitro* tests
- Look for changes in Regulations nad guidance documents that would upgrade the current testing requirements
  - Improve the quality of the biological products while maintaining the pure, safe, potent, and efficacious credo we so often speak of

Conclusions/Summary

- A potency testing policy must recognize the common features of each of the potency testing regiments and design standard guidelines for common requirements.
- Each potency test must be qualified, validated, have references, and be monitored by a consistent quality assurance method.