

Pfizer Animal Health

Technical Bulletin

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FarrowSure® GOLD B: Profiling efficacy and safety of a new, reformulated 2-mL dose vaccine

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Key Points

- Rigorous immunogenicity and field safety studies were conducted to evaluate the efficacy and safety of FarrowSure® GOLD B, the new 2-mL formulation of Pfizer Animal Health's combination vaccine for use as an aid in protecting breeding swine against porcine parvovirus (PPV), leptospirosis, and erysipelas.¹⁻⁶
- FarrowSure GOLD B protected 85% of pigs challenged with virulent *Erysipelothrix rhusiopathiae* at 18 weeks after vaccination.³
- The PPV, *Leptospira bratislava*, and *L. hardjo* fractions of FarrowSure GOLD B passed serological tests for non-inferiority to the licensed vaccine FarrowSure® B.^{1,2}
- Field safety studies indicated that FarrowSure GOLD B in combination with the swine influenza virus vaccine FluSure® was safe for use in pre-breeding gilts (2 doses) and in pregnant sows and gilts (dose given 2 to 4 weeks before farrowing).^{4,6}

FarrowSure GOLD B, introduced to the swine production industry in March 2008, is the 2-mL reformulation of Pfizer Animal Health's vaccine for use in healthy breeding swine as an aid in preventing reproductive failure caused by PPV, erysipelas caused by *Erysipelothrix rhusiopathiae*, and leptospirosis caused by *L. bratislava*, *L. canicola*, *L. grippotyphosa*, *L. hardjo*, *L. icterohaemorrhagiae*, and *L. pomona*. The vaccine is a liquid preparation of PPV grown on an established porcine cell line; a serum-free, clarified *E. rhusiopathiae* culture; and whole-cell cultures, prepared using a proprietary manufacturing process, of the six *Leptospira* serovars listed above. All eight vaccine fractions are chemically inactivated and adjuvanted with two adjuvants, including Amphigen®, to enhance the immune response.

Prior to introducing the 2-mL formulation, Pfizer Animal Health conducted a comprehensive series of immunogenicity and field safety studies to confirm vaccine efficacy and safety by demonstrating:

- Serological non-inferiority in swine of the PPV, *L. bratislava*, and *L. hardjo* fractions compared to the licensed product FarrowSure B
- Potency of the *L. canicola*, *L. grippotyphosa*, *L. icterohaemorrhagiae*, and *L. pomona* fractions by codified assays
- Duration of immunity (DOI) against *E. rhusiopathiae* in a challenge model
- Field safety in breeding-age swine when administered in combination with FluSure®



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Recapping Key Efficacy and Safety Studies

Non-inferiority of the PPV, L. bratislava, and L. hardjo fractions^{1,2}

The non-inferiority test model is widely accepted as a primary tool for comparing the immunogenicity of a new or reformulated vaccine to an already existing licensed product.^{7,8}

Non-inferiority studies were conducted with the PPV, *L. bratislava*, and *L. hardjo* fractions to compare the serological antibody responses of pigs vaccinated with 2-mL of FarrowSure GOLD B to the responses of pigs vaccinated with the 5-mL FarrowSure B product. In the PPV study, 28 or 32 pigs were assigned to each treatment group and 10 to the nonvaccinated control group; in the *L. bratislava* and *L. hardjo* study, 80 pigs to each group and 40 to the control group.

Treated pigs in all studies received two doses of their respective vaccine at a three-week interval. Blood samples were collected from each pig prior to each vaccination and again two weeks later (Day 35). Sera were analyzed by the hemagglutination inhibition (HI) test for antibodies to PPV and by the microscopic agglutination test (MAT) for antibodies to *L. bratislava* and *L. hardjo*. For serological equivalence, a non-inferiority value of 70% was considered passing.

RESULTS:

The non-inferiority values for the PPV, *L. bratislava*, and *L. hardjo* fractions of

FarrowSure GOLD B on Day 35 were 79.4%, 384.9%, and 164.2%, respectively (Table 1). All three fractions of the 2-mL FarrowSure GOLD B product passed the test for non-inferiority to the 5-mL FarrowSure B vaccine.

*Long-Term Efficacy of the Erysipelas Fraction*³

An erysipelas challenge study was conducted at 18 weeks post-vaccination to establish duration of immunity with the *E. rhusiopathiae* fraction of FarrowSure GOLD B. Twenty vaccinates and 10 controls were enrolled in the study. Following challenge with a National Veterinary Services Laboratory (NVSL) strain of *E. rhusiopathiae*, vaccinates and controls were monitored once daily for seven days according to the following three categories:

RECTAL TEMPERATURE

- Control pigs were considered infected if they showed a fever of at least 105.6°F (40.9°C) for at least two consecutive days
- Vaccinates were judged unprotected if they showed a fever at the lower threshold of 104.6°F (40.3°C) on any two consecutive days

MORTALITY RELATED TO CHALLENGE

To confirm that death was caused by the challenge agent, *E. rhusiopathiae* had to be recovered from the spleen or liver.

SYSTEMIC CLINICAL SIGNS OF ERYSIPELAS

- Depression
- Hyperemia, primarily evident over the

Table 1 — Serological antibody titers to PPV, *L. bratislava*, and *L. hardjo* and non-inferiority test results (Day 35) for FarrowSure GOLD B

Vaccine Fraction (assay)	Antibody Titer (GMT) by Treatment Group			Non-inferiority Evaluation	
	FarrowSure GOLD B (2-mL)	FarrowSure B (5-mL)	Sentinel Control	Test Value	Test Decision
PPV (HI)	63.1	54.0	4.0	79.4%	Passed
<i>L. bratislava</i> (MAT)	2565.7	512.0	26.9	384.9%	Passed
<i>L. hardjo</i> (MAT)	92.2	42.2	2.4	164.2%	Passed

HI = hemagglutination inhibition; GMT = geometric mean titer; MAT = microscopic agglutination test

- ears and underline
- Skin lesions characteristic of erysipelas
- Joint involvement characterized as lameness or stiffness

If controls showed clinical signs of erysipelas but failed to meet criteria in the other two categories during the seven-day post-challenge period, they still qualified as infected by having a positive culture on Day 7 following challenge.

Any vaccinate showing clinical signs was automatically considered unprotected against erysipelas.

A valid challenge study required that at least 8 of the 10 control pigs become infected as determined by at least one of the evaluation criteria.

RESULTS:

Table 2 presents results of the erysipelas duration of immunity challenge study:

- 80% of controls qualified as infected on the basis of temperature alone.
- 85% of vaccinates were protected following a virulent challenge at 18 weeks following vaccination. Three

vaccinates had a qualifying fever and only one of these pigs exhibited hyperemia.

Safety Studies^{4,6}

To test the safety of the new 2-mL formulation of FarrowSure GOLD B-FluSure, field studies were conducted in commercial production units located in Indiana, Michigan, and North Carolina. Altogether, 205 pre-breeding gilts and 611 gestating sows and gilts were enrolled.

INDIANA STUDY PROTOCOL⁶

In the Indiana study, 205 pre-breeding gilts approximately 18 to 20 weeks of age were vaccinated intramuscularly on Day 0 with 2 mL of either one of two serials of FarrowSure GOLD B-FluSure followed by a second 2 mL dose three weeks later (Day 21). Gilts were observed for immediate post-vaccination reactions after each injection. Clinical observations were made and injection sites scored on Days 1 through 3, 10, 22 through 24, and 35. The scoring system (Table 3) ranged from 0 to 3; injection site reactions scored as a 3 were considered clinically relevant. All adverse reactions were

Table 2 — Results of the 18-week *E. rhusiopathiae* duration of immunity challenge study conducted with FarrowSure GOLD B

Treatment Group	No. of Pigs	No. of Pigs meeting disease criteria*	No. of Pigs Protected	% of Pigs Protected
Controls	10	8	2	20
FarrowSure GOLD B	20	3†	17	85

*Temperature for two consecutive days: ≥105.6° F for nonvaccinated controls
 ≥104.6° F for FarrowSure GOLD B vaccinates

†2/20 by fever alone; 1/20 by fever and hyperemia

Table 3 — Injection site scoring system for all sites in the FarrowSure GOLD B-FluSure field safety studies

Score	Criteria
0	No visible injection site.
1	A visible injection site < 1.5 cm diameter zone of cutaneous erythema. No evidence of irritation.
2	Injection-site swelling 1.5 - 5.0 cm diameter with or without cutaneous erythema, visible subcutaneous or intramuscular swelling. May be evidence of irritation, such as occasional rubbing against the injection site.
3	Injection-site swelling > 5.0 cm diameter, visible subcutaneous or intramuscular swelling, accompanied by evidence of irritation such as persistent rubbing at injection site. May be pink or reddish in color. May or may not have exudates.

observed until resolution. On Days 4 through 9 and 11 through 35, trained site staff made general health observations for injection-site reactions, changes in appetite, systemic reactions, lame animals, and any other abnormal observations. The Investigator reviewed all abnormal findings to determine whether they were attributable to vaccination.

MICHIGAN AND NORTH CAROLINA PROTOCOLS^{4,5}

At each of the sites in Michigan and North Carolina, approximately 300 gestating sows and/or gilts were vaccinated intramuscularly on Day 0 with a 2 mL dose of either one of two serials of FarrowSure GOLD B-FluSure (approximately 100 animals per serial) or a saline placebo (approximately 100 animals) at approximately two to four weeks prior to farrowing. Sows/gilts were blocked by parity class (0,1, or ≥ 2) for allotment to treatment. All of the breeding females were observed for immediate post-vaccination reactions. Clinical observations were made and injection sites scored (Table 3) once daily on Days 1 through 3, 9, and 21. As in the Indiana study, only injection site reactions scored as 3 were considered as clinically relevant. General health observations (injection-site reactions, changes in appetite, systemic reactions, reproductive abnormalities, lame animals, and others) were recorded daily by trained farm staff on Days 4-8 and 10-21, or until farrowing for sows and gilts that had not farrowed

by Day 21. In the North Carolina study, sows/gilts that farrowed before Day 21 were only observed until farrowing. Reproductive data were transcribed from farrowing cards or PigChamp™ records. Abortion data, litter information (alive/stillborn/mummies/dead), and percent of litters normal at farrowing were recorded but not analyzed.

RESULTS — PRE-BREEDING GILTS (INDIANA):

Table 4 presents results of the safety study conducted in pre-breeding gilts. Of the 205 vaccinated gilts, only one showed a clinically relevant injection-site reaction during the period immediately after vaccination (Day 1). Characterized as raised and slightly pink in nature, the reaction resolved within one day. No other reaction was described as clinically relevant (score of 3) on Days 1 through 3 or 10. None of the general health observations performed by trained site staff on Days 4 through 9 and 11 through 35 were attributed to vaccination. Of the pre-breeding gilts revaccinated (n = 202) on Day 21, only one exhibited a clinically relevant injection-site reaction during the immediate post-vaccination period. By Day 25, this lone reaction was resolved (4 days post-vaccination). No other clinical observations were attributed to the vaccines on Days 22 through 24 or on Day 35. The data indicated that FarrowSure GOLD B-FluSure was safe for use in pre-breeding gilts when administered according to label directions.

Table 4 — Injection-site reactions in pre-breeding gilts (Indiana)

	Treatment	No. of Gilts	% of Gilts*
First Vaccination	Serial 1	103	1.0
	Serial 2	102	0.0
Second Vaccination†	Serial 1	101	1.0
	Serial 2	101	0.0

*Injection site score of 3 (> 5 cm) on Days 1, 2, or 3 after vaccination.

No injection site reactions were observed by the Investigator on Days 10 or 35, or by the farm staff on any of the other study days.

†Two gilts were unsuitable for continuing on the study for health reasons unrelated to vaccination and were removed by the Investigator. One additional gilt was revaccinated with the incorrect serial, and the data after revaccination were not included in the summary and analysis.

RESULTS —GESTATING SOWS AND GILTS (MICHIGAN AND NORTH CAROLINA):

Results of injection-site scoring for gestating sows and gilts enrolled in the Michigan and North Carolina safety studies are recorded in Table 5 and Figure 1. At the Michigan site, 9 (8.8%) sows/gilts vaccinated with Serial 1 and 11 (11.0%) vaccinated with Serial 2 had scores of 3 on days 1, 2 or 3 post-vaccination. Described as a red and/or flat or raised area, the reactions were of short duration, with only a few (6 with Serial 1; 6 with Serial 2) present for more than a single day. No scores of 3 were observed on Day 9 or after. No abscesses were

recorded during the study. At the North Carolina site, 11 (10.7%) sows/gilts receiving Serial 1 and 10 (9.9%) receiving Serial 2 had an injection site score of 3 on days 1, 2, or 3 post-vaccination. The reactions were described as a raised area with no discoloration. Only two sows/gilts had a score of 3 (one each with Serials 1 and 2) for more than one day, and no score 3 reactions were reported on Day 9. Farm staff described injection sites as a raised area with no discoloration in 24 sows/gilts on other days of the study. No sows/gilts had an injection site reaction remaining on Day 21 and no abscesses were recorded during the study.

Table 5 — Injection-site reactions in gestating sows and gilts (Michigan and North Carolina)				
Site	Treatment	No. of Animals	% of Animals*	
			Score 3 ever	Score 3 >1 day
Michigan	Placebo	100	0	0
	Serial 1	102	8.8	5.9
	Serial 2	100	11.0	5.0
North Carolina	Placebo	104	0	0
	Serial 1	103	10.7	1.0
	Serial 2	101	9.9	1.0

*Injection-site score 3 (>5 cm) on Days 1, 2, 3, or 9 after vaccination.

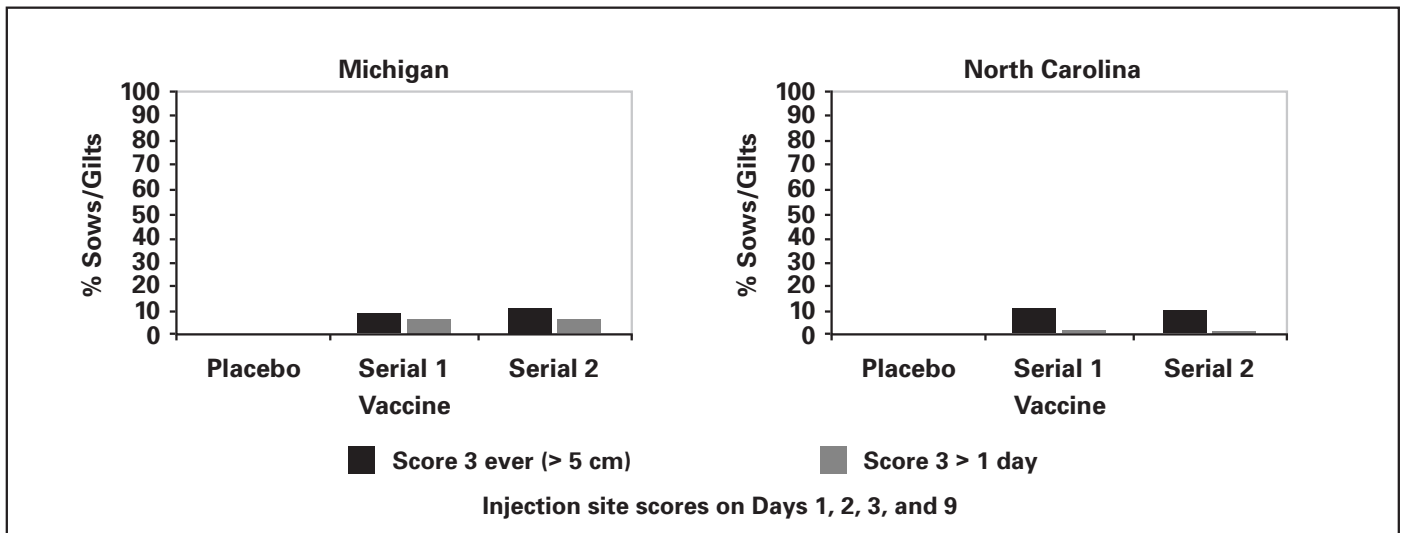


Figure 1 — Percentage of pregnant sows/gilts with injection-site reactions.

Clinical observations other than injection-site reactions attributed to vaccination on Days 1 through 3 and Day 9 are reported in Table 6. At both sites, no clinical observations were evident on Day 21 after vaccination. Only four additional observations were recorded at the Michigan site. These sows/gilts were depressed or uncomfortable and left feed on a single post-vaccination evaluation time point. No sows/gilts had abnormal general health observations attributed to vaccination by the Investigator on any other study days. At the North Carolina site, six sows/gilts (placebo, n = 1; Serial 1, n = 3; Serial 2, n = 2) were anorexic on a single day and 19 (placebo, n = 4; Serial 1, n = 10; Serial 2, n = 5) had a decreased appetite at some point during the three

days immediately following vaccination. One of Serial 1 sows/gilts was also depressed during the same observation period and one was off feed on Days 4 and 5. Swelling was observed in front of the injection site on Day 9 in six sows/gilts. No other clinical signs or abnormal health observations were attributed to vaccination on any other study day.

No abortions occurred in vaccinated sows/gilts at either the Michigan or North Carolina sites; however, at the North Carolina site five abortions were observed in the control group sows/gilts. Although the data were not statistically analyzed, farrowing information was collected at each site. Tables 7 and 8 summarize the mean and percent born alive, mean num-

Table 6 — Other pre-farrowing clinical observations (Michigan and North Carolina)

Site	Treatment	No. of Sows/Gilts	% Ever with Clinical Sign*
Michigan	Placebo	100	0
	Serial 1	102	2.0
	Serial 2	100	2.0
North Carolina	Placebo	104	4.8
	Serial 1	103	14.6
	Serial 2	101	8.9

*Clinical observations, other than injection-site reactions, attributed to vaccination and scored on Days 1 through 3 and on Day 9. None were present on Day 21 at either site.

Table 7 — Farrowing data across all parities at Michigan site

Treatment	No. of Litters Observed	Reproductive Assessment				
		Mean Born Alive	% Born Alive	Mean Stillborn	Mean Mummies	% of Normal Litters
Placebo	100	11.7	92.4	0.8	0.3	100
Serial 1	100	12.3	91.9	1.0	0.2	100
Serial 2	98	11.1	92.3	0.9	0.1	100

Table 8 — Farrowing data across all parities at North Carolina site

Treatment	No. of Litters Observed	Reproductive Assessment					
		Mean Born Alive	% Born Alive	Mean Stillborn	Mean Mummies	Mean Low Viability	% of Normal Litters
Placebo	99	11.4	88.6	0.6	0.9	0.0	100
Serial 1	104	11.9	91.4	0.5	0.7	0.0	100
Serial 2	101	11.5	89.7	0.6	0.7	0.1	99

ber of pigs stillborn, mean number of mummies, mean low viability (North Carolina only), and percent of normal litters across all parities at each site. The five control group sows that aborted at the North Carolina site and their litters were not included in the reproductive variables documented in Tables 7 and 8. Data collected from pregnant sows/gilts at these two sites indicate that FarrowSure GOLD B-FluSure is safe for use in gestating swine.

Cumulatively, the field safety studies conducted with FarrowSure GOLD B-FluSure involved substantial numbers of breeding swine and showed that two vaccine serials had a good safety record. Observed adverse events, injection-site reactions, and other clinical observations were transient and qualitatively inconsequential. The studies indicated that two doses of FarrowSure GOLD B can be safely administered to pre-breeding gilts and that booster doses can be safely given to pregnant sows as late as two to four weeks prior to farrowing (73 to 101 days of gestation).

Discussion

The 2-mL reformulation of FarrowSure GOLD B has been designed to maintain the superior efficacy associated with FarrowSure B against eight of the leading causes of reproduction failure in swine while at the same time providing a solid safety profile under field use conditions. Efficacy was established in a series of serological and challenge-of-immunity studies that demonstrated:

- Non-inferiority of the PPV, *L. bratislava*, and *L. hardjo* fractions when compared with the same fractions of FarrowSure B
- Potency of the *L. canicola*, *L. grippotyphosa*, *L. icterohaemorrhagiae*, and *L. pomona* fractions by codified tests

- Duration of immunity with the erysipelas fraction that extended to 18 weeks after administration of the second vaccine dose

To assure safety, field studies involving substantial numbers of pre-breeding gilts and gestating sows and gilts were conducted at commercial sites. These studies established that:

- FarrowSure GOLD B-FluSure was safe for use in pre-breeding gilts when both doses of vaccine were administered according to label directions.
- FarrowSure GOLD B-FluSure administered to pregnant sows and gilts at 2 to 4 weeks prior to farrowing resulted in reactions that were minimal in number, of little consequence in severity, and transient in duration.
- Variations in reproductive measurements in pregnant sows and gilts vaccinated with FarrowSure GOLD B-FluSure were within the production norms of the commercial test sites.

Based on results of the efficacy studies, producers can expect comparable levels of protection against parvovirus, erysipelas, and leptospirosis by using the 2-mL FarrowSure GOLD B product as they would from using the 5-mL FarrowSure B product. Based on field safety studies, producers can also expect that the reformulated 2-mL vaccine is safe for use in breeding-age and gestating swine.

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