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**United States Department of Agriculture**

Animal and Plant Health Inspection Service

Veterinary Services

Washington, DC 20250

# VETERINARY SERVICES MEMORANDUM NO. 800.209

**TO:** VS Management Team (VMST)
Directors, Center for Veterinary Biologics
Biologics Licensees, Permittees, and Applicants

**FROM:** John R. Clifford */s/ Jere L. Dick, for*
Deputy Administrator
Veterinary Services

**SUBJECT:** Bovine Corona Virus and Rotavirus Master Reference Qualification by Colostral Antibody Titers

## I. PURPOSE

The purpose of this memorandum is to inform interested parties that the Center for Veterinary Biologics (CVB) will allow the qualification of Master References used for serial release of vaccines containing inactivated bovine corona virus (BCV) and bovine rotavirus (BRV) based on agent-specific colostrum antibody titer, if there is a well-characterized relationship between the colostrum antibody titer and efficacy by passive immunity in neonatal calves.

## II. BACKGROUND

*In vitro* relative potency tests rely on the use of a Master Reference whose potency has been related to efficacy. Studies to qualify (reference qualification) or requalify (reference requalification) Master References have typically been conducted as vaccination-challenge studies in the target species. Vaccines containing BCV and BRV antigens that utilize an *in vitro* potency test for serial release have required vaccination-challenge studies for each pathogen. These studies are conducted in three stages: (1) vaccination of pregnant cattle, (2) feeding neonatal calves the colostrum, followed by (3) challenge of neonatal calves with one of the pathogens. At times, this challenge model system may not closely mimic field conditions, because the pathogenesis of neonatal diarrhea typically involves more than a single pathogen. Such studies are also complicated by the scarcity of adult cattle that are naïve to BCV and BRV. Consequently, study results utilizing experimental challenge models can be difficult to reproduce.

BCV and BRV vaccines are used to vaccinate cattle in order to improve the colostrum-derived immunity of neonatal calves nursing vaccinated cattle compared to those nursing

unvaccinated cattle. The protective mechanism is due, in part, to the high level of antibodies in colostrum directed against the disease-causing agents. A potential correlate of vaccine efficacy and, consequently, potency is the level of antibodies found in the colostrum of the vaccinated dams. It is reasonable that a particular level of agent-specific antibody in colostrum is associated with adequate protection in neonatal calves.

III. ACTION

A. *Titer-Response Relationship* - The CVB will consider proposals to qualify/ requalify BCV and BRV Master References by colostral antibody titer, provided there is a functional titer-response relationship between the agent-specific colostrum titer and the pathogen-specific response to challenge. A functional titer-response relationship means that the probability of the response can be predicted from the colostral titer with reasonable precision.

B. *Study Design* - The titer-response relationship must be estimated from studies designed for that purpose and specify the primary outcome either with a case definition that categorizes calves as affected or unaffected by challenge or with an explicit measure of disease severity. The antibody titers of the colostrums must span a range from a level associated with low efficacy to a level associated with high efficacy. This may require experimental formulation of colostrum mixtures with known antibody content. To do so, colostrum from vaccinated cattle may be diluted with colostrum from nonvaccinated cattle.

C. *Required Titer* - If there is a functional titer-response relationship, and the titers and response span a suitable range, a statistical model of the functional relationship can be estimated. The model may then be used to predict the response probability associated with any particular antibody titer. The required titer is that for which the expected probability of a vaccinated calf being unaffected by challenge is 80% ($ED_{80}$). The $ED_{80}$ must be estimated with enough precision so that its confidence interval is no wider than 35%.

D. *Master Reference Qualification or Requalification* - Conduct a study with a minimum of 20 vaccinated animals. Include a sentinel group of five animals to monitor exposure during the study. Cattle used in the vaccination-challenge studies are not required to be seronegative for BCV and BRV. In studies to qualify or requalify references based on colostral antibody levels, the animals should have a serostatus similar to those used in the vaccination-challenge studies that established the titer-response relationship.

1. *BRV* - A BRV Master Reference may be qualified or requalified if at least 80% of the vaccinated cattle have a colostral antibody titer that meets or exceeds the $ED_{80}$.

2. *BCV* - It is often difficult to isolate the role of the BCV-specific titer-response relationship from protection afforded by other antigens present in the vaccine complicating the estimation of the BCV titer-response relationship.

   If the BRV titer-response relationship has been well characterized, and a high level of protection against BCV challenge has been demonstrated in passively immunized calves, the CVB will consider requests for reference qualification by colostral titer for BCV also. If approved, the BCV $ED_{80}$ will be the 80th percentile of the distribution of the BCV colostral antibody titers observed in the pivotal efficacy studies.

E. *Antibody Titration Assay* - The test method used to titer or quantify the antibody level in colostrum must be validated as per Veterinary Services Memorandum 800.112.

IV. SCOPE AND IMPLEMENTATION

This policy is effective immediately for BRV and BCV antigens as an alternative to target animal challenge and may be applied to currently licensed products, those in the prelicense stage, and future products.