Implications of Potency Specifications

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Implication of the Lower Limit Potency Specification Choice & Confidence Level

VS
Balancing Act

Vaccine efficacy:
Ability of a vaccine to work as intended to protect from illness.

Vaccine-associated risk:
Probability increased adverse event that harm the individuals or population.

Policy Driven Decisions

• Every vial at or above the end of dating specification?
• Isn’t goal to ensure that what is marketed and administered is comparable to what was tested?
• Efficacy was determined with ½ of vials below the “MPD”, so why do 99% need to above “MPD” at the end of dating.
• Assumption that all product is used on the last day of dating?
• Assumption that efficacy is a dichotomous (binary) outcome?
The goal ... is to identify a minimum release limit (LRL) such that a lot with a potency test result at the minimum release limit (LRL) has a pre-specified assurance (usually based on 95% confidence ...) of retaining a mean potency at or above the desired minimum requirement (LL) at end-expiry.”

Krause - Goals of stability evaluation throughout the vaccine life cycle (2009)
Real World Example - MLV

• Efficacy potency – $4.6 \log_{10}$

• Review of stability data
  – CVB agreed the real-time stability data showed a mean potency loss of zero over the shelf life.
  – CVB assessed an additional assay variation overage of $0.3 \log_{10}$ based on the range of repeated titers observed across the time points and serials.
  – CVB originally set the release at – $5.5 \log_{10}$
  – CVB required an increase to – $5.8 \log_{10}$
    • 16X the efficacy potency
    • 10X the EU release level

• EU release – $4.9 \log_{10}$
Real World Example 2 - MLV

• Efficacy potency – 0.4 $\log_{10}$

• Review of Stability data
  – Mean potency loss of 0.2 $\log_{10}$ over the shelf life.
  – CVB originally set the release potency at 2.0 $\log_{10}$
  – CVB required an increase to – 2.8 $\log_{10}$
    • over 100 X the efficacy potency
    • 40X the EU release level

• EU release – 1.2 $\log_{10}$
When antigen content is significantly increased, simply cannot assume a vaccine will have the same biologic / clinical behavior as the level used to establish efficacy

- Safety
- Efficacy
- Formulation, Cost & Trade
SAFETY
Adverse Events

• Concern about driving increased levels of adverse events by significantly increasing potency levels.
  – Antigen, Adjuvant, “Constituent” material

• Dogs and Cats
  – Correlation between number of doses and AE
Feline Viral Vaccine

- Increased input of antigen fluids to ensure potency requirements were met
- Increased adverse events were reported from the field
Equine Live Viral Vaccine

• Field safety testing at the minimum release dose resulted in no safety issues

• Required overage resulted in increased local/systemic reactivity at a level that has generated a movement among horse owners against use of the vaccine.
Anti-Vaccine Movement

- Potential to drive the anti-vaccine movement among certain types of animal owners.
  - Primarily companion animal and equine
EFFICACY
Altered Immune Response

- Concern about changing the efficacy of products in an unpredictable manner
  - Tolerance / interference
  - The level of the antigen impacts the nature of the immune response
    - As antigen increases the humoral response increases and the cellular response decreases
More Is Not Necessarily Better

- Increased antigen doesn’t necessarily correlate with increased efficacy
Bovine Killed Bacterial –
increased potency requirement

**Monovalent**
- Passes potency
  - Generates the appropriate and expected serologic response

**Large Combination**
- This fraction cannot pass potency
  - Cannot incorporate sufficient antigen to generate the necessary serologic response in vaccinates
Antigen / Adjuvant

• Altering the antigen / adjuvant interaction

  – Specific sequences/ratios to optimize

  – When antigen is increased over a constant level of adjuvant, it changes the types of cells in the lymph node within which the antigen can be identified
FORMULATION, COST & TRADE
Formulation Capability –
Example 1

• A $0.2 \log_{10}$ difference in the required overage precluded the commercial launch of a product due to manufacturing constraints.
Formulation Capability – Example 2

- A product is on extended backorder due to an inability to produce the necessary yield to accommodate the required overage
  - Could be released based on stability data if the lower limit was the level used to demonstrate efficacy.
  - Vets are currently using lower potency versions of this same product off-label
    - The release and through-dating levels of these “low titer” products are above the demonstrated protective dose for the product that can’t be sold.
Formulation Capability – Example 3

• Bovine Killed Viral
• 10 years of safe and efficacious use in field
  – No reports from field of lack of efficacy
• After stability study
  – CVB looked at maximum variance and worst case scenario
  – Relative potency required at release raised from 1.0 to 2.4 (significant increase)
• Product cannot be profitably made at this level
  – Pulled from market after a decade of use
Dilution

• As antigen content increases more vaccine users will dilute vaccine
  – Current practice in many poultry operations
  – Current practice to some extent in swine
  – ½ dose practice in small weight dogs / cats
  – Can introduce uncertainty and potential for contamination
  – It moots the overage policy for sophisticated end users
Cost & Trade

• Increased costs due to increased antigen content will be passed along to customers

• Lack of Harmonization hinders international trade
  – Increased antigen levels harm the ability of US labeled product to compete in foreign markets with product manufactured with lower antigen content in Europe or other regions.
Conclusion

Rather than pursuing an approach that will harm animals and their owners, CVB should follow the rest of the world in its approach to evaluating stability and the setting of release and end of dating specifications.