Historical Perspective on Regulation of Potency of USDA Regulated Vaccines

Industry Perspective
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Canine Parvovirus was discovered as the causative agent of a new, often lethal, enteric disease of dogs in collaboration with Cornell and other labs.

End Result - An unexpected lifetime career developing veterinary biologics began.
Agenda

• Historical vs. current definitions of key titers
• Technological advances – potential impacts on variance
• The “Titer Creep” phenomena
• Personal observations on safety vs. lack of efficacy
• Impacts on costs, resources and new product development
• Questions
The diverse world of Vet Bios

- Includes:
  - Viral, bacterial, toxoid, *protozoal*
  - Live and inactivated
  - Conventional, *rDNA*, *synthetic protein*
  - Large combinations

- For use in:
  - Livestock to companion animals
  - Large to small, four legged to fins
  - Large integrated farms to back yards to homes

All regulated by a common set of regulations overseen by the USDA-CVB, including potency requirements
1. Immunogenicity Titer – Level demonstrated as protective in the host animal Immunogenicity study(s)
2. Titer through dating (0.7 logs-5x) over immunogenicity from MLV, 2X for bacterial vaccines and some bacterins
3. Release titer (0.5 logs -3.2x) over outdate titer for MLV
4. Maximum Release titer – maximum titer demonstrated as safe in host animal for certain markets (10X for MLV/2X for Inactivated). Product can not exceed in these markets (e.g. EU)
   • Of interest – Japan requires 100X for MLV and 10 X for inactivated – purpose to see what reaction you might get from too high a titer
Key studies

- **Host Animal Immunogenicity**
  - MID: Minimum Dose required for efficacy
  - MPD: Minimum Protective Dose (Demonstrated by Immuno Study)

- **Confirmation of Dating**
  - Through Dating Specification (Minimum Titer through dating)
  - Release Specification (Release Titer)

- **Host Animal Safety**
  - Maximum Titer

Dose response study – note that these do not always determine the MID.
Technological advances - Virus Titrations in the early 80’s

1. Manual dilution using 1 ml pipettes (that cotton plug stops all the bugs for mouth pipetting right?)
2. Metal flamed diluters
3. Rubber bulbs, hand diluters
4. First signs of pipetters
5. Microtiter plates for CPE, chamber slides for FA
6. No monoclonal antibodies, ELISA etc
Technological advances
Virus Titrations in the early 80’s

1. Basic Techniques
   • 10 fold dilution (usually $10^{-1}$ to $10^{-8}$)
   • 4-5 wells/dilution
   • Endpoints calculated by Reed-Muench or Spearman-Karber

2. Replications
   • 5X for immunogenicity vaccines
   • Single or duplicate for serials (per Production Outline)

3. Error range approximately 0.3 logs, common causes:
   • Age and cell density
   • Technique, quality of conjugates
   • Vial to vial variability
   • General sensitivity of the assay
Technological advances in the 80’s-90’

• Monoclonal antibodies
  • FA with an actual black background,
  • ELISA testing
• ELISA
  • Early antigen coated plates
  • Current sandwich ELISA
  • Concept of Relative Potency Assay
  • Increasingly sophisticated calculations
• Improved equipment
  • Multi-channel pipetters
  • Titration robots
• Error range for ELISA is more quantitative, but on average 0.1-0.2 RP viral product were still 0.3 logs.
Relative Potency – Some Lessons learned

1. Must know relationship between reference and test sample
   - In this case the fish was close to the camera making it look much bigger

2. Reference stability
   - If the reference decreases in potency, RP of test vaccine “appears” to increase
   - Need for reference requalification studies and more detailed guidance

Reference (known) – length of the two men’s arms

Fish – unknown (vaccine), a world Record catfish?
Mounting Requirements

- 9 CFR 113.8
- VSM 800.90
- VSM 800.92
- VSM Draft 110
- VSM 800.112
- VSM 800.211
- Revised VSM 800.112

- Parallel line immunoassay (linearity, specificity & reproducibility)
- Reference Preparation, Storage & Requalification
- Procedures (in vitro & in vivo) for monitor reference stability
- Full curve parallelism, assay verification parameter & stability monitoring using a combination of tools & controls
- Extended dating, incremental changes; legacy assays vs. new assays
- New Assays

Thanks to Shelly Zager - Zoetis
Based on a standard distribution curve if you assemble at your target value, 50% of titers will be above your target, but 50% will also be below.
Where does “titer creep” occur

• Requalification studies
  • Master Seed requalification - formerly required at 3 years, followed every 5 years after original immuno (prior to 1990).
    • In most cases the trend was for titers to increase 0.1-0.3 logs per requalification
  • Reference requalification – prior to VSM 800.211 was tied to reference. For product reference this could be as often as every 18 months.
    • In many cases RP of new reference was slightly higher than the previous reference

• Manufacturing
  • Serial production: Not wanting to see a 50% scrap level most firms add 0.3 to 0.5 (or 0.1-0.2 RP) to release titer to assure satisfactory results
Lack of Efficacy vs Safety
(personal observations)

• Primary causes of lack of efficacy
  • Maternal antibody override with MLV vaccine (e.g. CPV breaks in puppies prior to 16 weeks of age)
  • Strain variance or the emergence of new strains (e.g.) H2N3
  • Improper handling of vaccines (e.g. exposure to sunlight, storage of vaccines for extended periods following rehydration, improper cleaning of vaccinators)
  • Diet deficiencies (e.g. lack of Selenium in range cattle diet)

Bottom line – low titer vaccine was not the problem in most cases
Lack of Efficacy vs Safety
(personal observations)

• Safety Concerns due to high antigen level
  • Animals off feed or failure to thrive, poor feed conversion, decreased milk production
  • Local reaction (multiple causes),
  • Complaining pet owners – soreness, lethargy
  • Endotoxin reactions (may not be due to high antigen levels)
  • Interference with other vaccines/fractions administered concurrently or as a combination product

As a rule safety complaints far outnumbered lack of efficacy complaints
Historical Economic impact

- Cost of additional antigen for overage (0.7 logs)
- Additional cost of for “antigen creep” over time
- Difficulty in making specific combinations or products
- For international (largely EU) products
  - Time justifying overage
    - Old “because that’s how it’s always been and it’s the reg”
    - Newer “allows for 0.3 error in immuno titer determination and 0.3 log error in release determination and extra an 0.1 just because”
  - Issues with maximum allowed titer (can end up with narrow range between release at maximum)
  - Cost of international facility to make products for that region as an alternative.
Potential new impacts

• Still will not have a globally harmonized system
• Resources in testing new products and retrospectively testing older products if firm chooses
• Availability of product
  • Costs may not justify MUMS products
• General confusion for buyers (veterinarians etc.) as standards and dating change
• Likely no impact on product efficacy, potential increase in safety issues if titers increase
Questions - Comments