Pre-harvest STEC vaccine approvals: Policy & Process

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Virus-Serum-Toxin Act of 1913
Virus-Serum-Toxin Act

…it is unlawful to:

- Sell worthless, dangerous, contaminated or harmful biologics
- Ship biologics unless they are:
  - Prepared in compliance with USDA regulations
  - Prepared in a licensed establishment
- CVB has a regulatory responsibility to ensure that licensed products comply with the provisions of the VSTA
Product Types

- Vaccines
- Bacterin and Bacterial Extracts
- Toxoids
- Bacterin-Toxoids
- Antitoxins
- Antiserum and Antibody Products
- Diagnostics
- Immunomodulators and Immunostimulants
- Allergenic extracts
- Includes Preharvest Vaccines
CVB Notice No. 05-07 “Biologics for Reduction of Colonization and/or Shedding in Animals”

- Clarified authority of the Center for Veterinary to regulate certain categories of biological products
  - Identifies managing the carrier state of disease as part of the management of disease.
    - Definition of biological products 9CFR Part 101.2
  - Describes the limits of the authority agreed upon by APHIS and FDA
    - “Animal vaccines targeted at reduction or elimination of a carrier state of organisms that can infect other animals (even if that infection is only rarely associated with significant clinical disease in animals)”
Establishes conditions necessary for APHIS jurisdiction
- Administered to animals only
- Act primarily by direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response.
- Label claims must be
  - factual
  - Supported by data
  - Restricted to reduction in colonization and/or shedding
How to license PHFS vaccines

- Multiple guidance documents to cover the majority of licensing issues
- CVB Notice 12-09
  - Describes how firms may engage the CVB to lay out a path to licensure
The steps that satisfactorily demonstrates P,S,P,E of the intervention

- A demonstration of the purity and identity of the seed and cell line
- Demonstration of a consistent vaccine production process
- Demonstration of efficacy, where efficacy generally reflects the prevention or mitigation of clinical disease in host animals and isn’t confounded by other interventions or variables
The steps that satisfactorily demonstrates P,S,P,E of the intervention (con’t.)

- Demonstration of safety in the host animal in a full-scale field trial setting
- Validation of a potency assay that measures the potency of serials of vaccine
- Successful production of commercial scale serials of vaccine (prelicensing serials)
Specific to PHFS vaccines

- Same basic framework
- Vaccines are targeted at the reduction or elimination of the carrier state of organisms
- Show a significant, meaningful, and relevant efficacy
  - Significant decrease in the number of animals colonized and/or numbers of organisms shed by vaccinated animals
The difficulties of demonstrating efficacy

- What is the baseline to compare to?
- Not a clinical disease of feedlot cattle
- No established challenge model
- No serologic correlate to vaccine efficacy
- Some cattle will clear, and some will continue to carry it
- Those carriers may sporadically shed the organism
- Widely variable prevalence within pens
- Requires large numbers (multiple pens/feedlots)
Additional issues

- Herd prevalence related to multiple factors
  - Environmental conditions
    - Mud, dust, humidity, ambient temperature, length of day, etc.
  - Diet
    - Different diets and changing diets
  - Stress levels of animals
  - Other management factors
  - Seasonal variation (although findings vary geographically)
  - Previous exposure
  - There are a number of different strains
    - Cross protection appears to be weak
    - Cattle can re-infect with other strains
Additional issues (con’t.)

- Relationship between colonization and shedding
  - Pass through vs. colonized
- Overall herd prevalence vs. Super-shedder
  - Which is more important to the intervention?
  - Very low prevalence can make data interpretation difficult as animals change status
- What’s the duration of immunity?
- At what point in the production process should efficacy determination be targeted?
  - Limits of authority
  - Is the effect great enough not to be lost when the cattle are presented for slaughter
PHFS vaccine challenges

- Multiple factors affect prevalence in field settings
- Limitations associated with experimental vaccination-challenge studies
- Guidance published in VSM 800.98 and VSM 800.202
Bottom line

- Conditional licenses are an option
  - Purity and safety fully established
  - Efficacy
- Expectation of efficacy for PHFS vaccine
  - The product should consistently result in some degree of positive vaccine effect
Labeling PHFS vaccines

- Labels and advertising must contain only factual statements supported by data.
- Should indicate how the product was evaluated.
- No food safety or human health claims, either implicit or explicit will be allowed.
Questions?