

Synchronized Breeding Made Simpler

The FDA's approval of the CIDR is deemed the first reproductive advancement in 20 years.

Story by **Corinne Blender**



It's not breaking news that the Eazi-Breed™ CIDR® Cattle Insert exists. Producers have been talking about the controlled internal drug release (CIDR, pronounced "seeder") insert for estrus synchronization for some time as the product was being evaluated at the research level. With the U.S. Food and Drug Administration's (FDA's) approval of the product June 16, 2002, the talk will turn to action during the next breeding season for many beef producers.

"I've been waiting for them to get them on the market for a

long time," says Troy Marple, purebred beef specialist at Kansas State University (K-State). "We have been talking about them for a long time. We just haven't been able to let anybody use them."

Many beef producers were aware of the product because of its use by cattlemen in Canada, where the CIDR was approved several years ago. Extensive research published from Canada and from New Zealand, where the CIDR actually originated, began to draw the attention of progressive artificial insemination (AI) users and embryo transfer (ET) centers in the United States.

"The first time I ever saw

CIDRs was in 1992 at a meeting in Canada, and no one in the United States talked very much about them at the time," says Kirk Gray, owner of Cross Country Genetics-North Inc., an ET center in Westmoreland, Kan. Gray says research from other countries was available to the public early on, while research from U.S. universities began around the mid-1990s.

"We didn't see much general use of CIDRs until Syncro-Mate-B went away. And then it was like the floodgates opened," Gray says. "CIDRs were coming in from both the North and the South to all kinds of people." Syncro-Mate-B was a progestin implant that was inserted into the animal's ear. The CIDR essentially offers the same type of reproductive manipulation, making it an ideal backup product for most ET centers now that Syncro-Mate-B is no longer made.

The CIDR is now marketed worldwide exclusively by Pharmacia Animal Health of Kalamazoo, Mich., which bought the marketing license from InterAg of Hamilton, New Zealand.

Why all the talk?

"I feel very fortunate that we have been able to do some of the test research with them," Marple says. "We were pretty scared when they yanked Syncro-Mate-B off the market because we do enough embryo work around here. It is hard to set up donors and recipients unless you have a Syncro-Mate-B or a CIDR."

The CIDR is a T-shaped

insert (see photo) that is impregnated with progesterone, the same hormone that is secreted by the corpus luteum (CL) in the cow. The CIDR is inserted into the animal using a device that resembles a bolus gun. While the insert is in place, the female should not come into heat because the progesterone prevents estrus and ovulation.

"It is the first product that we have had approved in beef and dairy for reproductive control for more than 20 years," says Darrel Kesler, Extension reproductive biologist at the University of Illinois, Urbana-Champaign. Kesler was part of the early trial work in the FDA approval process.

While the insert is in the animal's vagina, it continually releases progesterone. Its removal and the corresponding injection of Lutalyse® (a prostaglandin, or PGF) triggers a drop in the female's progesterone level that results in estrus and ovulation.

"What it is being used for is A) to synchronize estrus and B) to hasten either puberty or postpartum cyclicity," Kesler says.

Once the CIDR is in place, only a small portion of the tail remains visible. Kesler says the product did undergo a slight change when researchers noticed curious or bored animals pulling on the tails of the CIDR and, in some cases, pulling the entire CIDR out.

"The ones that we used in the trials that we did for FDA approval had a white tail. We found some of the animals actually pulled them out," he

► **Above:** The Eazi-Breed™ CIDR® Cattle Insert is a progesterone vaginal insert used to synchronize estrus and hasten either puberty or postpartum cyclicity in the beef cow and heifer. The product was approved for marketing and use in the United States June 16, 2002.



► The CIDR is inserted into a cow's vagina where it releases progesterone. The T-shaped device has collapsible wings that allow it to stay in place until removed.

PHOTOS COURTESY OF PHARMACIA ANIMAL HEALTH

says. "So we had a little higher loss than what we should have had."

The design of the product has since been modified, and the one that is on the market has a blue tail. "For most of the cattle that are being treated, that blue tail blends in pretty nicely with the feces and the black hair and isn't really noticeable," Kesler says. The retention rate is high, somewhere near 98%, he adds.

FDA approved protocol

To gain FDA approval, the CIDR was tested at seven sites across the United States, including New York, Florida and several Midwestern states.

"To get clinical approval, they have to have a certain number of testing sites and they have to follow very strict FDA recordkeeping and monitoring regulations," Kesler says of the time-consuming process. "It is monitored very closely, so every time you do something you write it down. It is very, very detailed."

The CIDR protocol consists of placing the insert into a cow's vagina for seven days; then, 24 hours before removal, injecting

the cow with a regular dose of Lutalyse. Heat will generally occur very quickly (within 2-3 days) after the CIDR is removed on Day 7.

"One of the nicest things I like about them is they really tighten your heat. You can expect a cow in heat 48 hours after you pull them out," Marple says. Most of your cows are going to come into heat within a 12-hour window. "Sure, there is going to be a sporadic one here and there, but they really tighten down the synchronization."

In Kesler's research, following the FDA-approved protocol, the CIDR synchronized pregnancies in about 50% of the beef heifers that had not yet reached puberty, while less than 10% were synchronized without any treatment (see Table 2).

"It really jump-started those heifers into cyclicity," he says. "It can be used to synchronize those that are cycling and to jump-start those that aren't and synchronize them as well."

Research opens more doors

University researchers have been evaluating other protocols

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PHOTO BY CORINNE BLENDER

► Troy Marple, purebred beef specialist at Kansas State University, says the CIDR is an easy product to use for setting up donors and recipients in his embryo transfer program. "They are a great product and the most advantageous thing to me is that they are so user-friendly," he says.

Table 2: Pregnancy rates using the CIDR in FDA beef heifer study

	Pregnancy rate*	
	Prepubertal	Cyclic
Control	6%	9%
PGF	6%	19%
CIDR + PGF	28%	49%

* Treatment P < 0.01.

Source: Darrel Kesler, Extension reproductive biologist at the University of Illinois, Urbana-Champaign

Six-factor comparison of MGA and the CIDR

Darrel Kesler, Extension reproductive biologist at the University of Illinois, Urbana-Champaign, says there are advantages to the MGA® (melengestrol acetate) and prostaglandin (PGF) system, as well as to the newly approved Eazi-Breed™ CIDR® (controlled internal drug release) Cattle Insert and PGF system.

"MGA is probably not as convenient in the beef cow. But MGA does work very nicely in beef heifers. It is a progesterone; it will jump-start those anestrous beef heifers as well," Kesler says. Product effectiveness would be very similar for both the CIDR and the MGA in a beef heifer.

Kesler has done extensive research with both products. He poses the following six considerations when comparing the two products:

- "Cost-wise, there is nothing cheaper than MGA and prostaglandin. Although the CIDR is not going to be expensive, it is definitely going to be more expensive than MGA and prostaglandin."
- The MGA system requires about 35 days from the first day of feeding to breeding. With the CIDR system, you remove it seven days after insertion, and the cows are in estrus about two days after that. "You are cutting the time frame down by about 75%."
- The number of animal handlings would favor the MGA system. With the MGA system you only have to handle them to give the PGF injection and then to breed them. With the CIDR system, you handle them at least three times, possibly four depending on when you give the PGF shot.
- "With the MGA system you treat the whole group. You don't do any subgrouping. But with the CIDR system you could actually go

into a group of 100 animals and treat 50 of them, then come back a week later and do the other 50."

► "I've done field studies with the MGA system. Because it is such a long time frame and there are many steps involved, people do mess up on that system occasionally. With the CIDR system there is less chance of error because you put them in on a Monday and you come back the next Monday and you pull them out. You can't get much more straightforward than that."

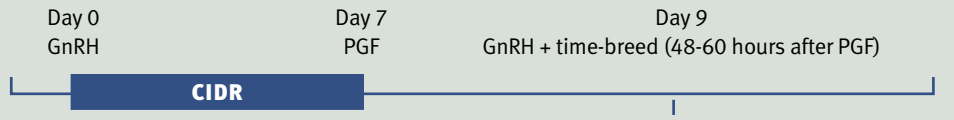
► "We know the MGA system is very robust and can be used in almost any scenario and work very effectively. We don't have that data yet for a CIDR."

"I have it down to three advantages for MGA and three advantages for the CIDR system. It depends on your management system. That's why I call it a tool for the reproductive toolbox," Kesler says. "For one operation the CIDR may be the ideal way to go. For another operation MGA may be the ideal way to go."

Table 1: Advantage analysis of MGA/PGF synchronization and CIDR/PGF synchronization

Advantage	MGA/PGF	CIDR/PGF
Cost	Y	
Shortest time (from initiation)		Y
Fewer number of handlings	Y	
Flexibility of groupings		Y
Less chance of scheduling error		Y
Robustness	Y	

Fig. 1: CoSynch-CIDR system



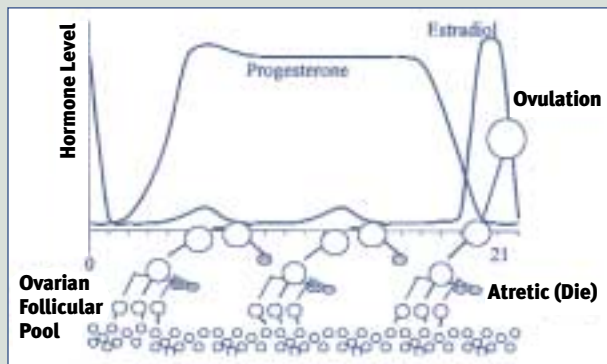
Source: Jeffrey Stevenson, professor of reproductive physiology at Kansas State University

Table 3: Effect of CoSynch + CIDR on pregnancy rates

Status	Progesterone ₄ at PGF	No.	CoSynch	CoSynch + CIDR
Cyclic	High	234	58%	58%
Cyclic	Low	99	43%	79%
Anestrus	High	62	40%	53%
Anestrus	Low	55	38%	66%

Source: Lamb et al. (2001)

Fig. 2: Development of follicular waves during the 21-day estrous cycle of cattle. Estrogen levels peak at approximately 21 days, and progesterone levels are elevated from Day 5 to Day 17.



using the CIDR for several years under investigative new animal drug licenses authorized by the Center for Veterinary Medicine (CVM) of FDA. Some of those studies have reported higher success rates than the studies supporting the product's FDA approval.

Jeffrey Stevenson, professor of reproductive physiology at K-State, was the lead researcher with Marple in some studies conducted at K-State. Believing the addition of an injection of gonadotropin-releasing hormone (GnRH) would foster better results, they used the CIDR with the CoSynch protocol.

CoSynch-CIDR involves

injecting GnRH when the CIDR is inserted, removing the CIDR after seven days and then injecting a prostaglandin. Forty-eight hours later, he injected another dose of GnRH and time-bred (See Figure 1).

Their first study using CoSynch in combination with a CIDR resulted in pregnancies in 66% of the cows. The control group, which received the CoSynch protocol alone, had a 61% pregnancy rate. Stevenson says that was high, with pregnancy rates of 30% to 50% being more common using CoSynch alone without the CIDR.

"It varies from year to year depending on the body

condition of the cows," Stevenson says, "which is a reflection of the winter and their winter supplementation program."

The CIDR will always produce better results, Stevenson adds. But the key is using the two protocols in combination.

"If you just put a CIDR in a cow for seven days you will induce some cycling activity. What really gets the cow started is giving an injection of GnRH when you put in the CIDR," he says. "They do two different things. GnRH will cause the follicle to ovulate, and that forms the first corpus luteum. The CIDR by itself can do that, but it won't induce ovulation at a very high rate. The CIDR acts mostly on the uterus, basically preparing the uterus for pregnancy."

Without exposure to progesterone (e.g., the CIDR insert), the GnRH injection would likely cause a suckled beef cow to ovulate and the CL would form, Stevenson explains. But it would be short-lived, and the cow would probably be back in estrus in about eight to 12 days.

"So even if she were inseminated and the egg fertilized, before the embryo could develop to a sufficient point, the corpus luteum would regress prematurely and the uterus would kick the embryo out," he says. "The uterus has to be progesterone-primed. In other words, it has to be exposed to some progesterone or it will cause the corpus luteum to be short-lived."

The progesterone prevents early release of PGF from the uterus, which would cause a short-lived CL. "That's why the CIDR is really important in the system. As progesterone is released, it is absorbed by the vagina. Basically it helps prepare the uterus to carry a normal embryo after she conceives at the next estrus."

Will it work for me?

Kesler says this product is just another device for the reproductive toolbox, one that can be used in combination with other tools. The CIDR isn't expected to be too expensive, with prices speculated anywhere from \$6 to \$8, but that price could be a limiting factor.

PGF can synchronize cows and heifers that are cycling without the need of progesterone at a cost of about \$3, Stevenson says. But, Kesler adds, "It only works on those that are on Day 5 of the cycle or greater. It will not be effective on animals that are on Day 0 through Day 4. You're not working with 100% of the animals when you use prostaglandin alone."

If you could identify which cows were cycling, the most cost-effective approach might include a combination of protocols. Stevenson refers to a regional research project (NC-113) that included K-State, Illinois (Kesler), Minnesota and Missouri locations as an example.

Out of the 450 cows in that study, 234 were identified by blood tests to be cyclic (high progesterone: spontaneous cyclicity established before GnRH with a CL present just before the PGF injection; see Table 3). There was no difference in the 58% pregnancy rate with CoSynch alone and the 58% pregnancy rate with CoSynch plus the CIDR. Those cows could have been as successfully synchronized and

Aled without the added cost of the CIDRs.

With the 99 cows identified by blood tests to be cyclic (low progesterone: spontaneous cyclicity established before GnRH but no CL present just before the PGF injection), the research achieved a 79% pregnancy rate with CoSynch plus the CIDR vs. 43% with CoSynch alone. With the anestrus cows (high progesterone: anestrus before GnRH but in response to GnRH ovulation occurred and a CL formed before the PGF injection), researchers achieved a 53% pregnancy rate with the CoSynch-CIDR combination, 40% without. Rounding out the study, the 55 cows that were blood-tested and found to be anestrus (low progesterone: anestrus before GnRH, no response to GnRH and no CL formed before the PGF injection) had a 66% pregnancy rate with the CIDR, 38% without. So, for a total of 216 cows, the CIDR made vast improvements on pregnancy rates.

"In just more than half the cows you will probably get a real benefit from using the CIDR," Stevenson says. "The question is, how can you know which cows are cycling when you start the breeding season? And short of taking blood samples from cows, which is impractical, what could one do?"

Identify effective uses

Stevenson identifies a couple ways that producers could determine on which animals the CIDRs would have an effect. He says the first scenario could include applying heat detection patches (about \$1.50 each) three weeks before initiating the program. Tail chalk, which is used more commonly in dairies, could offer the same identification option. Or you could watch the entire herd for heat, which is too time-consuming or impractical for most.

"That would be one way to eliminate the cycling cows that we would not put CIDRs in," Stevenson says. "That's the cheapest way to do it." CoSynch alone can be just as effective with the animals found cycling during this time.

Another scenario producers could enact involves dividing the cows by a few common denominators, including calving dates, body condition scores (BCSs) and cow age. Identify animals that are at risk for not conceiving in the first week of the breeding season. These are the candidates for a CIDR.

The cows that calve late in the season, thin cows, and your 2-year-old cows are at greater risk of being anestrus, Stevenson points out.

Whether producers should use the CIDR in all animals, or try to determine in which animals the CIDR would be most effective, depends on the individuals and their goals for their breeding program.

"If you talk to purebred seedstock producers who will be selling heifers and lots of bulls, they would probably go with what I would call a 'Cadillac' program because the chances of their getting more calves in that first week are probably better with the CIDR. But it might not be as cost-effective for a commercial producer to do the same thing," Stevenson says. "The commercial producer has probably got to look for a way to tailor-make this system so it uses a little more expensive treatment with those cows at risk and a little cheaper system on the cows that are probably cycling."

Apply these helpful hints

► For the greatest chance of success, Stevenson urges producers to follow the protocol. "You'd be surprised at how many people we get phone calls from who say, 'I gave this injection yesterday. I know it was supposed to be given today or tomorrow. ...'"



PHOTO BY SHAUNA ROSE HERMEL COURTESY OF BEEF MAGAZINE

► Heat patches are one way producers can identify cows or heifers that should not need a CIDR insert for estrus synchronization, says Jeffrey Stevenson, professor of reproductive physiology at K-State. He says identifying animals that have already expressed heat at the beginning of the breeding season will help some producers save the extra cost of using the CIDR when it isn't necessary.

Cleanliness is a must when using CIDRs

Anyone who has worked with the Eazi-Breed™ CIDR® Cattle Insert will stress the importance of good sanitation practices. "No. 1," says Troy Marple, purebred specialist at Kansas State University (K-State), "cleanliness is next to godliness with these things. You're putting it in a pretty sensitive area in a female, and you just don't want to take anything in there with the CIDR."

Darrel Kesler, Extension reproductive biologist at the University of Illinois, Urbana-Champaign, also stresses the need for wearing latex or plastic gloves when handling this product. The outside of the insert has progesterone on it, which could affect the handler.

"But more importantly, our hands have bacteria on them," he adds. "Even if you wash, you will still have some bacteria on your hands. And if you handle them with your ungloved hands, it is very likely that you will introduce into the vagina some bacteria as well as the insert. You need to wear gloves."

► Kesler describes inserting the CIDR as similar to AIning, except the CIDR is deposited in the vagina. He says you have to be easy with the animal. He advises using a lubricant to help make the insertion process easier.

► "Imagine that vagina being about as long as my two fists together," Stevenson says. "Slide

the CIDR in all the way until you hit resistance, which means you're hitting the cervix.

"When you push in the insert device plunger to release the CIDR, you don't want to be pulling back at the same time," Stevenson warns. "When you pull out the insertion device,

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you really can't push the CIDR back up in again because its wings open up. . . . You have to make sure you position it clear up against the cervix," Stevenson says.

► If you see an animal in heat when you think you have a CIDR in place, you should do some checking. "Most generally, when a CIDR is in, the cow is not going to come into heat," Marple says. "The only time you are going to see a heat with one of those is if somehow it just came out."

Still, he says, if you do notice a cow in heat, don't just assume the CIDR fell out. He brings the cow in to check if the CIDR has turned around, causing the tail to disappear. "I think we have only had two of them turn in the several hundred that we have put in," he says. "If you don't reach in there and look for it you won't realize it is still in there. That's why you always want to double-check it." He says when a CIDR is turned is the only time he has ever witnessed any infection.

► Careful insertion of the CIDR after cleansing the vagina opening is very important. To make the insertion process successful, sanitary and easy, Gray advises dipping the CIDR, while it is in the gun, into a disinfectant-water solution. This lubricates the CIDR and helps the technician position it correctly.

► To discourage penmates from curiously pulling the CIDR out, Kesler says the tails can be trimmed. "You have to be careful not to cut it off too

short," he says, adding that as the animal stands for a few minutes, the CIDR will settle into position. "That typically means it goes just a little bit deeper. So if you cut the tail too short you may not see the tail exteriorized at the vulva."

► Those who have used the CIDR say it is important to make sure the cow is clean when you insert it. Stevenson goes a step further. "If you put the cow's tail over your left shoulder, take your left hand and just open the vulva to expose where it is really clean, then you slide the CIDR through against the clean lips of the vulva, you won't take anything inside. That's the real key to it," he says.

"We have put hundreds of these in during the last four or five years, and it is really hard to clean a cow up in the back. If you are running 100 Angus cows through the chute that have been on wheat pasture, you can imagine how greasy green they will be," Stevenson adds. "You just have to be as clean as you can."

It's hard to predict the extent of use the product will see this year because the CIDR was approved too late for most spring breeding programs, Stevenson says. Mid-winter may offer more insight when fall calves begin their breeding programs.

"They are a great product," Marple says. Most advantageous, he adds, especially compared to progestin products of the past, is their ease of use. "Jeff and I put 130 CIDRs in one morning in about 30 minutes, and we took them out in less than 10 minutes," he explains. "It takes longer to run them through the chute than it does to pull them out. You just grab the tails and pull them out."



Steps for inserting and removing the CIDR:



1. Shift the animal's tail to one side and clean the vulva.



2. Make sure the tail of the CIDR insert is on the underside of the applicator to ensure the tail will be hidden from curious penmates.



3. Open the lips of the vulva and insert the applicator at a slightly upward angle, moving forward over the pelvic bone until it meets resistance.



4. Dispense the insert from the applicator by depressing the plunger, then slowly withdraw the applicator.



5. To prevent removal by penmates, you may clip the tail, but be careful not to clip it too short because the CIDR will usually settle deeper inside the animal.



6. To withdraw the insert, give the tail a gentle but firm pull.