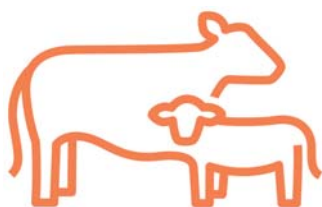


TECHNICAL BULLETIN

AUGUST 2014



Fetal Protection Indications Give Bovi-Shield GOLD[®] FP[®], CattleMaster[®] GOLD FP[®], and PregGuard[®] GOLD FP[®] Important Advantages

Key Points

- Modified-live virus (MLV) vaccines have played a pivotal role in helping reduce reproductive losses associated with infectious bovine rhinotracheitis caused by bovine herpesvirus type 1 (BHV-1) and bovine virus diarrhea caused by bovine virus diarrhea virus (BVDV), and in a survey were named the second most important animal health innovation of the past 50 years.¹
- MLV vaccines help provide a clinically effective, and long lasting protection.²⁻⁷
- Vaccines containing all killed viral (KV) components need 2 doses administered in a narrow booster interval and even then they can fail to help provide protection sufficient to achieve fetal protection label claims for BVD or IBR.
- Surveillance data indicate that laboratory confirmed MLV-associated IBR abortions in pregnant cattle are rare and predominantly occur when MLV vaccines are not used according to label instructions.^{13,14}
- None of the vaccines composed of all KV components have a fetal protection (FP) label claim against IBR abortions or an indication for prevention of persistent infection (PI) caused by BVDV.
- A Fetal Protection Guarantee program gives producers confidence that cattle properly vaccinated with BOVI-SHIELD GOLD[®] FP[®], PREGGUARD[®] GOLD FP[®], or CATTLEMASTER[®] GOLD FP[®] will be free from IBR-associated abortions and that calves born to vaccinated cows or heifers will not be persistently infected with BVDV.

By virtue of *in vivo* replication in the host, MLV bovine respiratory-reproductive vaccines help provide a clinically effective, rapid, and long lasting protection compared to their KV counterparts.^{2,7}

Fetal infection followed by pregnancy wastage, including abortion, and the birth of persistently infected calves, are some of the most costly consequences of two common viral diseases of cattle, infectious bovine rhinotracheitis (IBR) caused by bovine herpesvirus type 1 (BHV-1) and bovine virus diarrhea (BVD) caused by BVD virus (BVDV) types 1 and 2. In fact, some epidemiologists believe that the cost of reproductive loss in the cattle industry well exceeds the cost of bovine respiratory disease, the traditional focus of infectious disease in cattle.^{8,9} Expressly to curtail IBR- and BVD-associated reproductive disease, parenteral modified-live virus (MLV) BHV-1 and BVDV vaccines with a fetal protection (FP) claim in addition to a respiratory indication were introduced a decade ago and have become mainstays of the cow-calf industry.

Although MLV agents are attenuated by serial passages in tissue culture, FP vaccine labels specify the following precautions, (1) primary vaccination of heifers and cows should be given 30 to 60 days prior to breeding (and this should be the second FP immunization given) and (2) pregnant cows or calves nursing pregnant cows should be vaccinated only when the dam has been previously vaccinated within the past 12 months. These practices help ensure that pregnant heifers and cows will have a sufficient degree of pre-existing strain-specific immunity prior to exposure to that MLV vaccine during pregnancy, to help minimize the possibility of vaccine-induced fetal infection and abortions.

Producers have a choice between MLV and inactivated/killed-virus (KV) vaccines for the major bovine viral respiratory-reproductive diseases (IBR, BVD, parainfluenza type-3, and bovine respiratory syncytial virus infection). KV vaccines can be utilized in pregnant cows without the preconditions

described for MLV vaccines, but they lack demonstrated fetal protection label claims for IBR abortions or BVD PI calves. KV vaccines typically elicit a less complete immune response of shorter duration compared to MLV vaccines.²⁻⁷ A hybrid vaccine (CATTLEMASTER® GOLD FP®) contains a blend of modified-live and killed viruses, and is safe for use in pregnant cows without preconditions while carrying fetal protection label claims for IBR abortions and BVD PI's. The choice between the vaccine options has become a matter of debate due to occasional reports of increased incidence of abortions in herds where MLV BHV-1 vaccines were used.^{3,10,11} This technical bulletin provides current Zoetis pharmacovigilance data, diagnostic laboratory survey data on IBR incidence, and data on abortions in cattle vaccinated with BOVI-SHIELD GOLD FP (Zoetis) MLV respiratory-reproductive vaccines. Additionally, this technical bulletin discusses the risks and benefits of MLV vaccines versus KV vaccines for prevention of IBR and BVD reproductive diseases, and label recommendations for proper use of BOVI-SHIELD GOLD FP to help achieve maximum efficacy and safety.

Rationale for MLV Vaccines

In 2013, Beef magazine conducted an online survey asking >45,000 subscribers to select the most important innovations of the past 50 years in the livestock industry. With good reason, MLV vaccines were named the second most important animal health innovation (ahead of long-acting antibiotics and beef quality assurance practices) and the eighteenth most important innovation overall.¹ By virtue of *in vivo* replication in the host, MLV bovine respiratory-reproductive vaccines help provide a clinically effective, and long lasting, demonstrated protection compared to their KV counterparts.²⁻⁷

Dramatic reductions in the prevalence of bovine respiratory-reproductive diseases can be attributed in part to widespread use of MLV vaccines. For example, in the 1960s and 1970s before the advent of MLV vaccines for bovine viral respiratory and reproductive diseases, BHV-1 associated “abortion storms” affecting 25% or more of the pregnant cows in a herd were often reported.^{5,12} In herds regularly vaccinated with MLV bovine respiratory-reproductive vaccines, such outbreaks are now rare, a <3% incidence of clinical bovine reproductive disease is considered a reasonable goal, and the disease-sparing effects of MLV IBR and BVD vaccines are well established.^{13,14}

No KV vaccines for IBR or BVD have a FP label claim against BHV-1 abortions or an indication against BVDV persistent infection (PI), the sequela that occurs when the immunologically naïve fetus is infected early in gestation with a noncytopathic strain of BVDV. Calves born with PI are lifetime shedders of BVDV and a principal driver of herd-to-herd transmission and maintenance of BVDV within herds and in the cattle population. MLV vaccines (in some but not all cases) have a FP claim for IBR abortions and a label indication for prevention of PI against BVDV types 1 and 2. As experts have noted, a truly successful BVD PI control program depends on prevention of fetal infection by proper vaccination, implementation of a BVD PI testing program, and removal of persistently infected cattle.^{9,15}

As the full implications of BVDV-PI have emerged, there has been increased emphasis in ensuring reproductive efficacy in bovine viral disease vaccination programs.⁹ BOVI-SHIELD GOLD FP, PREGGUARD GOLD FP, and CATTLEMASTER GOLD FP vaccines are designed to help meet both of these infectious disease challenges.

Modified-Live vs. Killed Virus Vaccines

The great advantage of MLV bovine respiratory-reproductive vaccines is their immunogenicity compared to KV vaccines. For example, investigators have found that vaccination of feedlot calves with a single parenteral dose of a MLV combination vaccine as early as 72 hours before challenge resulted in reduced post-challenge IBR clinical signs and BHV-1 titers in nasal secretions.¹⁶ Vaccinated calves in that study also had 39% to 76% greater weight gains compared to non-vaccinated controls.

In another study, BHV-1 seronegative calves were given a single parenteral dose of either of two commercial MLV-IBR vaccines five days before BHV-1 challenge.¹⁷ Despite the short post-vaccination interval, when compared to non-vaccinated control calves, MLV-vaccinated calves had substantially better protection from clinical disease, decreased viral shedding, and a marked increase in interferon- γ expression, an indicator of cell-mediated immunity (CMI). MLV agents for BHV-1 and BVDV also have an extended duration of immunity. For example, BOVI-SHIELD GOLD FP has demonstrated a 12-month duration of immunity against IBR-abortion and PI caused by BVDV types 1 and 2.

The limitations of a KV vaccine for prevention of BHV-1 abortion and stillbirth were illustrated in a study where seronegative heifers (n = 21) were vaccinated with a commercial KV IBR-BVD vaccine (Vira Shield® 6, Novartis) prior to breeding.¹⁸ Despite receiving two vaccine doses, the pregnant heifers had a BHV-1 confirmed abortion rate of 14.3% (3/21). Although the reduction in abortion rate was lower compared to what occurred in non-vaccinated controls (all 14

As experts have noted, a truly successful BVD PI control program depends on prevention of fetal infection by proper vaccination, proper biosecurity and biocontainment, and removal of persistently infected cattle.^{9,15}

The Wyoming authors concede that incidence data was not generated by a controlled study, and laboratory diagnosis of abortions was not reported, so a true assessment of the relationship between vaccination and abortion cannot be made.¹⁰

aborted), not all vaccinated heifers were protected and the study results were not compatible with an approved FP indication.

Reports of Vaccine Associated Abortions

Veterinary Diagnostic Laboratory Study

A retrospective study of abortions reported by five university veterinary diagnostic laboratories found an overall IBR abortion rate of 1.4% (264/19,549) for the cases submitted from 2000 to 2010.¹⁹ Of the 19,549 abortion cases, 6,948 were tested for IBR. Of the cases tested for IBR from 2000-2005, the confirmed incidence of IBR abortions was 2.7% (108/4,032), versus an incidence of 5.3% (156/2,916) from 2006-2010. Although the increase was statistically significant ($p < 0.001$) for only one of the laboratories, this trend reflects an overall increase in IBR-confirmed abortions over the decade of the study.

Importantly, a careful analysis of matched pairs of BHV-1 positive submissions with a history of IBR vaccination and an equal number of random negatives found no association between vaccination and BHV-1 positive abortions ($p = 0.27$). Furthermore, analysis of unmatched data from submissions for which a complete vaccination history was available found that failure to vaccinate for BHV-1 was almost twice as common in cases of BHV-1 confirmed abortions (27.9%, 24/86) compared to BHV-1 negative cases (15%, 12/80, $p = 0.068$). This suggests that vaccination had a positive effect in helping prevent abortions from natural exposure to BHV-1. The authors concluded that, as a percentage of total abortions, a BHV-1 diagnosis over this ten year time period was rare, at 1.4% (264/19,459) and, did not appear to have a relationship

to increased MLV vaccination usage. To the contrary, increased MLV vaccination was associated with reduced diagnosis of IBR.

Wyoming State Veterinary Laboratory Report

A recent Wyoming State Veterinary Laboratory report addressed the incidence of all-cause abortions on a >5,000-head dairy herd in Utah over a four-year period (2008-12).¹⁰ When use of a MLV BHV-1 vaccine given according to label directions was discontinued in 2009, abortion prevalence in this herd decreased from a weekly high of 1.6% (85/5,300) in vaccinated cows to 0.7% (44/6,200) in non-vaccinated cows (herd size is approximate based on a graphic depiction of data). The authors concluded that vaccination was associated with increased risk of reproductive loss.

While a circumstantial relationship between vaccination and abortions seemed to exist in this herd, several aspects of the report should be noted. As the authors conceded annual incidence data were not generated by a controlled study comparing the number of abortions in vaccinated and non-vaccinated cows during the same time period, so a true assessment of the relationship between vaccination and abortion cannot be made. Laboratory diagnosis of any of the abortions was not reported, so the number attributed to BHV-1 (whether from natural infection or vaccination) or other pathogens is unknown.

While the highest weekly abortion rates in the dairy herd occurred in vaccinated cows, so did the lowest, and on a repeated basis. The abortion rate in vaccinated cows was <10 per week for at least 16 weeks during a 20-month period from 2008-10. In contrast, the abortion rate in non-vaccinated cows never dropped below 10 for any week during a 28-month period from 2010-12.

Stated another way, for at least 16 weeks, abortions in vaccinated cows were suppressed to a level (<10/week) that was never achieved even once by non-vaccinated cows. Interpreted in this light, vaccination could be considered to have had a positive effect in helping prevent abortions from natural exposure to the abortigenic viruses BHV-1 and BVDV. The annual incidence of abortions in the herd throughout the four-year period of 15%, whether in vaccinated or non-vaccinated cows, was very high by most standards.^{8,20} This suggests that management factors or infectious disease other than IBR were causing an unusually high rate of abortions in the herd.

Inappropriate use of MLV vaccines typically involves failure to administer a prebreeding dose of MLV vaccine to heifers approximately 30-60 days prior to breeding.

Pharmacovigilance Monitoring Data

The Veterinary Medical Information and Product Support (VMIPS) Group at Zoetis maintains a rigorous pharmacovigilance program to monitor any customer-reported failure of product efficacy and safety, including those related to the company's bovine viral respiratory-reproductive vaccines. Their findings related to the Zoetis FP vaccine franchise, including customer reports of abortions and other reproductive loss in vaccinated cattle, have been compiled on an annual summary basis going back to 2002. The metric used by the USDA for monitoring product performance is the number of adverse reproductive events (AEs) per 10,000 doses distributed. This metric has consistently been in the range of 0.02 to 0.04 per 10,000 distributed since BOVI-SHIELD GOLD FP was introduced in 2002.²¹ Sales of the various vaccines in the FP group have averaged >16 million doses annually, an

indication of the extent to which beef and dairy producers have embraced the use of MLV bovine viral respiratory-reproductive vaccines in general and their acceptance of BOVI-SHIELD GOLD FP specifically.²²

While such data is useful in evaluating product performance, the number of AEs is not synonymous with an incidence rate for the following reasons:

- The company does not know precisely how many animals were vaccinated, only the number of doses sold.
- Not all doses were used in pregnant animals.
- Pregnant heifers vaccinated with a FP vaccine are really the population of interest, not pregnant cows, which generally have some prior BHV-1 exposure and rarely have diagnosed, vaccine-associated abortions.

In an effort to provide some further context around the AE numbers, an effort was made to overcome these confounding factors by using pregnant heifers population estimates compiled by the National Animal Statistics Service (NASS) of the USDA vaccination practices reported by the National Animal Health Monitoring survey, and Zoetis sales data. Using these data, an estimated rate of laboratory-diagnosed BHV-1 abortions reported to Zoetis for pregnant heifers can be calculated. **Table 1** shows the rates for heifers vaccinated according to label directions with BOVI-SHIELD GOLD FP for the five-year period 2007-11.^{21,23-25}

The BHV-1 abortion rate in vaccinated pregnant beef, dairy, and all heifers was 1.82, 0.22, and 0.54, respectively, per 10,000 doses sold. The considerably higher abortion rate in pregnant beef heifers was probably due to a higher overall level of immunity in dairy cattle as a result of more frequent vaccination prior to breeding. The USDA has not

Pregnant cows generally have prior BHV-1 exposure and rarely have diagnosed, vaccine-associated abortions.

Table 1. Estimated rate of reported IBR diagnosed abortions in heifers vaccinated with BOVI-SHIELD GOLD FP according to label recommendations, 2007-11^{21,23-25}

Bovine population	Estimated no. doses used in pregnant heifers (000s)	Reported IBR abortions per 10,000 doses	EU frequency grouping*
Dairy	3,010	0.22	Very rare
Beef	1,094	1.82	Rare

EU = European Union Veterinary Medicinal Products, Summary of Product Characteristics, June 2007.²⁵

*Rare = >1 but < 10 per 10,000 animals; very rare = <1 per 10,000 animals.

Producers that opt to not use a MLV vaccine due to a safety concern related to IBR need to understand the risk they are assuming as it relates to KV vaccines, which offer no label indications for IBR abortions and BVD PI's.

established comparators for these numbers. However, these numbers can be put in perspective by using the European Union's (EU) guidelines for AE frequency.²⁶ Using those standards, BHV-1 abortion rates in heifers properly vaccinated with BOVI-SHIELD GOLD FP are characterized as either very rare (<1 case per 10,000 animals) in dairy heifers or rare (>1 but <10 cases per 10,000 animals) in beef heifers and in the overall sample population.

Pharmacovigilance data are necessarily imprecise and not synonymous with incidence or prevalence data compiled in an epidemiological study. However, it is another measure of relative frequency of BHV-1 abortions in vaccinated cattle. The vaccine-associated data compiled by Zoetis for its bovine FP vaccines indicate that post-vaccination abortions predominantly occur in heifers rather than in multiparous cows because most cows have been previously vaccinated or naturally exposed, and that this type of AE is predominately due to inappropriate off label use of the vaccine. Using accepted criteria for AE reporting, abortions in cows vaccinated according to label recommendations with BOVI-SHIELD GOLD FP vaccines are rare and AEs overall are low.

Protection against BVDV Persistent Infection

A comprehensive program to help prevent bovine viral respiratory and reproductive diseases assumes that cattle will be vaccinated against BVD as well as IBR. Beef and dairy producers who use a MLV IBR-BVD vaccine potentially benefit not only from FP against BHV-1 abortions but protection against BVDV-associated PI, a condition that only results from *in utero* infection. In some beef herds and dairies, the multi-systemic effects of BVD usually represent a greater disease-management challenge than IBR. BVD is usually subclinical in adult cattle.³ Thus, fetal infection early in gestation before the fetus becomes immunocompetent can escape notice until the reproductive effects become evident in the form of early embryonic death, mummifications, and open cows. The more dire consequences of BVDV infection in a herd are due to the persistently infected calf transmitting infection to other herd mates, resulting in a variety of clinical manifestations including respiratory disease, digestive tract infections, mucosal disease and death. In addition, persistently infected calves in close proximity to pregnant cows contribute to more persistently infected calves in the following years' calf crop. Producers that opt to not use a MLV vaccine due to a safety concern related to IBR need to understand the

risk they are assuming as it relates to the fact most BVD KV vaccines do not provide BVD PI protection. Other BVD syndromes include respiratory disease, digestive tract infections, thrombocytopenia, and high-mortality mucosal disease.

None of the IBR-BVD KV vaccines have a FP claim against BHV-1 abortions or an indication for prevention of BVDV-PI. Choosing a KV IBR-BVD vaccine can forfeit the reproductive efficacy indications that a MLV vaccine can help provide against these abortigenic viruses. Producers who opt to use a IBR-BVD KV vaccine to help avoid the small likelihood of MLV-associated BHV-1 abortions risk reproductive loss from BVDV infection, not to mention the possibility of PI that can maintain the presence of the virus in the herd.

The ability of BOVI-SHIELD GOLD FP to prevent BVDV-associated viremia in heifers and PI in their calves was demonstrated in two challenge-of-immunity studies. In the first study, vaccinated heifers (n = 20) and placebo control heifers (n = 10) were bred 56 days after vaccination.²⁷ Heifers were challenged intranasally with a heterologous strain of BVDV type 2 on day 146, five months after vaccination. Post-challenge BVDV viremia occurred in all 10 control heifers but none of the vaccinated heifers. Persistent BVDV infection occurred in the nine live calves born to non-vaccinated control

heifers but in none of the 18 calves born to vaccinated heifers. Uniform occurrence of BVDV viremia in control heifers and PI in control calves affirmed the severity of challenge in this study.

A second challenge study, conducted by investigators at Auburn University, provided a direct comparison of the efficacy against BVDV-PI provided by two commercial MLV BVD vaccines and a KV vaccine.⁶ Twenty beef heifers in each of the respective vaccine groups were vaccinated at weaning, 28 days post-weaning, at one year of age and 28 days later. All vaccinated and 10 non-vaccinated control heifers were then commingled from 68 to 126 days of gestation with three animals persistently infected with BVDV. Rather than a one-time challenge, this study placed pregnant heifers in continuous contact with persistently infected cattle, mimicking the type of challenge that often exists in field settings.

As shown in **Table 2**, BVD viremia was detected in all 10 control heifers and BVD PI in all 10 of their calves, confirming that widespread exposure to BVDV occurred during the lengthy contact-challenge period. Only the heifers vaccinated with BOVI-SHIELD GOLD FP were completely protected from post-challenge BVD viremia and from BVD PI in their calves. It was noteworthy that despite multiple vaccine doses, only half the heifers given the KV vaccine were protected

Only the heifers vaccinated with Bovi-Shield GOLD FP were completely protected from post-challenge BVD viremia and from BVD PI in their calves.⁶

Producers who opt to use an all Killed vaccine to avoid the remote chance of MLV BHV-1 abortions face risk of BVD associated reproductive loss in addition to the overall complex calf health consequences of BVD herd infection that extends throughout the production cycle.

Table 2. Auburn University study results comparing efficacy of commercial MLV and KV vaccines against BVDV viremia in pregnant heifers and persistent infection in their calves⁶

Test group	Post-challenge incidence of BVDV infection	
	Viremia in dams	Persistent infection In calves
Nonvaccinated controls	10/10	10/10
BOVI-SHIELD GOLD FP 5 (Zoetis)	0/20	0/20
Commercial MLV vaccine	1/20	0/20
Commercial killed-virus vaccine	10/20	2/18

from BVDV viremia and that two of their calves (10%) developed BVD PI, an incidence of PI that would be sufficient to expose numerous susceptible animals and establish BVDV within a herd.

The Zoetis Fetal Protection Guarantee

As an affirmation of the confidence it has in the protection and 12-month duration of immunity provided by its bovine FP vaccines, Zoetis offers a Fetal Protection Guarantee against IBR abortions and BVDV PI in calves born to cows and heifers vaccinated according to label directions. The Zoetis FP Guarantee applies to all vaccines in the BOVI-SHIELD, PREGGUARD, and CATTLEMASTER vaccine families with a FP indication (see **Table 3**). Under the terms of the guarantee, the cost of diagnostic testing to obtain laboratory confirmation of BVDV PI or IBR abortions will be assumed by Zoetis. If a positive diagnosis for BVDV PI or an IBR abortion is established, Zoetis will pay for the loss of the value of the animal.

The requirements of the Fetal Protection Guarantee are that:

- Cows or heifers should have been vaccinated with a Zoetis FP vaccine approximately 30 days prior to breeding initially and annually thereafter.
- Heifers should receive at least two doses of BOVI-SHIELD GOLD FP or PREGGUARD GOLD FP, with the second dose given approximately 30 days prior to breeding.

The Fetal Protection Guarantee supports BOVI-SHIELD GOLD PF, CATTLEMASTER GOLD FP, and PREGGUARD GOLD FP products. The program is administered by the company's VMIPS group (reached at 800-366-5288). Proof of purchase is required, and calves born to BVDV-PI dams do not qualify for the guarantee.

Table 3.
Zoetis line of vaccines covered by a Fetal Protection (FP) guarantee

Bovi-Shield GOLD® FP®
PregGuard® GOLD FP® 10
CattleMaster® GOLD FP®

Summary

The greatest economic impact of IBR and BVD is reproductive loss due to IBR abortions in pregnant cows and BVD persistent infections in calves.^{8,9}

For this reason, modified-live virus (MLV) IBR and BVD vaccines with a fetal protection (FP) claim, such as BOVI-SHIELD GOLD FP, are widely used by beef and dairy producers.

There have been occasional reports of suspected or laboratory confirmed IBR abortions in pregnant cows and heifers that were vaccinated during gestation with MLV IBR vaccines. Epidemiologic and pharmacovigilance data indicate that these adverse events are rare and often the result of failure to use MLV vaccines according to label instructions. In particular, producers need to better understand the importance of a prebreeding vaccination program for heifers or naive cows, and be mindful not to overlook veterinarian pre-breeding vaccine recommendations.

IBR-BVD KV vaccines do not have a fetal protection label claim against IBR abortions or an indication for prevention of persistent infection (PI) caused by BVDV. BOVI-SHIELD GOLD FP, PREGGUARD GOLD FP, and CATTLEMASTER GOLD FP have fetal protection label claims, and by virtue of *in vivo* replication in the host, help provide clinically effective, and long lasting protection.

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