

Licensing of Vaccines as Pre Harvest Interventions by the Center for Veterinary Biologics

The Center for Veterinary Biologics (CVB), a unit in Veterinary Services under APHIS in the USDA, under the jurisdiction of the Virus-Serum-Toxin Act, regulates veterinary biologics products in the U.S. The licensing of a veterinary biological product, further described here as a vaccine, involves a series of steps that satisfactorily demonstrates the purity, safety, potency, and efficacy of the intervention. In simplest terms, this involves:

- A demonstration of the purity and identity of the seed and cell line used in producing the immunogen
- Development of a consistent vaccine production process in approved facilities
- Demonstration of efficacy, where efficacy generally reflects the prevention or mitigation of clinical disease in the host animal
- 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 and testing of commercial scale serials of vaccine

The licensing of pre-harvest vaccines follows this same basic framework except the vaccines are targeted at the reduction or elimination of carrier state of organisms (CVB Notice 05-07). This notice indicated products would be required to show significant, substantively meaningful, and clinically relevant efficacy as defined by APHIS. Additionally, the notice indicated that for claims of reduction of colonization and/or shedding, products must demonstrate the ability to cause a substantial decrease in number of animals colonized and/or numbers of organisms shed by vaccinated animals. To date, a limited number of studies have been designed and conducted to explicitly address these criteria. Licensing pre-harvest products can present some unique challenges due to the multitude of variables, some of which are poorly understood, that affect prevalence in the field setting (e.g., *E. coli* O157:H7) and the limitations associated with experimental vaccination-challenge studies. CVB's experience has been that in some cases industry has moved forward with studies without adequate consideration of study designs reflective of these factors, which has resulted in studies being conducted that cannot reasonably be expected to represent the performance of the intervention in general use (e.g., a population of feedlots).

As a step to make available vaccines to meet an emergency situation, limited market, local situation, or other special circumstances, the CVB can issue a Conditional License for products that have demonstrated safety and purity and for which a "reasonable expectation of efficacy" exists. The criterion for demonstrating a reasonable expectation of efficacy varies based on the circumstances. For pre-harvest vaccines considered to date, CVB has applied the expectation that the product will *consistently* result in some degree of positive vaccine effect consistent with the criterion provided in CVB Notice 05-07. As indicated in CVB Notice 09-03, a conditional license for a vaccine intended to reduce the prevalence and shedding of *Escherichia coli* O157:H7 in cattle has been issued.