

Challenges to selection of products to implement breeding management protocols

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Estrus synchronization protocols are based on biology

The presentation by Dr. Rhinehart in these proceedings, Physiology factors affecting success to reproductive technologies, identified 1) the hormones that naturally control the estrous cycle of cattle, 2) the hormones commercially available for use with the recommended breeding management protocols, 3) mode of biological action of the hormones commercially available, and 4) when/how the various hormones can be used to manage estrus and breeding of beef cattle.

Recommended estrus synchronization protocols are based on extensive field research

The Multi-state Beef Reproduction Task Force (BRTF) in cooperation with the Beef Reproduction Leadership Team (BRLT) provides science based recommendations for the application of reproductive technologies for beef cattle production, including the yearly update of the estrus synchronization protocols for beef cows and beef heifers (Johnson et al, 2011). Criteria for an estrus synchronization protocol to be included on the yearly protocol sheet are: 1) a minimum of animal handling, preferable 3X or less including AI; 2) use as few injections/insertions of pharmaceuticals as possible while maintaining effectiveness; 3) must be effective for both estrous cycling and non-estrous cycling females; and, 4) a single page each for beef cows and for beef heifers with no more than three (currently have four for heifers) protocols per quadrant. Yearly, the BRTF reviews new research to determine if a new protocol should be added to the Protocol Sheet based on data indicating the protocol 1) increases fertility, or 2) reduces the number of animal handlings without compromising fertility, or 3) reduces the cost without compromising fertility, and 4) does not pose regulatory concerns. BRTF recommends any change to the BRLT; extensive and intensive discussion leads to a decision to change or not.

The presentations by Dr. Patterson and by Dr. Johnson in these proceedings provide an overview of the Protocols recommended for 2016 and guidance as how to assure compliance with each protocol. Protocols range from a single injection of a prostaglandin (PGF) associated with estrus detection and AI (beef heifer) to more extensive management using an intravaginal progesterone (CIDR®) plus injections of gonadotropin releasing hormone (GnRH) and prostaglandin F_{2α} (PGF) with fixed-time AI (TAI) without estrus detection (beef heifer and beef cow).

Products required for recommended estrus synchronization protocols

The products available (Table 1) for estrus synchronization protocols (Figures 1 and 2) are progestogens (MGA® or melengestrol acetate and EAZI-BREED CIDR®), prostaglandins (Lutalyse®, ProstaMate®, In Synch®, Estrumate® and estroPLAN®), and gonadotropins (Cystorelin®, Factryl®, Fertagyl®, OvaCyst®, and GONAbreed®). 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. Additionally, progestogens will allow beef cows and heifers that are “close” to beginning estrous cycling, but have not begun, to initiate estrous cycles that are fertile. The corpus luteum (CL) is regressed when PGF_{2α} and PGF_{2α} analogs are administered during days 6 through 18 of the estrous cycle, resulting in cattle returning to estrus on about days 2 through 6 post-injection. Gonadotropin releasing hormone (GnRH) induces the release of an ovulatory surge of LH resulting in ovulation of a dominant follicle or initiation

of a new follicular wave. No products are identified for luteinizing hormone (LH) and estradiol-17_β. Since LH is released by GnRH, no LH product is needed. However, estradiol-17_β has been identified in scientific publications and currently is being used with various breeding management protocols in non-US countries.

Process for Regulatory Approval of Products Used in Animal Health, Including Those Required for Estrous Synchronization Protocols

Products developed for the animal health market in the US are regulated by the Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM). New Animal Drug Application (NADA) Regulations are described in the Code of Federal Regulations (CFR). During the investigational phase, Investigational New Animal Drug (INAD) Regulations (21 CFR 511), an INAD number is assigned by CVM and data derived from research conducted under the regulations form the basis for the New Animal Drug Application (NADA). CVM must be notified of all drug shipments (21 CFR 511.1 (b)) for studies in target animals.

The Technical Sections of the NADA are identified in 21 CFR 514 and are: 1) Chemistry, Manufacturing, Control (CMC); 2) Target Animal Safety (TAS); 3) Target Animal Effectiveness (TAE); 4) Public Safety (Human Food Safety; HFS); 5) Environmental Assessment (Safety, EA).

Chemistry, Manufacturing, Control (CMC) Section assures the purity and potency of the product and documents the duration of product stability. Studies and assays must be completed consistently with Good Manufacturing Practices (GMP) for production and Good Laboratory Procedures (GLP; 21 CFR 58) for analytical procedures. The manufacturing process must not introduce harmful substances into the air, the water, and the land; this is assured through Local, State and Federal Environmental Regulatory Agency regulations and inspections of manufacturing facilities.

Target Animal safety (TAS) studies include tolerance studies to identify the margin of safety between the effect dose and toxic doses and toxicity studies (IX, 3X, 5X doses), to determine safety for the target animal under conditions of use, identify signs/effects related to drug toxicity, and estimate margin of safety. A complete accounting and adequate reports of the studies are required to be submitted to CVM and the studies must be completed consistently with Good Laboratory Procedures (GLP) and FDA Guideline #185/VICH GL 43.

Target Animal Efficacy (TAE) studies include multi-location studies to establish effectiveness of the label dose(s). A complete accounting and adequate reports of the studies are required to be submitted to CVM and the studies must be completed consistently with Good Clinical Practices (GCP) and FDA Guideline # 85/VICH GL 9.

For an application for a generic (Abbreviated NADA; ANADA), bioequivalency is required for approval under the pioneer product NADA approval

Public Safety, Human Food Safety (HFS), studies include toxicology and metabolism of the product to determine tissue residue depletion in the target animal tissues and to determine withdrawal times following treatment of the animal on farm/ranch. Withdrawal time is based on conservative statistical estimates based on a safe concentration of product and tissue residues post-drug last administration. A complete accounting and adequate reports of the studies are required to be submitted to CVM and the studies must be completed consistently with Good Laboratory Procedures (GLP) and FDA Guideline #3.

Environmental Assessment (EA) (safety) of both the Animal Health Product and the metabolized by-products-produced by the treated animals must not harm the environment. The information from these studies is reviewed by FDA/CVM and a Risk Assessment is completed. Assurance of no harmful effect on the environment from use of the product is based on the studies required by, reviewed by, approved by, inspected by, and the results of the studies reviewed by the FDA/CVM (FDA Guideline #89; VICH GL6; VICH GL38).

In general, the process of review and approval is to submit to CVM a Product Development Plan for input by CVM personnel. Protocols for each study are submitted to CVM for review and concurrence prior to initiation. Upon NADA approval by CVM, the approval is published in the Federal register, the Freedom of Information (FOI) is available to the public, and sale of product can begin.

Duration of the Process is on the order of 6 to 15 years and cost is on the order of \$8 million to \$30-\$40 million to NADA approval. Interval to NADA approval is shorter and cost is less for a generic product (ANADA) but “usually” longer and more costly for new entities, such as biopharma, antibiotics and some hormones (has been up to 18 years and \$50+ million).

Product label

Product Labels are written based on the data and conclusions resulting from the CMC, TAS, TAE, HFS, and EA Sections of the NADA.

Labeling for non-prescription (over the counter or OTC) new animal drugs includes adequate directions for use by the layman under all conditions of use for which the new animal drug is intended, recommended, or suggested in any of the labeling or advertising sponsored by the applicant.

Labeling for prescription (Rx, available only from a licensed veterinarian) veterinary drugs provides adequate information for use under which veterinarians can use the new animal drug safely and for the purposes for which it is intended, including those purposes for which it is to be advertised or represented.

Product labels for non-prescription products state the indication(s) for use (estrus synchronization, treat cysts in cattle, regress CL, treat disease, etc) and in what class of animals (dairy cows, beef cows, dairy heifers, beef heifers, sows, gilts, etc), a description of the product (sterile solution, suspension, device, etc), withdrawal period (none, days, etc), user safety warning(s), animal safety warning(s), recommendations for safe and effective use, directions for use (dose, route), storage and handling, and how supplied.

Product labels for prescription products state Federal law restricts this drug to use by or on the order of a licensed veterinarian, the indication(s) for use (estrus synchronization, treat cysts in cattle, regress CL, treat disease, etc) and in what class of animals (dairy cows, beef cows, dairy heifers, beef heifers, sows, gilts, etc), a description of the product (sterile solution, suspension, device, etc), withdrawal period (none, days, etc), user safety warning(s), animal safety warning(s), recommendations for safe and effective use, directions for use (dose, route), storage and handling, and how supplied.

In general, FDA-CVM requires studies to be completed in each class of livestock for which a product label is sought. Classes of livestock for cattle are dairy cow, dairy heifer, beef cow, and beef heifer. Because the product label for various products used to accomplish successful estrus synchronization protocols for cattle were developed either independently of estrus synchronization or specifically for estrus synchronization, there is “disconnect” between some of the specific product labels and use in estrus synchronization protocols.

Because animal studies (TAS, TAE, HFS, EA) for NADA approval, thus a product label, are so expensive, most animal health products have a product label for the specific indication (use) and class of livestock that is consistent with an acceptable return on investment.

Relationship between products to implement breeding management protocols and product labels

Table 1 identifies the hormone categories, the products available within each hormone category, and the product label for each product. Table 2 identifies the products available for sale that are used in combination for estrus synchronization protocols and their product labels. The following compares product label (Tables 1 and 2) with estrus synchronization protocols (Figures 1 and 2).

Figure 1

BEEF HEIFER PROTOCOLS - 2016

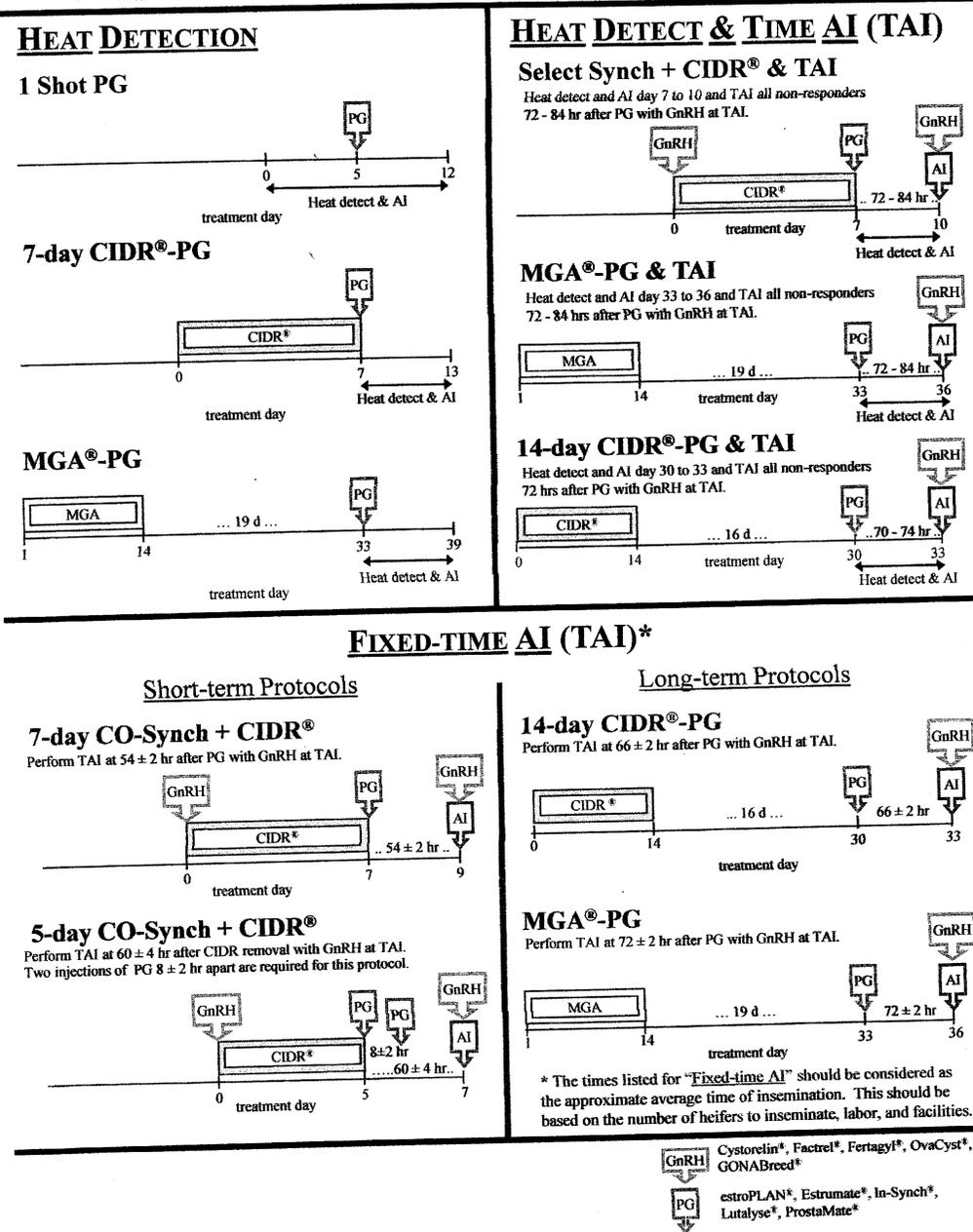


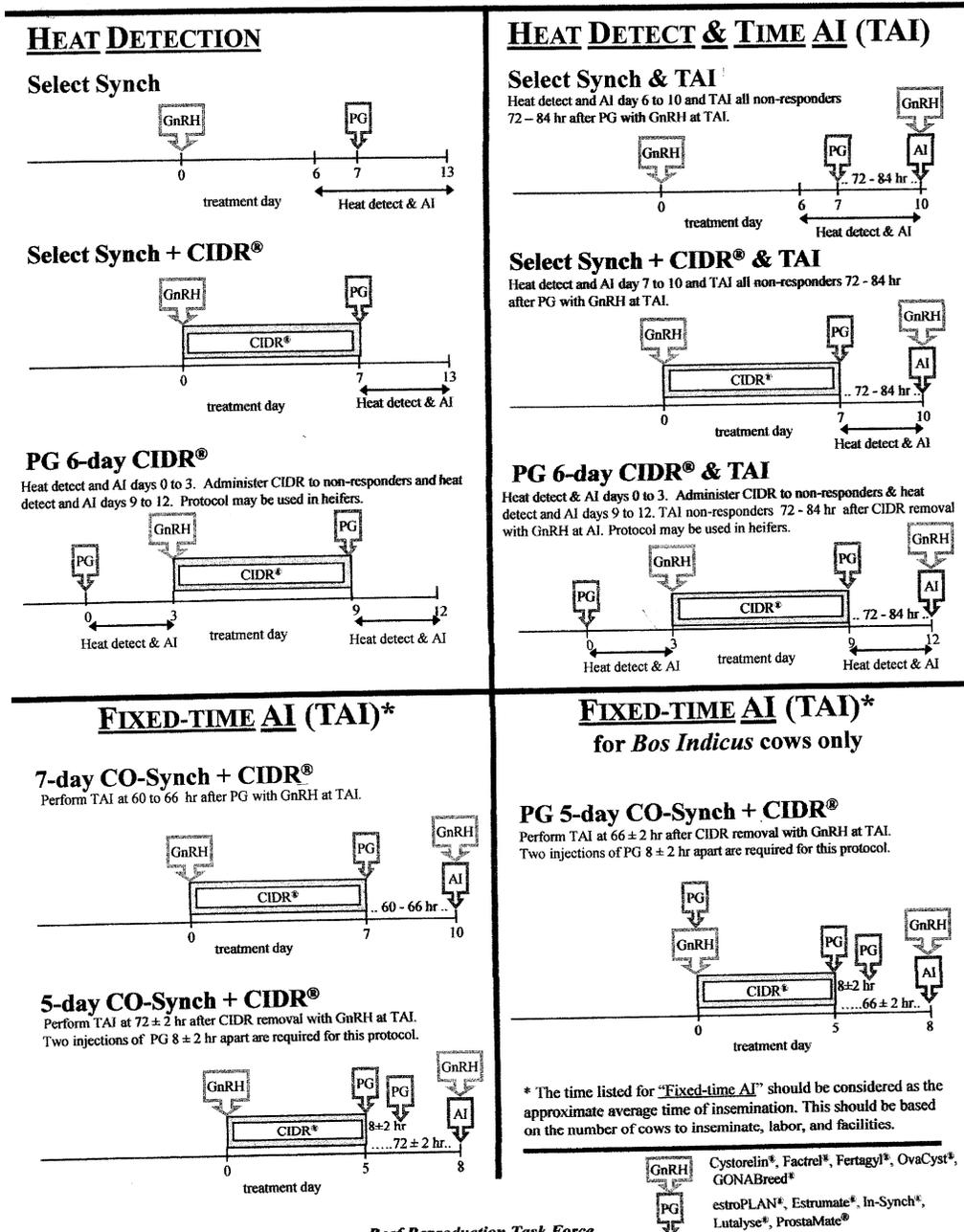
Figure 1. Beef heifer protocols

The a) 1 Shot PG + AI @ estrus, b) 7-day CIDR®-PG + AI @ estrus, c) MGA®-PG + AI @ estrus, d) MGA®-PG & TAI, e) 14-day CIDR®-PG & AI estrus/TAI, f) 14-day CIDR®-PG & TAI and g) MGA®-PG & AI estrus/TAI each have a label claim; see "Hormone Label and Estrus Synchronization Protocols" relative to use of GnRH.

The h) Select Synch + CIDR® & TAI, i) 7-day CO-Synch + CIDR®, and the j) 5-day CO-Synch + CIDR® do not have specific label claims; the failure is due to no CVM approval for specifically using a GnRH with CIDR®; see "Hormone Label and Estrus Synchronization Protocols" relative to use of GnRH.

Figure 2

BEEF COW PROTOCOLS - 2016



Approved 8-16-2015

Beef Reproduction Task Force

Figure 2. Beef cow protocols

The a) Select Synch and b) Select Synch & TAI each have a label claim; see “Hormone Label and Estrus Synchronization Protocols” relative to use of GnRH.

c) Select Synch + CIDR, d) PG 6-day CIDR, e) Select Synch + CIDR & TAI, f) PG 6-day CIDR & TAI, g) 7-day CO Synch + CIDR, h) 5-day CO Synch + CIDR, and i) PG 5-day CO Synch + CIDR & TAI do not have specific label claims. The failure is due to no CVM approval for specifically using a GnRH with CIDR®, and for PG 5-day CO Synch + CIDR having one day when PG plus GnRH are injected and one day with two injections of PGF; see “Hormone Label and Estrus Synchronization Protocols” relative to use of GnRH.

Product (hormone) label and estrus synchronization protocols (Figures 1 and 2)

MGA. Nonprescription (OTC). Used consistently with a label use. Because MGA is a steroid and steroids are considered by FDA-CVM to be a class of hormones with greater concern for human health, the data for the beef heifer approvals is not deemed sufficient for determining MGA to be safe and effective for use in beef cows.

PGF. Prescription (Rx). Appears to be used consistent with specific label except for the double injection at 8 ± 2 hours.

GnRH. Prescription (Rx). Each GnRH product is labeled for ovarian follicular cysts; each is for dairy cows except Factrel which is for cattle.

CIDR. Nonprescription (OTC). Use is consistent with label for estrus synchronization and initiation of estrous cycling in beef cows and heifers.

CIDR + Lutalyse (OTC + Rx). Use is consistent with 7-day label with Lutalyse injected on d6 or d7; use of CIDR for other than 7-days with Lutalyse is not on the label.

GnRH + PGF (Rx). Factrel, Fertagyl and GONAbreed each are approved for use with a PGF for estrus synchronization; Factrel and Fertagyl for lactating dairy cows but GONAbreed for dairy and beef cows. The specific label for each of the combinations gets “close” to the estrus synchronization protocol recommendations regarding times of injections, but not necessarily times for TAI.

Estrogen. No estrogen is currently approved in the US for use in estrus synchronization of cattle. Syncro-Mate-B® (SMB), 6 mg Norgestomet (a progestogen) subcutaneous implant for 9 days plus injection of 3 mg Norgestomet and 5 mg estradiol valerate (an estrogen) at implantation was approved by FDA-CVM in 1982 for synchronization of estrus/ovulation in cycling beef cattle and non-lactating dairy heifers. Sale of SMB ceased in the 1990s due to a limited market; cost of contract manufacture was not consistent with acceptable income from sale of Syncro-Mate B®.

During various ARSBC conferences over the past 10 years the topic of “need” for an estrogen for more effective estrus synchronization protocols has been intense, with advocates both for and against speaking passionately for their position. Additionally, estrogen products are available and in use with estrus synchronization protocols in non-US countries, such as Brazil. Steroids, especially estrogen, testosterone and progesterone, and their analogs, have been perceived by regulatory authorities worldwide as needing special scrutiny relative to human food safety when used in food animals. Thus, estradiol cypionate (ECP) was withdrawn voluntarily from the market a few years ago by Pfizer Animal Health, primarily due to the limited market relative to cost of addressing the issues posed.

If a company or group of investors decided to pursue approval of an estrogen for use in estrus synchronization protocols, the pathway is clear as to do so (see “Process for Regulatory Approval of Products Used in Animal Health” above). Based on criteria used by BRTF and BRLT (see “Recommended Estrus Synchronization Protocols are Based on Extensive Field Research” above), no recommended estrus synchronization protocol uses an estrogen.

Relationship among products to implement breeding management protocols (Tables 1 and 2), biology of action, and product labels (Figures 1 and 2)

The Process for Regulatory Approval of Products Used in Animal Health (see above) assures that each product is safe and efficacious for the label indication(s), which is a measure of the biologic actions of the active ingredient(s). Additionally, and very importantly, meat, and milk if dairy, products are safe for human consumption.

Progestogen.

MGA, a progestogen, is approved OTC for use in beef heifers for estrus synchronization and has an extensive research history from 1965 to document safety and efficacy. The original FDA-CVM approval (1968) was for feedlot heifers to increase ADG, improve FE and suppress estrus. However, extensive research was completed for estrus synchronization of beef cows and beef heifers (Lauderdale, 2010). Because the estrus synchronization market was small compared to the feedlot market and the challenges posed by FDA-CVM for approval of a hormone, The Upjohn Company chose to not pursue a label claim for estrus synchronization until the 1990s. The additional cost for a beef cow claim over the cost for the beef heifer claim was too great relative to market size, thus only the heifer claim today.

CIDR delivers the natural hormone progesterone and is approved OTC. The biology of the estrous cycle of the bovine and the scientific literature documented a need for estrus inhibition (progestogen) and luteolysis (PGF) in order to achieve a more precise return to estrus for estrus synchronization. Therefore, the combination of CIDR (for 7-days to decrease potential for aged follicles and reduced fertility with longer days of use) and PGF to regress the corpus luteum (CL) was selected for multi-site studies to secure the label claim. Subsequent research, published in peer reviewed scientific journals, documents further precision of estrus synchrony can be achieved by managing follicles with GnRH. Use of a progestogen to block estrus and stimulate some cows and heifers to initiate estrous cycling, use of PGF to regress CL, and use of a GnRH to both initiate a new follicular wave and subsequently used to ovulate a dominant follicle for TAI, pregnancy rates on the order of 55% to 65% can be achieved consistently. The CIDR is used in current estrus synchronization protocols to inhibit estrus and to stimulate estrous cyclicity in beef cows and heifers. Although the precise label use for CIDR is not followed in some of the recommended estrus synchronization protocols, based on less than or more than 7-day insertion, this does not pose either an animal or human food safety difficulty.

Prostaglandin (PGF)

Other than the double injection at 8±2 hours, PGF is being used consistently within label. Since PGF is cleared from the animal in hours, and the animals are in the breeding herd to remain for at least weeks to months, there is not human health hazard associated with these dual injections.

Gonadotropin Releasing Hormone (GnRH)

The biologic action of GnRH is to release luteinizing hormone (LH) from the pituitary. LH is required for complete follicular maturation and ovulation. Thus, GnRH, due to its ability to release LH and being produced synthetically with an acceptable return on investment compared to LH, was selected to treat ovarian follicular cysts in cattle. Original labels (1970s-1980s) were based on the market opportunity being lactating dairy cows to treat ovarian follicular cysts. With the understanding in the late 1980s that cattle have follicular waves and that control of follicular waves could provide more precise estrus synchronization, the “new label” for GnRH products was secured for use with a PGF for estrus synchronization. Because the estrus synchronization total market opportunity is “small”, and the largest segment of that market is lactating dairy cows, the lactating dairy cow is the only label for Factrel and Fertagyl, but beef and dairy cows are labeled for GONABreed.

Estrogen

In the absence of any approved product for use in cattle and regulatory authority concern regarding human food safety from consumption of animal products following use of estrogens, the decision to not use a compounded estrogen product seems to be in the best interest of regulatory authorities, veterinarians and producers.

Combinations

Combinations of PGF and progesterone and GnRH and PGF are approved in cattle for estrus

synchronization. The biologic action of the classes of hormones (progestogen, PGF, GnRH) and the doses and routes of delivery being the same as approved via NADAs provide confidence that they do not provide animal safety or human food safety concern. Data published in peer reviewed scientific journals identified enhanced efficacy for estrus synchronization for beef cows and beef heifers.

Dilemma: How do I select a breeding management protocol?

As individuals, we make decisions influenced by our history, education, philosophy, culture and tolerance for “hassle factors”.

Each product being used for estrus synchronization protocols is being used consistently with its natural biologic action: PGF to regress CL; GnRH to release LH to cause ovulation or luteinization of follicles; progestogens to block estrus and to stimulate estrous cycling. Doses and routes of delivery of the products used in the estrus synchronization protocols are consistent with their NADA approvals. Each hormone elicits its biologic effect through a separate receptor, therefore no interference (TAS, HFS) should result when used in the recommended estrus synchronization protocols.

Each product has a NADA/ANADA supporting target animal safety (TAS) and human food safety (HFS).

1) NADA 108-901, June 9, 2014 identified the original NADA approvals for Lutalyse, Factrel and EAZI-BREED CIDR were sufficient to determine no additional target animal safety or human food safety studies were required for approval of Lutalyse with Factrel and Lutalyse with EAZI-BREED. NADA 139-237, June 28, 2013 identified serum concentration of gonadorelin (GnRH) and dinoprost (PGF) return to baseline within hours after intramuscular injection, therefore no potential interaction is expected, especially when the interval between injections is 30 hours or greater.

2) ANADA 200-134, April 23, 2015 and ANADA 200-541, January 17, 2013, identified the original NADA approvals for Estrumate and Fertagyl/GONAbreed were sufficient to determine no additional target animal safety or human food safety studies were required for approval of Estrumate with Fertagyl/GONAbreed. Based on rapid depletion of residues of cloprostenol (PGF) and gonadorelin (GnRH), there is sufficient time between sequential uses of the two products to preclude any potential interaction between the two drugs.

3) No specific NADA exists at this time for use of GnRH with a progestogen, although a NADA exists for use of CIDR (progesterone) and Lutalyse (PGF). The extensive scientific literature reporting effectiveness of a progestogen, GnRH and PGF allows a defensible interpretation of no adverse effect on cattle (no TAS concern). Based on NADA/ANADA cited above and the biology of the three hormone, no interference would be expected from use of GnRH with a progestogen relative to HFS, especially when considering the rapid clearance and prolonged interval between treatment and potential for slaughter for human consumption (months to a year or more). Additionally, NADA 141-200, July 22, 2010, reported the concurrent use of Lutalyse (PGF) and CIDR (progesterone) did not result in milk residues being greater than expected.

The only exception to 30 or more hours or days between sequential injections of PGF and GnRH, relative to NADA approvals, is injection of PGF plus GnRH at the same time in the Beef Cow *Bos Indicus* estrus synchronization protocol, “PG 5-day CO-Synch + CIDR”.

The question of efficacy (TAE) for every estrus synchronization protocol is not addressed in specific NADA/ANADA labels. However, efficacy has been addressed via sufficient numbers of studies with sufficient numbers of beef cows/heifers to allow each estrus synchronization protocol to be recommended by qualified and competent beef cattle Extension Personnel.

Two obvious responses to the question, *How Do I Select a Breeding Management Protocol*, are:

1) I will use only products and protocols that comply with specific label indications. If I choose this approach I should minimize sanction from fellow veterinarians and FDA-CVM but I will not be able to

provide the estrus synchronization protocols that provide the greatest opportunity for increasing the percentage of the beef herd estrous cycling at the start of the breeding season and the most effective TAI opportunities.

2) I will use products and protocols that I am confident are consistent with the intent of the label. If I choose this approach I may incur sanction from fellow veterinarians and FDA-CVM but I will be able to provide the estrus synchronization protocols that provide the greatest opportunity for increasing the percentage of the beef herd estrous cycling at the start of the breeding season and the most effective TAI opportunities.

Disclosure

J.W. Lauderdale received a PhD (1968) from the University of Wisconsin in Endocrinology and Reproductive Physiology. He was employed by The Upjohn Company (Pharmacia & Upjohn, Pharmacia) Animal Health business from 1967 to 1998. From 2000 to the present he is President of Lauderdale Enterprises, Inc. consulting in the animal health industry. Major research was directed at increasing the efficiency of post-partum cow and post-partum sow reproduction, the role of prostaglandin $F_{2\alpha}$ in the regression of the corpus luteum and as a practical means for controlling the estrous cycle of cattle and mares and time of parturition in swine, the use of steroids for enhancement of productive efficiency of beef cattle, and the development of bovine somatotropin to enhance the efficiency of milk production of dairy cows. He actively participated with regulatory authorities directly in the US, Canada, European Union, World Health Organization and indirectly through employee colleagues in Mexico, Brazil, Argentina, Chile, Japan, Korea, New Zealand and Australia for animal health product approvals and regulatory decisions. He was President of the American Society of Animal Science (ASAS, 2003) and President of the Federation of Animal Science Societies (FASS, 2005). He does not receive income from companies or universities involved with use of the hormones used in the estrus synchronization protocols or income from use of the estrus synchronization protocols. The content of this paper reflects his perspectives.

Table 1. Hormone category, products available within each hormone category, and product label for each product.

| Hormone Category | Product ^a | Product Label Relative to Estrus Synchronization |
|--|--|--|
| Progestogen | MGA [®] (melengestrol acetate)-OTC | Increased ADG, improved FE, estrus suppression in feedlot heifers. Suppression of estrus in beef heifers for breeding. |
| | EAZI-BREED CIDR [®] (progesterone)--OTC | Synchronization of estrus in suckled beef cows, and replacement beef and dairy heifers; advancement of first postpartum estrus in suckled beef cows; advancement of first pubertal estrus in replacement beef heifers. See Combinations. |
| Prostaglandin F _{2α} (PGF _{2α}) and analogs | Lutalyse [®] (dinoprost tromethamine)--Rx | Estrus synchronization: 1) double 10-12 day injection, AI at estrus or AI at 80 hr (TAI); 2) single injection, AI at estrus. Beef cows and heifers. Unobserved (silent) estrus in lactating dairy cows with a CL. See Combinations. |
| | ProstaMate [®] --Rx | ANADA of Lutalyse. |
| | InSynch [®] --Rx | ANADA of Lutalyse |
| | Estrumate [®] (cloprostenol sodium)--Rx | Estrus synchronization: 1) double 11 day injection, AI at estrus or AI at 72 hr or 72 +96 hr (TAI); 2) single injection, AI at estrus; unobserved (silent) estrus. Cattle. |
| | estroPlan [®] --Rx | ANADA of Estrumate |
| Gonadotropin releasing hormone (GnRH) | Cystorelin [®] (gonadorelin diacetate tetrahydrate)--Rx | Ovarian follicular cysts. Dairy cattle. |
| | Factrel [®] (gonadorelin hydrochloride)--Rx | Ovarian follicular cysts. Cattle. See combinations. |
| | Fertagyl [®] (gonadorelin diacetate tetrahydrate)--Rx | ANADA of Cystorelin. Ovarian follicular cysts. Dairy cattle. See combinations. |
| | OvaCyst [®] (gonadorelin diacetate tetrahydrate)--Rx | ANADA of Cystorelin. Ovarian follicular cysts. Dairy cattle. |
| | GONAbreed [®] (gonadorelin acetate)--Rx | ANADA of Cystorelin. Ovarian follicular cysts. Dairy cattle. See combinations. |
| Estrogen | None | |
| Combinations | EAZI-BREED CIDR [®] + Lutalyse [®] -OTC & Rx | Estrus synchronization of beef cows and heifers. |
| | Factrel [®] + Lutalyse [®] --Rx | Estrus synchronization-lactating dairy cows. |
| | Fertagyl [®] + Estrumate [®] --Rx | Estrus synchronization-lactating dairy cows. |
| | GONAbreed [®] + Estrumate [®] --Rx | Estrus synchronization-lactating dairy cows and beef cows. |

^a OTC is nonprescription/over the counter; Rx is prescription, licensed veterinarian only.

Table 2. Products used in combination and their label indication.

| Combination (Company) | Label for Estrus Synchronization |
|---|---|
| EAZI-BREED CIDR® + Lutalyse® (Zoetis AH) | Insert CIDR for 7 days. Inject Lutalyse on d6 or d7. AI at estrus. Beef and lactating dairy cows and beef and dairy heifers. |
| Factrel® + Lutalyse® (Zoetis AH) | Inject Factrel d0. Inject Lutalyse d6-8. Inject Factrel d9. TAI 48 hr after Lutalyse & TAI OR 48 hr after Lutalyse plus 24 hr after Factrel & TAI OR 56 hr after Lutalyse plus 18 hr after Factrel & TAI. Lactating dairy cows. |
| Fertagyl® + Estrumate® (Intervet AH) | Inject Fertagyl d0. Inject Estrumate d6-8. Inject Fertagyl 30-72 hr after Estrumate. TAI 8-24 hr after Fertagyl OR AI at estrus. Lactating dairy cows. |
| GONAbreed® + Estrumate® (Parnell Technologies) | Inject GONAbreed d0. Inject Estrumate d6 -8. Inject GONAbreed 30-72 hr after Estrumate. TAI at 0-24 hr after GONAbreed OR AI at estrus. Beef cows and lactating dairy cows. |

Literature cited

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