

USDA Requirements for Testing Bovine Viral Diarrhea Vaccines for Fetal Protection

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Current Regulations and Guidance

- Title 9 Code of Federal Regulations (9CFR)
Section 113.215—MLV BVD vaccine
- 9CFR Section 113.311—killed BVD vaccine
- 9CFR Section 112.7(e)
- Center for Veterinary Biologics Notice
02-19
- Veterinary Services Memorandum 800.110

9CFR 113.311

- First published 1974; last amended 1991
- Immunogenicity requirement:
 - 20 vaccinates, 5 controls
 - Challenge 14-28 days post-vaccination
 - Valid test:
 - 4/5 controls must be leukopenic
 - At least 19 vaccinates must have 1:8 or > VN titer
 - At least 19 vaccinates must remain clinically healthy

9CFR 113.215

- First published 1990—no amendments
- Immunogenicity established “by a method acceptable to APHIS”
- Serial potency or batch release requires that 4/5 calves vaccinated generate a VN titer of 1:8 or greater *or*
- After challenge with a virulent strain of BVD, 2/3 control calves must show a temp rise to 104.5° and develop respiratory or other clinical signs of BVD and 4/5 vaccinated calves must remain healthy and afebrile.

9CFR Sections for BVD Products

- Neither section addresses issues related to reproductive disease or reproduction-related label claims.

9 CFR 112.7(e)

- In the case of bovine rhinotracheitis vaccine containing modified live virus, all labeling except small final container labels shall bear the following statement, “Do not use in pregnant cows or in calves nursing pregnant cows.” *Provided*, That such vaccines which have been shown to be safe for use in pregnant cows may be excepted from this label requirement by the Administrator.

9 CFR 112.7(e)

- Although label statement not specifically required, BVDV vaccines containing modified live virus also carry a label warning not use in pregnant cows or in calves nursing pregnant cows
- *Unless* there is acceptable data to support safety in pregnant cows

CVB Notice 02-19

- Vaccine Claims for Protection of the Fetus against BVDV
- Clarifies data needed to support various label claims against reproductive effects of BVDV
- Applicable to all BVDV products
- Due to complexity of BVDV disease, separate, specific claims for various aspects of the disease necessary

CVB Notice 02-19

- Aids in prevention of abortion
- Aids in prevention of persistently infected calves
- Aids in prevention of fetal infection or aids in prevention of fetal infection, including persistently infected calves

Aids in prevention of abortion

- Fetal death, with resorption or mummification, or abortion may occur following BVD infection in early to mid-gestation up to 120 days
- Abortion must occur in an acceptable proportion of nonvaccinated control cattle
- Appropriate challenge strains must be used in vaccination/challenge studies *or* acceptable field studies may be performed

Aids in prevention of persistently infected calves

- Infection of fetus with noncytopathic BVD before fetus achieves immunocompetence (~120 days gestation) may result in persistent infection and immunotolerance. Such calves may be born alive and survive for varying periods up to adulthood; they are persistent carriers and shedders of BVD and are seronegative
- Challenge pregnant cattle at 75-90 days of gestation and perform virus isolation on fetal tissues on, or after, 150 days of gestation

Aids in prevention of fetal infection

- Claim may also include persistently infected calves
- When infection (with cytopathic or noncytopathic BVD) of the dam occurs in late gestation (>150 days), there may be fetal infection with antibody formation
- Challenge pregnant cattle at 75-90 days of gestation and perform virus isolation on tissues of fetuses on or after 150 days of gestation plus challenge pregnant cattle at 180 days of gestation and evaluation fetuses (or calves) at, or after, ≥ 220 days of gestation

Veterinary Services Memorandum

800.110

- Provides guidance for claiming an exemption to 9CFR 112.7(e)
- To obtain label claim indicating modified live IBR and/or BVD vaccine may be used in pregnant cows, and calves nursing pregnant cows

V.S. Memo 800.110

- Modified live BVDV vaccine containing noncytopathic BVDV may **not** be recommended for use in pregnant cows or calves nursing pregnant cows

VS Memo 800.110

- 1200 pregnant heifers and cows
 - 3 groups of 400 animals each, representing each stage of pregnancy
 - All cattle followed through parturition
- Randomization
 - Vaccine group; modified live test vaccine
 - Control group; inactivated vaccine or PBS

VS Memo 800.110 Data

■ Abortions

- Animals that do not deliver a live calf
- Abortions due to diagnosed causes other than BVDV or IBRV excluded from data analysis
- Aborted calves should be necropsied and results included in report
- Study must be repeated in any trimester group in which abortion rate exceed 5%
- Exemption may not be approved if rate of abortion due to IBRV or BVDV exceeds 0.5% in any trimester group

V.S. Memo 800.110 Data

■ BVDV

- Pre-suckling serum samples from at least 100 randomly chosen calves from second and third trimester groups tested for antibody to IBR, BVD Type 1 and BVD Type 2; no exemption if any positive test

■ Adverse Events monitoring

- CVB may monitor adverse events reported to firm after exemption; if evidence of safety problems is encountered, CVB will take appropriate actions

Adverse Events

- 9CFR 116.5—Reports
- If, at any time, there are indications that raise questions regarding the purity, safety, potency, or efficacy of a product...the manufacturer must immediately notify APHIS concerning the circumstances and the action taken, if any.
- Notification may be made by mail to Director, Center for Veterinary Biologics, Inspection and Compliance, 510 South 17th Street, Suite 104, Ames, IA 50010–8197; by electronic mail to cvb@usda.gov; by fax to (515) 232–7120; or by telephone to (515) 232–5785.

Report Adverse Events

Contact: Manufacturer & CVB

<http://www.aphis.usda.gov/vs/cvb/ic/adverseeventreport.htm>

or by

Phone: 1-800-752-6255

Fax: (515) 232-7120

**Mail: Center for Veterinary Biologics
510 S. 17th Street, Suite 104
Ames, IA 50010**