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# Pre-harvest STEC vaccine approvals: Policy & Process

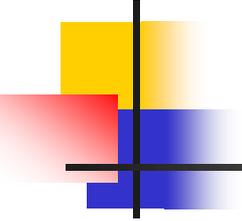
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Ames, Iowa 50010



# Virus-Serum-Toxin Act of 1913





# Virus-Serum-Toxin Act

...it is unlawful to:

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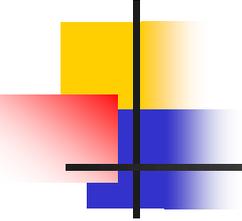
- Sell worthless, dangerous, contaminated or harmful biologics
- Ship biologics unless they are:
  - Prepared in compliance with USDA regulations
  - Prepared in a licensed establishment
- CVB has a regulatory responsibility to ensure that licensed products comply with the provisions of the VSTA



# Product Types

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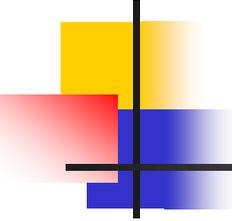
- Vaccines
- Bacterin and Bacterial Extracts
- Toxoids
- Bacterin-Toxoids
- Antitoxins
- Antiserum and Antibody Products
- Diagnostics
- Immunomodulators and Immunostimulants
- Allergenic extracts
- Includes Preharvest Vaccines



# CVB Notice No. 05-07 “Biologics for Reduction of Colonization and/or Shedding in Animals”

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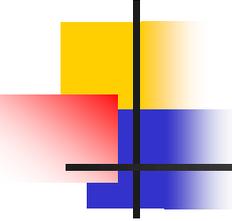
- Clarified authority of the Center for Veterinary to regulate certain categories of biological products
  - Identifies managing the carrier state of disease as part of the management of disease.
    - Definition of biological products 9CFR Part 101.2
  - Describes the limits of the authority agreed 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”



## CVB Notice No. 05-07 (cont' d)

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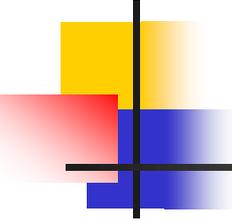
- Establishes conditions necessary for APHIS jurisdiction
  - Administered to animals only
  - Act primarily by direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response.
  - Label claims must be
    - factual
    - Supported by data
    - Restricted to reduction in colonization and/or shedding



# How to license PHFS vaccines

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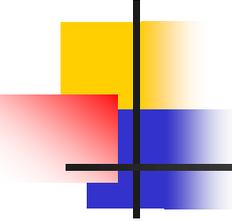
- Multiple guidance documents to cover the majority of licensing issues
- CVB Notice 12-09
  - Describes how firms may engage the CVB to lay out a path to licensure



# The steps that satisfactorily demonstrates P,S,P,E of the intervention

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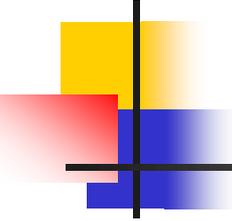
- A demonstration of the purity and identity of the seed and cell line
- Demonstration of a consistent vaccine production process
- Demonstration of efficacy, where efficacy generally reflects the prevention or mitigation of clinical disease in host animals and isn't confounded by other interventions or variables



## The steps that satisfactorily demonstrates P,S,P,E of the intervention (con't.)

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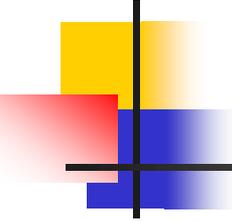
- Demonstration of safety in the host animal in a full-scale field trial setting
- Validation of a potency assay that measures the potency of serials of vaccine
- Successful production of commercial scale serials of vaccine (prelicensing serials)



# Specific to PHFS vaccines

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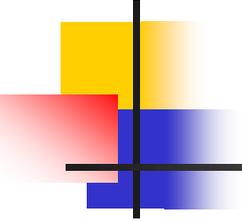
- Same basic framework
- Vaccines are targeted at the reduction or elimination of the carrier state of organisms
- Show a significant, meaningful, and relevant efficacy
  - Significant decrease in the number of animals colonized and/or numbers of organisms shed by vaccinated animals



# The difficulties of demonstrating efficacy

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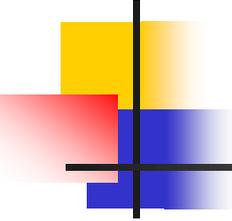
- What is the baseline to compare to?
- Not a clinical disease of feedlot cattle
- No established challenge model
- No serologic correlate to vaccine efficacy
- Some cattle will clear, and some will continue to carry it
- Those carriers may sporadically shed the organism
- Widely variable prevalence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



# Additional issues

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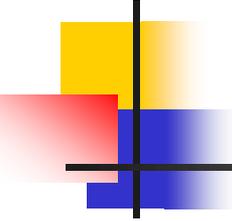
- Herd prevalence related to multiple factors
  - Environmental conditions
    - Mud, dust, humidity, ambient temperature, length of day, etc.
  - Diet
    - Different diets and changing diets
  - Stress levels of animals
  - Other management factors
  - Seasonal variation (although findings vary geographically)
  - 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.)

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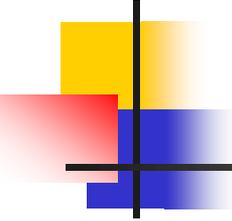
- Relationship between colonization and shedding
  - Pass through vs. colonized
- Overall herd prevalence vs. Super-shedder
  - Which is more important to the intervention?
  - Very low prevalence can make data interpretation difficult as animals change status
- What' s the duration of immunity?
- At 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

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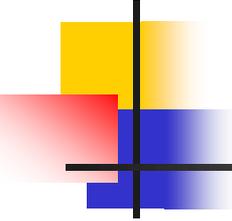
- Multiple factors affect prevalence in field settings
- Limitations associated with experimental vaccination-challenge studies
- Guidance published in VSM 800.98 and VSM 800.202



# Bottom line

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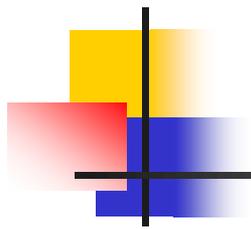
- Conditional licenses are an option
  - Purity and safety fully established
  - Efficacy
- Expectation of efficacy for PHFS vaccine
  - The product should consistently result in some degree of positive vaccine effect



# Labeling PHFS vaccines

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- 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



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Questions?