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PRODUCT DEVELOPMENT FOR ESTROUS SYNCHRONIZATION: BEEF CATTLE

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Introduction

Physiological principals underlying synchronization of estrus identified 1) hormones naturally controlling the estrous cycle of cattle, 2) hormones commercially available, 3) mode of action of the hormones commercially available, and 4) when/how they might be used to manage estrus and breeding of beef cattle.

The products available are progestogens (melengestrol acetate (MGA) and progesterone delivered via CIDR), prostaglandin F_2 alpha ($PGF_{2\alpha}$ and $PGF_{2\alpha}$ analogs), and gonadotropin releasing hormone (GnRH). Progesterone and progestogens block estrus. If delivered for sufficient time, removal of the progestogen block will allow cattle to return to estrus in a pre-determined synchronized interval. $PGF_{2\alpha}$ and $PGF_{2\alpha}$ analogs regress the corpus luteum (CL) when administered during d 6 through 18 of the estrus cycle, resulting in cattle returning to estrus on about d 2 through 6 post-injection. GnRH induces the release of an ovulatory surge of LH resulting in ovulation of a dominant follicle or initiation of a new follicular wave.

Cattle estrous synchronization was perceived in the late 1950s and 1960s to meet an unmet need of beef cattle producers who desired to utilize artificial insemination (AI). During the 1950s, frozen bovine semen was developed and AI with progeny tested bulls became recognized as effective to make more rapid genetic progress for milk yield and beef production. In the 1950s and 1960s, a major detriment to AI in beef cattle was the requirement for daily estrus detection and AI over 60-90 d or more. Ulberg et al. (1951) reported progesterone injected daily in cattle would block estrus. Based on this information and understanding of the bovine estrous cycle in 1960, progesterone injected daily or a progesterone analog (progestogen) delivered daily for 18 d was the only potential means for cattle estrous synchronization. Progesterone is not active orally; and at that time, there was no identified delivery method for progesterone that was economically acceptable to the beef industry. $PGF_{2\alpha}$ and GnRH were not known at the time.

Definitions

- *Estrus Detection Rate:* The number of heifers detected in estrus divided by the total number of heifers. Estrus % was calculated for each interval of interest (ED).
- *Conception Rate:* The number of heifers pregnant divided by the number of heifers detected in estrus and AI'd. Conception rate was calculated for first service only (FSCR).
- *Pregnancy Rate:* The number of heifers pregnant divided by the total number of heifers. Pregnancy rate (PR) was calculated for each interval of interest.

Progestogens

In the 1960s, scientists in both academia and commercial organizations believed an orally active progestogen delivered under farm and ranch conditions at an economically attractive price would both meet an unmet need in the beef industry and would generate income for the successful company.

A 1965 Brook Lodge Conference, *Ovarian Regulatory Mechanisms,* featured the thought and research leaders in reproductive biology of domestic animals and was the scientific discussion that launched and/or reinforced existing fledgling cattle estrous synchronization progestogen development programs (Duncan et al, 1966).

Companies actively seeking economically attractive orally active progestogens during the 1960s for use in estrous synchronization of cattle were The Upjohn Company, Elanco, Squibb, American Cyanamid, Searle and Syntex. MGA (melengestrol acetate) is the only orally active progestogen developed from those research efforts and available today for cattle estrous synchronization. G.D. Searle developed Norgestomet. The product was a hydron implant containing 6.0 mg norgestomet placed in the ear for 9-d plus a 2.0 mL injection of 3.0 mg Norgestomet and 5 mg estradiol valerate. SynchroMate-B was approved under NADA 097-037 in the late 1970s or early 1980s for synchronization of estrus/ovulation in cycling heifers. The product was marketed as SyncroMate-B but is no longer available. An excellent review of SyncroMate-B studies was published by Odde (1990).

MGA

MGA, approved by the Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) in February 1968 (Federal Register, 1968), is indicated for increased rate of weight gain, improved feed efficiency, and suppression of estrus in heifers fed in confinement for slaughter. The original research, 1960 through 1969, at The Upjohn Company was directed to achieve FDA approval for estrus synchronization of beef cattle; however, that label claim was delayed until 1997 due to numerous business, political and regulatory decisions.

Zimbelman et al (1970) published the original MGA estrus synchronization data for beef cattle. MGA was fed to pens of cattle at 0.5 or 1.0 mg per head daily for 10-d or 14-d or 18-d in numerous trials (Tables 1, 2). Cattle in both MGA and control groups were observed for estrus daily and were AI'd at detected estrus consistent with the AI recommendations of the 1960s. Cattle expressed estrus during d 3-8 after the last MGA feeding. MGA was interpreted to be effective to synchronize estrus in beef cattle as measured by the similar estrus detection rates for cattle of the MGA group during the six-day synchronized interval, d 3 through 8 after last MGA feeding, compared to the percentage of controls detected in estrus over 20 d (70% vs 71%; Table 1). However, the percentage of MGA fed cattle detected in estrus during the first 20 d was greater than the controls (86% vs 71%). These data demonstrated the ability of an orally active progestogen, MGA, both to synchronize estrus and to initiate estrous cycles in some percentage of cattle not expressing estrus at the beginning of the breeding season. This ability of progestogens to "jump start" estrus cyclicity in cattle "approaching estrus, but not there" has been confirmed by research subsequent to these studies.

Table 1. Percentage of cattle in estrus d 3-8 after MGA. MGA studies 1965-1969 (Zimbelman et al., 1970). Numbers in parentheses represent the lowest and highest % among the 15 herds.

	Synchronized	Days 1 to 20	Trials	Cattle
MGA[a]	70 (39-95) %	86 (50-100) %	15	556
Control[b]		71 (28-90) %	15	829

[a]MGA group-fed at 0.5 or 1.0 mg per head daily for 10-d, 14-d, or 18-d.
[b]Control cattle were not fed MGA but were fed the carrier.

The conception rate to AI at the estrus detected during d 3-8 after the last day of MGA feeding was about 72% of the herd-mate control cattle bred over 21 d (38% vs 50%; Table 2). However, the conception rate of MGA cattle AI'd at the second post-MGA estrus, about d 21-28, was greater than the control cattle first service conception percentage (61% vs 50%; Table 2). These relative differences between MGA and controls for reduction of conception rate at first MGA synchronized estrus, but increased conception at second synchronized estrus have been confirmed in numerous studies reported subsequently to these data. The 28-d pregnancy rate continued to be greater for the MGA than the control group (Table 2) since MGA fed cattle had two opportunities to be detected in estrus and AI compared to about 1.3 opportunities for control cattle.

Table 2. Conception and pregnancy percentages. MGA studies 1965-1969 (Zimbelman et al., 1970). Numbers in parentheses represent the lowest and highest % among the 15 herds.

	Synchronized Estrus (d 3-8)		First Service	28-day Pregnancy Rate
	First	Second		
MGA[a]	36 (11-75) %	61 (8-100) %		56%
Control[b]			50 (24-91) %	48%

[a]MGA group-fed at 0.5 or 1.0 mg per head daily for 10-d, 14-d, or 18-d; 24-trials with 1,853 cattle.
[b]Control cattle were not fed MGA but were fed the carrier in 15 of the 24 trials with 537 cattle.

The data reported in Tables 1 and 2 for studies completed in 1965-1969 were the basis for the numerous estrus synchronization programs using MGA during the interval 1965 to 1997.

FDA approved, based on data supporting efficacy and safety, MGA to be fed at 0.50 mg/heifer daily for up to 24 d to suppress estrus in heifers intended for breeding and feeding MGA at this dose for this duration does not have a negative effect on reproduction; the efficacy data are reported in Table 3 (FDA/CVM, NADA 034-254 & 039-402 FOI, February 1997).

Table 3. Reproduction variables for estrous cycling heifers fed MGA for 24 d and inseminated at detected estrus during d 12 to 85 after last feeding of MGA or control diet.

	MGA Dose (mg/heifer daily)		
	0	0.5	1.5
No. Heifers	40	40	40
First Service Conception Rate	53	60 (.31)[a]	48 (.53)
S/C	2.4	1.8 (03.)	2.1 (.23)
Preg. Rate	65	90 (.04)	78 (.28)
Calving Rate	63	90 (.03)	78 (.21)

[a]P-value: within row contrasts with control values.

Progesterone

Progesterone is not active when delivered in the feed but is active when delivered parenterally. Since daily injections of progesterone are not practical, a sustained delivery for progesterone was required for progesterone to be a practical product for beef cattle estrus synchronization. Silastic was reported in the 1960s to be a delivery platform for progesterone but the technology was not available at that time for an economically attractive delivery for progesterone for cattle estrus synchronization. The Eazi-Breed™CIDR® (CIDR) contains progesterone and is inserted intravaginally in cattle for 7 d. The released progesterone blocks estrus of those cattle undergoing natural regression of the CL and allows all CL to be greater than 7-d at time of CIDR removal. The CIDR is removed and the cattle injected with $PGF_{2\alpha}$. Since all cattle will have either regressed CL but blocked from estrus by progesterone from the CIDR or a CL of 7 to 18 d, the stage where the CL will regress in response to $PGF_{2\alpha}$, estrus is synchronized following CIDR removal and injection with $PGF_{2\alpha}$. The Food and Drug Administration Center for Veterinary Medicine (FDA/CVM) approved Eazi-Breed™CIDR® (CIDR) to be used with $PGF_{2\alpha}$ for estrus synchronization of beef cattle (FDA/CVM, NADA 141-200 FOI, July 1997).

Lucy et al (2001) reported the effectiveness of the 7-d CIDR and $PGF_{2\alpha}$ for estrus synchronization of beef cattle. The data in Tables 4, 5 and 6 are adapted from that publication.

Table 4. Estrus synchronization rates, with numbers of cattle in parentheses, for beef cattle treated with 7-d CIDR and $PGF_{2\alpha}$. Estrus detected during the 3-d and 31-d post- $PGF_{2\alpha}$

	Treatments	Anestrous 3-d	Cyclic 3-d	Anestrous 31-d	Cyclic 31-d
Cows	Control	11 (151)	19 (134)	67 (151)	82 (134)
	CIDR+ $PGF_{2\alpha}$	45 (142)	72 (141)	66 (142)	91 (141)
Heifers	Control	7 (107)	17 (144)	54 (107)	87 (144)
	CIDR+ $PGF_{2\alpha}$	48 (105)	80 (116)	71 (105)	92 (116)

Table 5. Conception rates, with numbers of cattle in parentheses, for beef cattle treated with 7-d CIDR and $PGF_{2\alpha}$ and AI at estrus detected during the 3-d and 31-d post-$PGF_{2\alpha}$.

	Treatments	Anestrous 3-d	Cyclic 3-d	Anestrous 31-d	Cyclic 31-d
Cows	Control	38 (16)	58 (26)	58 (99)	64 (108)
	CIDR+ $PGF_{2\alpha}$	57 (63)	63 (101)	61 (92)	65 (127)
Heifers	Control	75 (8)	52 (25)	56 (55)	61 (124)
	CIDR+ $PGF_{2\alpha}$	58 (50)	61 (93)	57 (74)	61 (107)

Table 6. Pregnancy rates, with numbers of cattle in parentheses, for beef cattle treated with 7-d CIDR and $PGF_{2\alpha}$ and AI at estrus detected during the 3-d and 31-d post-$PGF_{2\alpha}$.

	Treatments	Anestrous 3-d	Cyclic 3-d	Anestrous 31-d	Cyclic 31-d
Cows	Control	4 (151)	11 (134)	42 (149)	58 (132)
	CIDR+ $PGF_{2\alpha}$	26 (141)	46 (140)	46 (140)	71 (139)
Heifers	Control	6 (107)	9 (144)	31 (104)	64 (143)
	CIDR+ $PGF_{2\alpha}$	28 (105)	49 (116)	50 (104)	69 (116)

The data reported in Tables 4, 5, and 6 are the basis for the numerous estrus synchronization programs using 7-d CIDR and $PGF_{2\alpha}$.

Both heifers and postpartum cows consistently express a "short luteal phase" following the first ovulation, and pregnancy rates are reduced when cattle are bred at this first estrus (Lauderdale, 1985; Perry et al, 1991; Werth et al, 1996). Progestogen administration to prepubertal heifers and postpartum cows has been reported, for at least 35 years, to initiate estrous cycling associated with normal fertility. However, if the degree of anestrus is due to ovaries with no follicular activity, the progestogen is not effective to induce estrous cycling. Thus, progestogens used in cattle estrus synchronization and breeding programs can increase the percentage of the cattle expressing estrus during the first 21 d of the breeding season (see Table 1, estrus in 20 d, 86% for MGA vs 71% for Control and Table 4, estrus in 3 d for anestrus cattle) and those estruses were fertile (see Table 5 for conception rate in 3 d, in anestrus cattle and Table 6 for pregnancy rate in 3 d, in anestrus cattle).

Prostaglandins

Kurzroc and Lieb (1930) reported the human uterus would either contract or relax upon instillation of fresh human semen. Goldblatt (1933) and von Euler (1934) reported strong smooth-muscle stimulating activity of human seminal plasma. von Euler (1935) reported strong smooth-muscle stimulating activity of seminal fluid from the monkey, sheep, and goat and in extracts of the vesicular glands of male sheep but not in a number of other species. von Euler prepared lipid extracts of sheep vesicular glands and found the strong smooth-muscle stimulating activity to be associated with a fraction containing lipid-soluble acids. The active factor was named prostaglandin. The new names prostaglandin and progesterone were published on the same page.

The 1965 Brook Lodge Conference cited above was the scientific discussion launching research and development of prostaglandins for domestic animal use. Specifically, during the discussion of W. Hansel's paper a question was asked if a family of agents known as prostaglandins, found in very high concentrations in semen, which have a pronounced effect on smooth muscle, might play a role in fertility regulation (Hansel, 1966). This question initiated research leading to the publication $PGF_{2\alpha}$ was luteolytic in the pseudopregnant rat (Pharriss and Wyngarden, 1969).

Subsequently, $PGF_{2\alpha}$ was reported to be luteolytic in the bovine (Rowson et al., 1972; Lauderdale, 1972; Liehr et al., 1972) and potential uses were described to control reproductive cycles in domestic animals (Inskeep, 1973). Numerous papers were published stating $PGF_{2\alpha}$ and $PGF_{2\alpha}$ analogs were luteolytic in cattle and the potential existed for them to have practical value for estrous synchronization. FDA approved a $PGF_{2\alpha}$ product, Lutalyse® Sterile Solution, for beef cattle and dairy heifer estrus synchronization programs with double injections in 1979 (FDA/CVM, NADA 108-901 FOI, 1979) and with single injections in1981 (FDA/CVM, NADA 108-901 FOI, 1981).

During the 1970s and 1980s, data were not available regarding follicular waves. Researchers investigating $PGF_{2\alpha}$ and its analogs recognized something other than the regression of the corpus luteum (CL), was contributing to the variance in both return to estrus in a predictable 48 hours and in pregnancy rates in response to timed AI (TAI). Identification of, characterization of, and management of follicular waves in cattle now allows for more consistent pregnancy rates resulting from TAI protocols utilizing $PGF_{2\alpha}$ products, with or without progestogens, and gonadotropin releasing hormone (GnRH).

Because the market for $PGF_{2\alpha}$ products was perceived, and then documented to be lucrative for companies, numerous $PGF_{2\alpha}$ products were approved and sold in various countries. Some of the products were Lutalyse/Dinolytic Pronalgon F (Upjohn), Estrumate/Planate and Equimate (ICI, with subsequent sale to numerous companies), Prosolvin (Intervet), Bovilene (Fort Dodge), Iliren (Hoechst), Alfabedyl (Hoechst-Roussel), and numerous generics throughout the world.

The concept for prostaglandin estrus synchronization is based on the data $PGF_{2\alpha}$ will not regress the CL during the first 5-d after ovulation/estrus. The approach for using $PGF_{2\alpha}$ to synchronize estrus in cattle is shown in Figure 1. Two injections of $PGF_{2\alpha}$ are given at an interval of 10 to 12 d. The responses presented in Figure 1 are based on all injected cattle estrous cycling. The two-injection scheme results in estrus synchronization on d 2-5 post-second injection of $PGF_{2\alpha}$. The original recommendation of 10 to 12 d between Lutalyse® injections was an attempt to minimize the d between injections but achieve a sufficient interval to assure regression of those CL not responsive to the first injection and those CL formed subsequent to regression of the CL after the first injection.

Figure 1. Concept for use of $PGF_{2\alpha}$ to synchronize estrus in beef cattle (11-d injection interval).

Day of estrous cycle at first $PGF_{2\alpha}$	Day to estrus post-first $PGF_{2\alpha}$	Day of estrous cycle at second $PGF_{2\alpha}$	Day to estrus post-second $PGF_{2\alpha}$
0-5	No response	11-16	2-5
6-16	2-5	6-9	2-5
17-21	0-5	6-11	2-5

Dose titration for Lutalyse® ($PGF_{2\alpha}$) sterile solution for cattle (Lauderdale et al, 1977; Lauderdale, 1979, Lauderdale et al, 1981; FDA/CVM, NADA 108-901 FOI, 1979).

Beef cows (9 herds, n=767) and beef heifers (9 herds, n=448) were investigated to estimate the optimal dose for Lutalyse®. Doses investigated were 0, 5, 15, 25 and 35 mg dinoprost injected intramuscular (i.m.) at an 11 (10 to 12) d interval. Response variables were percent in estrus and pregnancy rate for d 2-5 post-second injection. Walker-Carmer statistical estimates for the optimal dose, based on estrus and pregnancy rates, were 25.7 mg and 22.8 mg for beef cows, 25.1 and 21.5 for beef heifers, and 26.4 and 30.2 for dairy heifers. Based on these data, FDA/CVM approved a dose of 25 mg dinoprost as the dose for use in cattle (FDA/CVM, NADA 108-901 FOI, 1979). This dose was used in all subsequent studies to investigate the various breeding management programs with Lutalyse (Figure 2).

Papers can be found reporting the dose should be something less than the FDA CVM approved dose of 25 mg dinoprost (5 mL Lutalyse). Additionally, rumors abound the dose is too little for big framed cattle or “breed X”. However, those papers consistently report data based on single or minimal locations and minimal numbers of cattle. The dose of 25 mg dinoprost (5 mL Lutalyse) is the dose derived by a statistically valid process to consistently be effective across farms and ranches with various management styles and cattle types and sizes.

Figure 2. Double and single Lutalyse® injection estrus synchronization programs. Cattle injected with 5 mL Lutalyse® sterile solution (L; 25 mg $PGF_{2\alpha}$/33.5 mg dinoprost tromethamine; IM). AIE: inseminated 6 to 13 hours after detected estrus. TAI: inseminated at about 77 to 80 h after the second injection of Lutalyse.

Program Designation			Breeding Method					
LLAIE	L↓	L↓	AIE			AIE or Bull	AIE or Bull	
LLAI80	L↓	L↓		TAI		AIE or Bull	AIE or Bull	
LAIE		L↓	AIE			AIE or Bull	AIE or Bull	
AILAI			AIE		L↓	AIE	AIE or Bull	AIE or Bull
	-14 to –12	-1	0	3	5	9	22	27
Days before Breeding Season			Day of Breeding Season					

Double injection of Lutalyse® sterile solution beef breeding programs (Figure 2, (Lauderdale et al., 1974; Lauderdale, 1979; Lauderdale et al, 1981; FDA/CVM, NADA 108-901 FOI, 1979).

Cattle were injected i.m. with 5 mL Lutalyse® twice at an 11 (10-12) d interval. Cattle were AI'd either at detected estrus (LLAIE) or about 80 h (LLAI80) after the second injection (Figure2). Cattle of the control and LLAIE groups were observed for estrus twice daily and AI about 6 to 13 h after first observation of estrus. Cattle of the LLAI80 were AI'd at about 77 to 80 h after the second injection of Lutalyse® and were rebred at any estrus detected 5 d or more after the 80 h AI. Lutalyse® injection dates were established so the second injection of Lutalyse would be the day before the normal breeding season began.

Table 7. Estrus detection, conception and pregnancy rates for double injection program.

		Estrus Detect. Rate (%)		**Conception Rate (%)**		**Preg. Rate (%)**	
	TRT	**5-day**	**24-day**	**5-day**	**24-day**	**5-day**	**24-day**
Cows	**Control**	11	66	68	61	11	48
	LLAIE	47	70	61	66	34	55
	LLAI80	N/A	N/A	N/A	N/A	35	49
Heifers	**Control**	13	81	50	58	9	53
	LLAIE	66	84	55	54	38	56
	LLAI80	N/A	N/A	N/A	N/A	36	51

Beef cows (Table7). Beef cows from 24 herds with 1,844 cows were investigated. Significantly ($P < 0.05$) greater percentages of cows were detected in estrus during the first 5 d of the AI season for the LLAIE cattle (47%) compared to controls (11%). Fewer LLAIE cattle (47%) were detected in estrus at least once during the first 5 d compared to controls (66%) during the first 24 d (one estrous cycle) of the AI season, indicating cows were just starting to cycle at the beginning of the breeding season. First service conception rates were similar between control and LLAIE cattle for the first 5 d (68%, 61%) and d 1-24 (61%, 66%) of AI. These data reinforce previously reported data that conception rate was not altered significantly following use of $PGF_{2\alpha}$ (Hafs, et.al, 1975; Inskeep, 1973; Lauderdale et. al, 1974). Pregnancy rates were greater for both LLAIE (34%) and LLAI80 (35%) cattle compared to controls for 5 d (11%) and were slightly lower than controls for 24 d (48%). These investigations did not identify a significant difference in pregnancy rate between LLAIE (5 d of AI at estrus, 34%) and LLAI80 (single timed AI, 35%). Pregnancy rates generally were similar between control, and either LLAIE or LLAI80 cattle for d 1-24 (48% Control and 55%/49%) and 1-28 (52% Control and 61%/57%).

Beef heifers (Table 7). Beef heifers from 22 herds with 1,614 heifers were investigated. Significantly ($P < 0.05$) greater percentages of heifers were detected in estrus during the first 5 d of the AI season for LLAIE cattle (66%) compared to controls (13%). Fewer LLAIE cattle (66%) were detected in estrus at least once during the first 5 d compared to controls (81%) during the first 24 d (one estrous cycle) of the AI season, indicating not all heifers were cycling at the beginning of the breeding season. First service conception rates were similar between control and LLAIE cattle for the first 5 d (50%, 55%) and d 1-24 (58%, 54%) of AI. These data reinforce previously reported data that conception rate was not altered significantly following use of $PGF_{2\alpha}$ (Hafs, et.al, 1975; Inskeep, 1973; Lauderdale et. al, 1974).

Pregnancy rates were greater for LLAIE (38%) and LLAI80 (36%) cattle compared to controls for 5 d (9%) and were slightly lower than controls for 24 d (53%). These investigations did not identify a significant difference in pregnancy rate between LLAIE (5 d of AI at estrus, 38%) and LLAI80 (single timed AI, 36%). Pregnancy rates were similar between Control, and either LLAIE or LLAI80 for d 1-24 (53% Control and 56%/51%) and 1-28 (56% Control and 58%/50%).

For beef cows and heifers, the 80 hr timed AI reported herein had a similar pregnancy rate to the cows bred at estrus for 5 d. However, the success of timed AI was highly variable among herds and within herds over time. The basis for this response is the variation in control of follicular waves and in the percent of cattle anestrus at the beginning and 14-d prior to the breeding season. In those groups of cattle where timed AI worked well, the incidence of anestrus or pre-puberty was very low and the cattle were in the stage of the estrous cycle where follicular waves were “similar” among the cattle treated. We now know, based on an understanding of follicle waves, to achieve consistently high pregnancy rates using timed AI, follicular waves must be synchronized/managed and the lifespan of the CL must be managed. Follicle waves can be managed through the use of GnRH and the CL lifespan can be managed by use of $PGF_{2\alpha}$. With understanding of follicle waves, research documented the interval between Lutalyse® injections could be increased from 11 (10-12) d (the original recommendation) to 14 d to achieve more precise estrus control; higher pregnancy rates; and in many breeding management programs, an interval easier to accommodate work schedules. These results have been confirmed by repeated research studies and by use on-farm/ranch over the past 25 years.

Data submitted to FDA from the dose titration studies and the double injection studies led to approval for use of the double intramuscular injection of 5.0 mL (25 mg Dinoprost) Lutalyse Sterile Solution at 11 to 14 d for estrus synchronization of beef cattle and dairy heifers in 1979 (FDA/CVM NADA 108-901 FOI, 1979).

The 2.0 mL intramuscular injection of Estrumate was approved by FDA for estrus synchronization of beef cattle in 1982 (FDA/CVM NADA 113-645 FOI, 1982).

Single injection of Lutalyse® sterile solution beef breeding programs (Figure 2, Lauderdale et al, 1981; FDA/CVM NADA 108-901 FOI, 1981).

The AILAI cattle management system requires observation of cattle for estrus and AI for 4 d, followed by injection of cattle not detected in estrus during those four d with 5 mL Lutalyse®, i.m., on the morning of d 5, followed by continued observation of cattle for estrus and AI accordingly on d 5 through 9 (Figure 2). Breeding for the remainder of the breeding season can be by AI, bulls or some combination of AI and bulls. The LAIE cattle management system is i.m. injection of cattle with 5 mL Lutalyse® on the day before initiation of the breeding season followed by observation of cattle for estrus and AI for 5 d (Figure 2). Breeding for the remainder of the breeding season can be by AI, bulls or some combination of AI and bulls. For the data presented, within herd comparisons were made between control and LAIE cattle and between control and AILAI cattle. In three additional herds, within herd comparisons were made among control, LLAIE and LAIE cattle.

AILAI, Beef Cows (Table 8**).** Beef cows, 5400, from 38 herds were investigated. Estrus detection rates were as anticipated (Table 8). There were no differences in first service conception rates, as would be expected (Table 8). Pregnancy rates were significantly greater for AILAI than controls by 9 d (39% vs 26%, $P<0.05$, Table 8) and approached being significantly different at 24 d (56% vs 54%, $P<0.10$, Table 8).

AILAI, Beef Heifers (Table 8). Beef heifers, 2761, from 19 herds were investigated. Estrus detection rates were as anticipated (Table 8). There were no differences in first service conception rates (Table 8). Pregnancy rates were greater ($P < 0.05$) for AILAI than control heifers for d 1-9 (45% vs 24%). Pregnancy rates were not different between control (55%) and AILAI (56%) heifers for d 1 through 24.

Table 8. Estrus detection, conception and pregnancy rates for single injection (AILAI) program.

	TRT	Estrus Detection (%) d			Conception Rate (%) d			Pregnancy Rate (%) d		
		1-5	1-9	1-24	1-5	1-9	1-24	1-5	1-9	1-24
Cows	Control	21	38	73	59	64	63	14	26	54
	AILAI	17	54	70	64	58	59	12	39	56
Heifers	Control	24	38	78	62	56	59	15	24	55
	AILAI	25	64	77	62	53	57	16	45	56

The percentages of cattle detected in estrus the first time, first service conception rates and pregnancy rates should be similar between controls and cattle assigned to the AILAI group for d 1 through 5 since the AILAI cattle would not have been injected with Lutalyse. That was the case for cows, except more ($P<0.05$) controls than AILAI cows were detected in estrus d 1-5 (Table 8).

The data on enhanced pregnancy rates after 9 d of AI with the AILAI management system are consistent with data published previously (Greene, et.al, 1977; Lambert, et. al, 1976; Lambert, et. al, 1975). The greater pregnancy rate in the AILAI group for d 1 through 9 demonstrated the effectiveness of Lutalyse®. The trend for more pregnancies in the AILAI group after 24 d of AI reinforces the AILAI management system was effective. The results of these studies have been confirmed by repeated research studies and by use on-farm/ranch over the past 25 years.

LAIE, Beef Cows (Table 9)**.** Beef cows, 1,592, from 12 herds were investigated. As expected, estrus detection rates were greater (P<0.05) for LAIE (57%) than controls (31%) for the first 5 d of AI but not different for d 1-24 (Table 9). Conception rates for cows of the LAIE group were greater than controls (P<0.05) for d 1-24 but not d 1-5 (Table 9). Pregnancy rates were significantly greater for the LAIE than control groups by 5 d (30% vs 14%, P<0.05, Table 9) but were not significantly different at 24 d (Table 9).

LAIE, Beef Heifers (Table 9)**.** Beef heifers, 727, from five herds were investigated. Estrus detection rates were greater (P<0.05) for LAIE (52%) than controls (28%) for the first 5 d of AI but not different for d 1-24 (Table 9). Conception rates for heifers of the LAIE group were greater than controls (P<0.05) for d 1-24 but not d 1-5 (Table 9). Pregnancy rates were significantly greater for heifers of the LAIE than controls by 5 d (28 vs 12%, P<0.05, Table 9) but were not significantly different at 24 d (Table 9).

Table 9. Estrus detection, conception and pregnancy rates for single injection (LAIE) program.

	TRT	Estrus Detection (%) d		Conception Rate (%) d		Pregnancy Rate (%) d	
		1-5	1-24	1-5	1-24	1-5	1-24
Cows	Control	31	68	49	53	14	56
	LAIE	57	76	54	63	30	60
Heifers	Control	28	82	47	53	12	49
	LAIE	52	83	52	57	28	55

These data are similar to those reported previously relative to use of the LAIE management system (Inskeep, 1973; Lauderdale et al., 1974; Moody, 1979; Turman et al., 1975). The pregnancy rates for 5 d of breeding in the LAIE management system demonstrated that system to be effective. The results of these studies have been confirmed by repeated research studies and by use on-farm/ranch over the past 25 years.

Data submitted to the FDA from the single injection studies led to approval for use of the single intramuscular injection of 5.0 mL (25 mg Dinoprost) Lutalyse Sterile Solution for estrus synchronization of beef cattle and dairy heifers in 1981 (FDA/CVM, NADA 108-901 FOI, 1981).

Comparison of LAIE and LLAIE (Table 10). Cattle of the LLAIE system compared to cattle of the LAIE system should have about a 20-25% greater estrus detection rate and pregnancy rate for breeding during the first 5 d after $PGF_{2\alpha}$ since $PGF_{2\alpha}$ is ineffective or less effective as a luteolytic agent when injected during the first 5 d after ovulation (Lauderdale, 1972).

Comparison of LAIE and LLAIE, Beef Cows. Beef cows, 527, from three herds were investigated. The observed percentage differences between LAIE and LLAIE cows were 9% for first estrus and 22% for pregnancy rate (Table 10).

Comparison of LAIE and LLAIE, Beef Heifers. Beef heifers, 881, from three herds were investigated. The observed percentage differences between LAIE and LLAIE heifers were 23% for first estrus and 23% for pregnancy rate (Table 10).

Table 10. Estrus detection and pregnancy rates for LAIE vs LLAIE.

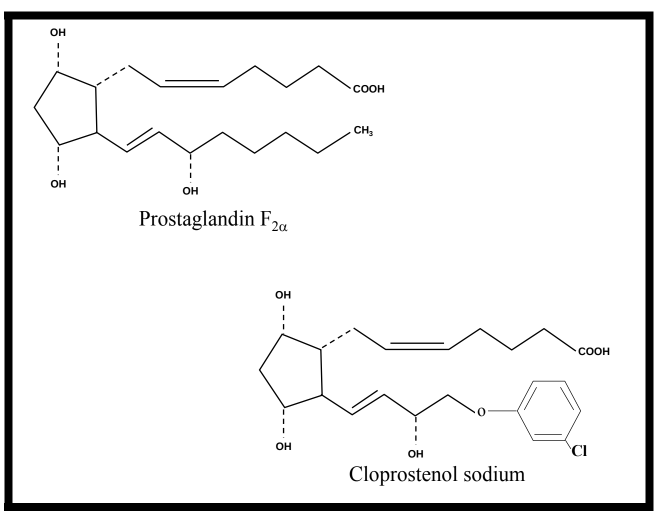
	Treatment	Estrus Detection (%) d (% diff. = LLAIE – LAIE)		Pregnancy Rate (%) d (% diff. = LLAIE – LAIE)	
		1-5	1-24	1-5	1-24
Cows	Control	32	64	16	48
	LAIE	67 (9%)	76	36 (22%)	58
	LLAIE	74	67	46	59
Heifers	Control	27	68	7	37
	LAIE	40 (23%)	68	17 (23%)	40
	LLAIE	52	70	22	38

Thus, the expected percentage differences of about 20-25% and the observed differences of 22%, 23% and 23% were similar in this limited study. The exception was the 9% difference observed for estrus detection for cows.

Prostaglandin $F_{2\alpha}$: product comparisons. Rumors abound regarding relative effectiveness of various $PGF_{2\alpha}$ products. The $PGF_{2\alpha}$ products either contain the natural $PGF_{2\alpha}$ or various analogs of $PGF_{2\alpha}$. Analogs of $PGF_{2\alpha}$ were developed to bypass patents existing at the time of initial marketing or to increase "potency" and/or decrease side effects. Although active ingredients and their properties differ among the various $PGF_{2\alpha}$ products, each $PGF_{2\alpha}$ product induces luteolysis by triggering a cascade of endogenous events ultimately leading to the regression of the CL. Each U.S. $PGF_{2\alpha}$ product has been approved by the FDA/CVM; to be approved by FDA/CVM each product had to have sufficient data documenting efficacy for the label indication. Efficacy is based on dose, route of administration, species, and endpoints for label indication(s). Some U.S. $PGF_{2\alpha}$ products have more label claims than others because the market did or did not justify the additional expense of securing said label claims.

One example of a $PGF_{2\alpha}$ analog compared to $PGF_{2\alpha}$ is Estrumate, containing cloprostenol sodium, and Lutalyse, containing the natural $PGF_{2\alpha}$ (Figure 3). The label for i.m. injection and dose is based on extensive field studies with cattle; the approved dose is 2 mL (0.5 mg) for Estrumate and is 5 mL (25 mg) for Lutalyse.

Figure 3. Chemical structures of $PGF_{2\alpha}$ (dinoprost) and a $PGF_{2\alpha}$ analog (cloprostenol).



Products containing $PGF_{2\alpha}$ analogs consistently require lower doses to regress the CL in cattle than products containing natural $PGF_{2\alpha}$. One rumor is $PGF_{2\alpha}$ products with $PGF_{2\alpha}$ analogs are more potent (lower dose) therefore more effective. There are hundreds of papers reporting use of $PGF_{2\alpha}$ products in cattle with response measured as return to estrus, conception rate and pregnancy rate. I interpret the scientific literature that there is "no difference" among the FDA/CVM approved $PGF_{2\alpha}$ products used in cattle. Anyone skilled in the art can select papers to show what they want, such as one $PGF_{2\alpha}$ product is better or worse than another. This can be accomplished since, either by chance or due to insufficient numbers of cattle on a study, a paper will report one $PGF_{2\alpha}$ product is numerically superior or inferior to another $PGF_{2\alpha}$ product, usually the differences are numerical but not statistically different, but the difference is interpreted to be real.

The $PGF_{2\alpha}$ and $PGF_{2\alpha}$ analogue products achieve efficacy through regression (luteolysis) of the CL. Following CL regression, progesterone concentrations decrease to baseline in about 24 hours. This allows maturation of the dominant pre-ovulatory follicle resulting in an increase in serum concentrations of estradiol-17β. Increased serum estradiol-17β concentration leads to the LH surge inducing ovulation. Increased serum estradiol-17β concentration stimulates the immune system in the uterus. These biological relationships are the basis for the label indications of the various $PGF_{2\alpha}$ products, synchronization of estrus, treatment of uterine infections such as pyometra, and induction of abortion in pregnant cattle.

Decrease in serum progesterone in response to luteolytic doses of Lutalyse and Estrumate is shown in Table 11 (Seguin et al, 1985). The data support an interpretation of similar rates of serum progesterone decrease between Lutalyse and Estrumate. Peer-reviewed studies comparing the efficacy of Lutalyse and Estrumate to synchronize estrus in cattle are summarized in Table 12. The data support an interpretation of similar estrus synchronization rates, conception rates and pregnancy rates following luteolytic doses of Lutalyse and Estrumate.

Table 11. Serum progesterone (P4) concentration following a luteolytic dose of Lutalyse and Estrumate (Sequin et al, 1985).

Hours after treatment	Lutalyse P4 (ng/mL)	Estrumate P4 (ng/mL)
0	3.34	3.21
2	1.54	1.56
4	1.36	1.37
8	1.05	0.99
12	0.45	0.36
24	ND[a]	ND
48	ND	ND

[a]ND; Not Detectable

Table 12. Peer-reviewed studies comparing the efficacy of Lutalyse® and Estrumate to synchronize estrus in cattle are summarized in the following table, courtesy of Fred Moreira.

Reference	Type[4]	N[5]	Estrus detection rate[1] (%)			Conception rate[2] (%)			Pregnancy rate[3] (%)		
			Lutalyse	Estrumate	*P*	Lutalyse	Estrumate	*P*	Lutalyse	Estrumate	*P*
Johnson, 1984	LDC	52	61.5	42.3	NS[6]	45.8	20.8	NS	54.2	29.2	NS
Seguin et al., 1985	NLDC	124	88.7	96.8	NS	60.0	64.3	NS	56.3	62.5	NS
	LDC	245	66.1	65.3	NS	51.2	50.6	NS	33.9	33.1	NS
Turner et al., 1987[7]	BC-BH	63	66.6	76.8	NS	50.2	44.1	NS	35.3	34.5	NS
Salverson et al., 2002	BH	1002	85.9	88.7	NS	66.5	67.5	NS	57.5	60.6	NS
Martineau, 2003	LDC-DH[8]	203	85.9	82.8	NS	33.7	41.8	NS	29.3	34.9	NS
	LDC-DH[9]	404	82.6	83.0	NS	38.6	46.6	NS	31.4	39.2	NS

[1] Percentage of animals detected in estrus relative to the total number of animals within each group.
[2] Percentage of animals conceived relative to the number of animals inseminated.
[3] Percentage of animals conceived relative to the total number of animals within each group.
[4] Type of cattle used in the study (LDC = lactating dairy cows; NLDC = non-lactating dairy cows; BC = beef cows; BH = beef heifers; DH = dairy heifers).
[5] Number of animals included in the experiment.
[6] NS = differences were not statistically significant.
[7]Pregnancy rates were calculated based on reported Least Square Means for estrus detection and conception rates.
[8] Includes only cows injected with LUTALYSE® and ESTRUMATE intramuscularly.
[9]Includes both intramuscular and intravenous route of administration for LUTALYSE® and ESTRUMATE.

The following published papers further address effectiveness of various $PGF_{2\alpha}$ products:

1. Comparison among dinoprost, cloprostenol and fenprostalene (Theriogenology 29:1193, 1988, Guay, Rieger, Roberge). No difference in serum progesterone (P4) rate of decrease (all P4 at baseline by 24 hr after injection). No difference in ova/embryos collected between D 6 and 8 of gestation.
2. Comparison among cloprostenol, alfaprostenol, prosolvin, and iliren (Theriogenology 17:499, 1982, Schams and Karg). P4 decreased to baseline in 24 hr for each. Visual inspection of the P4 patterns suggested support of the author's conclusion of "no difference" among the $PGF_{2\alpha}$ products.
3. Comparison between dinoprost and fenprostalene (Theriogenology 28:523, 1987. Stotts et al). No difference in P4 profile following injection on either d 6 or d 11 of the estrous cycle.
4. Comparison among dinoprost, cloprostenol and fenprostalene (Theriogenology 34:667, 1990. Desaulniers, Guay, Vaillancourt) . Similar pattern of return to estrus. However, 5/10 fenprostalene cattle, but zero cattle for dinoprost and cloprostenol groups, had P4 greater than 1 ng/mL at 48 hr, suggesting slower P4 decline with fenprostalene. However, note the data of "1)" and "3)" above did not show such a difference.
5. Comparison between dinoprost and cloprostenol. The series of papers by Macmillan et al using either dinoprost of cloprostenol and measuring return to

estrus/estrus synchrony, conception rate and pregnancy rate indicate to me "no difference" (Anim. Repro. Sci, 6:245, 1983/1984; NZ Vet. J. 31:110, 1983 and 43:53, 1983; Theriogen.18:245, 1982).

6. Comparison between dinoprost and cloprostenol (Theriogenology 21:1019, 1984. Donaldson). Estrus control similar, although the dose of dinoprost was 65 mg in three doses. I grant Donaldson has published other papers criticising dinoprost vs cloprostenol for embryo transfer use.
7. Tiaprost. (The Veterinary Record 114:418-421, 1984. AR Peters). P4 decreased to baseline in about 24 hours, a pattern reported above for various $PGF_{2\alpha}$ products.
8. Alfaprostol. (Theriogenology 24:737, 1985. Kiracofe, Keay, Odde). Pattern of return to estrus, day of estrous cycle response rate, conception rate and pregnancy rate patterns similar to those reported for various $PGF_{2\alpha}$ products.
9. Fenprostalene (Theriogenology 25:463, 1986. Herschler, Peltier, Duffy, Kushinsky). Patterns of P4 decrease and return to estrus similar to those reported for various $PGF_{2\alpha}$ products.
10. Comparison among dinoprost, cloprostenol and luprostiol (Theriogenology 33:943, 1990. Plata et al). Estrus response (5-d synchrony) and pregnancy rates did not differ among the $PGF_{2\alpha}$ products.
11. Comparison between luprostiol and cloprostenol (J. Anim. Sci. 67:2067, 1989. Godfrey et al). Brahman cattle. P4 declined but needed a dose of about 30mg luprostiol vs 0.5 mg cloprostenol and fertility apperaed depressed by that dose of luprostiol.

The scientific literature does not support a defendable interpretation when each $PGF_{2\alpha}$ product is used at the label dose; there are real differences among the $PGF_{2\alpha}$ products in efficacy. I propose technical service available per $PGF_{2\alpha}$ product makes the greatest significant difference among the products, assuming price to be competitive among them.

Ovarian Follicular Waves

During the 1970s and 1980s when MGA and $PGF_{2\alpha}$ were being researched and developed as products, data were not accepted that follicular waves existed in cattle. Researchers, during the 1960s-1980s, investigating both progestogen and $PGF_{2\alpha}$ estrus synchronization protocols recognized something other than the regression of the CL or block of estrus was contributing to the variance in consistency both of return to estrus and of acceptable pregnancy rates.

With the advent of ultrasound, cattle follicle waves were studied extensively and stages of follicular development were identified to be recruitment, selection and dominance and cattle have two or three follicle waves each estrous cycle (Ginther et al, 1996). Stage of follicular development (recruitment, selection and dominance) at the time of progestogen withdrawal or regression of the CL with $PGF_{2\alpha}$ is related both to the variance in return to estrus in the synchronized interval and to the pregnancy rate achieved. This is especially important with use of AI at a specific time (TAI) rather than AI only at the correct time during detected estrus.

Gonadotropin Releasing Hormone (GnRH)

As identified in the paper in these proceedings, *Physiological principals underlying synchronization of estrus*, GnRH and various GnRH analogs are capable of ovulating a dominant follicle and initiating a new follicular wave depending on the stage of follicular development.

However, the FDA approval for GnRH products is for treatment of ovarian follicular cysts in cattle. Cystorelin, the pioneer GnRH product (FDA/CVM NADA 098-379 FOI), was copied under the Generic Animal Drug and Patent Term Restoration Act (53 FR 50460, December 15, 1988) resulting in Fertagyl (FDA/CVM ANADA 200-134 FOI, 1996) and Fertilin (FDA/CVM ANADA 200-069 FOI, 2002). Each product is gonadorelin, the native GnRH, as a diacetate tetrahydrate salt. Each product is approved for use in dairy cattle via intramuscular or intravenous injection at 100 µg. Factrel (FDA/CVM NADA 139-237 FOI, 1989) is gonadorelin as the hydrochloride salt. Factrel is approved for use in cattle via intramuscular injection at 100 µg to treat ovarian follicular cysts in cattle. Each product has the identical peptide, gonadorelin, as the active pharmaceutical ingredient. Each product has the same dose (100 µg) approved by FDA for the same indication, treatment of ovarian follicular cysts in cattle.

GnRH Product Comparisons

Dose response data for Factrel are presented in Table 13. These responses to Factrel are similar to those for the other three GnRH products.

Table 13. Factrel dose response for treatment of ovarian follicular cysts in dairy cows (FDA/CVM NADA 139-237 FOI, 1989).

	Dose (µg/cow IM)					
Variable	0	50	100	250	100	250
No. Cows	22	22	20	21	89	101
D: Trt. to First Estrus	46	43	40	34	23	24
D: Trt. to Conception	45	50	48	46	37	32
% Conceived to First Estrus	36	41	60	29	61	58
% Pregnant in 60 D	64	73	80	62	NR	NR

Efficacy of Factrel versus Cystorelin for treatment of ovarian follicular cysts in dairy cows is presented in Table 14. These data, based on treatment of dairy cows with ovarian follicular cysts, support an interpretation of no detectable difference in biologic response between Factrel, the hydrochloride salt of gonadorelin, and Cystorelin (and its generics), the diacetate tetrahydrate salt of gonadorelin.

Table 14. Factrel versus Cystorelin for treatment of ovarian follicular cysts in dairy cows (FDA/CVM NADA 139-237 FOI, 1989).

	Factrel (100 μg/cow IM	Cystorelin (100 μg/cow IM)
No. Trials	7	7
No. Cows	149	121
D: Trt. To First Estrus	32	31
D: Trt. to Conception	44	37
% Conceived to First Estrus	44	40
% Pregnant in 60 D	69	69

Martinez et al (2003) reported data on the comparison of GnRH products. Data published to date demonstrated various differences and similarities when LH response was the end-point. However, data to date support an interpretation there are no differences among the products for initiation of a follicular wave or induction of ovulation, the two biological responses essential to effective use in estrus synchronization and breeding management protocols. Additionally, various publications report "half-doses" are "as good as" label doses. However, Dr. John Hall, Virginia Tech University (personal communication), shared the highest to lowest pregnancy rate among herds was 41% when a "half-dose" (50 μg) compared to 28% when a label dose (100 μg) was used. These data support use of the 100 μg dose to be more consistently effective than the 50 μg dose when pregnancy rate is the end-point.

Summary

Today we recognize effective programmed breeding requires synchronization of follicle waves, management of the CL lifespan, and induction of ovulation. Hormonal products representing progestogens, $PGF_{2\alpha}$, and GnRH are available for economically attractive breeding management for beef cattle. Thus, selection of an effective breeding program is dependant upon matching the components of follicle wave management (using a GnRH), CL lifespan management (using a $PGF_{2\alpha}$), estrus suppression and initiation of estrous cyclicity (using a progestogen), ovulation induction (using a GnRH), labor management, facilities management, and economic management consistent with the farm/ranch/dairy objectives.

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NOTES