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

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>No. ML P.C.</th>
<th>Total P.C.</th>
<th>% ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines &amp; Viruses</td>
<td>417</td>
<td>626</td>
<td>67</td>
</tr>
<tr>
<td>Bacterins &amp; Bacterial Extracts</td>
<td>0</td>
<td>179</td>
<td>0</td>
</tr>
<tr>
<td>Vaccines w/ Bacterin-Toxoids</td>
<td>0</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>Toxoids</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>FFM</td>
<td>78</td>
<td>171</td>
<td>46</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>639</strong></td>
<td><strong>1314</strong></td>
<td><strong>47</strong></td>
</tr>
</tbody>
</table>
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”?
“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 analogous 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
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 regimens 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.