Introduction

Anabolic steroids have been widely used in the beef cattle industry for over 50 years as safe and effective growth-promoting agents, and today, more than 90% of all feedlot cattle in the US receive some type of steroidal implant during their lifetime (NAHMS, USDA 2000). A list of approval of growth promotants by the FDA is shown in Table 1. Generally, implants have been shown to increase growth rate 8 to 28%, improve feed efficiency 5 to 20%, and enhance lean tissue mass of the carcass 3 to 10% (Duckett and Owens, 1997).

This improvement in production efficiency has multiple benefits: 1) it clearly and dramatically reduces production costs by reducing the amount of feed required per unit of gain (Avery and Avery, 2007); 2) it reduces the amount of land necessary to produce equivalent amounts of food for consumers; 3) it limits the production of greenhouse gases by reducing the number of animals required to produce equivalent amounts of beef (Avery and Avery, 2007); and 4) it extends cost savings to consumers by providing a year-round, affordable supply of beef at reduced prices (Lawrence and Ibarburu, 2006). Since animal products contribute significantly to the total caloric and nutrient intake in the human population, altering the composition of growth toward more lean tissue and less adipose tissue results in a healthier product with fewer calories that still is rich in beneficial nutrients.

In addition to steroidal implants, a newer class of orally active growth promotants, known as β-adrenergic agonists (BAA; Ractopamine-HCl; 2003 and Zilpaterol-HCl; 2006), have been approved for use in finishing beef cattle in the last decade. These products provide similar production benefits as steroidal implants, but differ in application and mode of action. Beta-adrenergic agonists are fed during the last 20 to 42 days of the cattle finishing period, depending on the specific product. The purpose of this paper is to explain how anabolic implants and BAA work and their benefits to beef cattle production.

Anabolic Steroids

Commonly used steroid compounds include estrogens, androgens, and progestins. These steroids can be classified as naturally occurring or synthetic as described in Table 2. The natural hormones listed in

Table 1. Chronological sequence of FDA approval of growth promotants used in the U.S. beef cattle industry.

| Growth Promotant                          | Year of FDA Approval |
|-------------------------------------------|----------------------|
| Oral diethylstibestrol (DES)              | 1954                 |
| DES implant                               | 1957                 |
| Estradiol benzoate / progesterone (steers)| 1956                 |
| Estradiol benzoate / testosterone propionate (heifers) | 1958 |
| Oral melengestrol acetate (heifers)       | 1968                 |
| Zeranol (36 mg) implants (cattle)         | 1969                 |
| Oral DES removed from market              | 1972                 |
| DES implants removed from market          | 1973                 |
| Silastic estradiol implant (cattle)       | 1982                 |
| Estradiol benzoate / progesterone (calves)| 1984                 |
| Trenbolone acetate (TBA) implants (cattle)| 1987                 |
| Estradiol (17-β) / TBA implants (steers)  | 1991                 |
| Bovine somatotropin (lactating dairy cows)| 1993                 |
| Estradiol (17-β) / TBA implants (heifers) | 1994                 |
| Zeranol (72 mg) implants (cattle)         | 1995                 |
| Estradiol (17-β) / TBA implants (stocker cattle) | 1996 |
| Ractopamine hydrochloride (cattle)        | 2003                 |
| Zilpaterol hydrochloride (cattle)         | 2006                 |

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Table 2. Growth-promoting steroid hormone classifications.

| Type                     | Natural                        | Synthetic                        | Progestins (hormone of pregnancy) |
|--------------------------|-------------------------------|----------------------------------|-----------------------------------|
| Estrogens (female hormone)| Estradiol-17beta              | Zeranol                          | Progesterone                      |
| Androgens (male hormone) | Testosterone                  | Trenbolone acetate               | Melengestrol acetate (orally-active) |

Table 2 are found in all mammals, regardless of gender. The three synthetic compounds used in beef cattle production to enhance growth rate and feed efficiency are zeranol, trenbolone acetate (TBA), and melengestrol acetate (MGA). Zeranol is classified as a nonsteroidal macrolide and is in a class of naturally occurring (found in nature; not produced in a laboratory) products referred to as β-resorcylic acid lactones. Zeranol was originally isolated from corn mold, and although it is a nonsteroidal compound, it has been shown to have estrogen-like biological activity in cattle. Trenbolone acetate was synthesized in 1967. Trenbolone acetate is a testosterone analogue that has 10 to 50 times the anabolic activity compared with testosterone (Bouffault and Willemart, 1983). This androgen growth promotant often is used in combination with an estrogen (most commonly estradiol [E₂]) to maximize growth rate and efficiency in cattle, especially steers. In 2012, it was estimated that nearly two-thirds of all implants marketed in the US were single implants of various concentrations of TBA and E₂ (TBA/E₂; P. Parker, Zoetis, Inc.). Growth-promoting implants containing various combinations of TBA and E₂ is the prominent type of implants used in the industry today. Melengestrol acetate is approved for use in feedlot heifers to suppress estrus and enhance efficiency of growth. Even though this is an exogenous, synthetic progestin, unique characteristics of this compound allow it to be active when fed to heifers at 0.40 mg/animal/day, and it is therefore not necessary to administer this compound as an implant. With rapid metabolism in the body of the animal and no detectable residues in edible tissues, no withdrawal period is required for MGA in heifers so cattle producers can feed the product safely up until harvest. Currently, MGA is approved only for feedlot heifers and cannot be fed to steers.

With the exception of MGA, which is orally active, the rest of the anabolic steroids are administered as compressed pellet-implants with various inert carrier compounds. These steroid-containing implants are administered in the back of the middle of the ear of cattle. Proper implanting of these compounds is important for both efficacy and safety. Once administered in the back of the ear, the active steroids dissolve slowly into the bloodstream in the ear. The compounds then are carried by special binding proteins in the bloodstream to all tissues of the body. Mode of action

Combined TBA/E₂ implants increase carcass protein by approximately 10% when compared to non-implanted steers. Much of this increase occurs the first 40 days following implantation. Growth-promoting implants containing anabolic steroids have been shown to induce postnatal skeletal muscle hypertrophy, in part, through increased circulating and locally produced (skeletal muscle) concentrations of a very important growth factor for skeletal muscle, IGF-I. Insulin-like growth factor-I is a potent stimulator of skeletal muscle growth and differentiation. It is thought to stimulate skeletal muscle protein synthesis and reduce skeletal muscle protein degradation. Specifically, TBA and estradiol-17β (TBA/E₂) implant administration to cattle has been reported to increase circulating IGF-I and skeletal muscle IGF-I mRNA abundance compared with non-implanted, control steers in several experiments. In addition, TBA/E₂ administration to steers resulted in an increase in the number of actively proliferating, satellite cells within 35 days of implantation. It is thought that the enhanced IGF-I production by the muscle fiber after administration of the steroid implants mediates the increased proliferative activity of these satellite cells. Based on the discussion in the previous section, increased proliferative activity of satellite cells should enhance the rate of muscle growth in cattle. Taken together, these findings strongly support a mechanism for steroid implant-induced muscle growth in beef cattle that involves increases in the local production of muscle IGF that,
in turn, enhances satellite cell activity and consequently increases skeletal muscle growth.

The effects listed above can be observed within days after implant administration. Early muscle growth stimulus is primarily hypertrophic in nature, which has been shown by depressed DNA:protein ratios. Prolonged (weeks-long) exposure to combined estrogenic/androgenic implants produces hyperplasia (increase in satellite cell nuclei) as well. In this case, quantity of muscle protein is increased but normal DNA/protein ratios are observed, indicating that proliferation of satellite cells resulted in an increased quantity of DNA in the muscle. Cell culture studies have shown that the mitogenic activity of sera from implanted steers is increased, providing support for the line of thinking that implants initially increase hypertrophy and ultimately increase hyperplasia to support increased muscle mass.

**Strategic use of steroidal implants as growth promotants**

Cattle producers have developed strategies to use the different combinations of implants based on breed and sex of cattle, marketing conditions, body condition, and estimated days on feed. Because implants promote the deposition of muscle rather than fat, the resulting beef carcasses tend to be leaner, with less marbling when harvested at similar days-on-feed as animals that have not been implanted. Therefore, to achieve the same degree of marbling, implanted cattle must be fed for longer and to a heavier body weight.

Implant strategies can be tailored to each animal type and marketing opportunity by increasing or decreasing the dose of hormone administered. For example, in large-frame continental cattle that may be surpassing acceptable carcass weight, a lower dose TBA/E, combination implant may provide an adequate dose of anabolic steroids to achieve acceptable gains without impacting quality grade at a given carcass weight. However, smaller-framed British breeds may benefit from higher dose combination implants to increase gain and body size and improve feed conversion efficiency without substantially reducing quality grade due to their genetic propensity to deposit intramuscular fat (marbling).

**Figure 1.** Implant protocol. The diagram above illustrates an example of an implant protocol for cattle of a projected finish body weight of 545 kg, with varying intake weights ranging from 275 to 365 kg. Feedyards project final body weights and gain potential of cattle upon arrival, and implant protocols are assigned to each lot to achieve production targets (body weight gain, efficiency, and carcass characteristics) within the constraints of cattle biological type and weight. TBA = Trenbolone acetate; E2 = Estradiol, and Z = Zeranol.

While no withdrawal before harvest exists for implants, to gain the optimal benefit of the implant, it is necessary to leave the implant in the animal until the majority of the compound has paid out, ranging from 50 to 200 d. While it is possible to “stack” implants (administer an implant while another implant that is still paying out), producers tend to use a combination implant that achieves the same purpose but in a more controlled manner. For this reason, it is advised that producers inquire about the implant history of an animal so an appropriate implant strategy can be applied and the optimal economic return can be achieved.

Implant strategies typically are developed by estimating the days on feed for cattle to achieve the desired harvest weight, and working back. For example, in Figure 1, the implant strategy will change based on the body weight of cattle arriving at the feedyard, even though they will all be harvested at similar harvest weights.

Typically, when cattle are implanted more than one time, strategies are developed in which the cattle are “stair-stepped” from mild to aggressive implants. Mild and aggressive refer to the potency of the implants. Researchers at South Dakota State University (Bruns et al., 2005) observed aggressive implanting during the early growth phases of the animals evaluated substantially reduced quality grade (decreased marbling/intramuscular fat deposition) at harvest. Therefore, utilizing mild implants during the rapid growth phases, followed by more aggressive implants when growth has slowed down, tends to provide adequate growth enhancement with minimal impact on capacity to deposit marbling.

Another factor that producers consider when assigning animals to an implant protocol is seasonality or weather. During the winter in the Midwestern US, for example, producers may choose a longer-acting implant to eliminate the need to process the animals during the winter cold or snow. In the desert Southwestern US, extreme high temperatures during the summer encourage producers to implant with a long-lasting implant in late spring to avoid processing during the heat.

**Performance response to steroidal implants**

Currently, 29 growth-promoting products are approved for use and marketed in the US, 27 of which are steroidal implants. These products vary in active ingredients, dosage, and carrier compounds. The dose of active hormone is the primary determinant of performance response; however, if nutrients (primarily protein and/or energy) are limiting, cattle will not respond to an increased dose of hormone. Another determinant of the absolute response to implants is the inherent genetic potential for growth of each animal. As the growth rate of the non-implanted animals increases, so does the added benefit from the implant. However, the percentage response to the implant may not change dramatically. With respect to feedlot performance, Duckett and Owens (1997) reviewed 33 independent implant studies that compared performance of non-implanted
cattle with those given a combination androgenic/estrogenic implant. Implanting increased average daily gain 21% and improved feed efficiency 11% in feedlot cattle. In addition, carcass weight was increased 7% due to implanting. The majority of feedlot implant studies have been conducted using a time-constant termination point for all treatments. Given this restriction, the aforementioned review also reported a 5% increase in ribeye size, a 7% decrease in fat cover, a 5% decrease in marbling score, and a 17% decrease in percent of carcasses grading Choice or better. This indicates that although implanted cattle gain faster than non-implanted cattle, they do not accumulate fat at a rate proportional to their increased growth. If cattle are harvested at different fat-content endpoints, we would normally expect lower marbling content.

A small number of studies have been conducted where cattle, having been treated with different dosages of implant, are harvested at multiple times and, hence, at fat-content endpoints. Hutcheson et al. (1997) reported that when the dosage of a TBA/E2 implant was increased by 50% (120/24 vs. 80/16 mg TBA/mg E2), an additional 22 days on feed resulted in similar average daily gain, feed-to-gain ratio and a similar percent of carcasses grading Choice and Prime for the higher dosage compared to the lower dosage at the earlier time endpoint. However, at the higher dosage and the later time point, hot carcass weight also increased by 25 kg. Preston et al. (1999) reported that based on a review of 24 studies, steers and heifers implanted with combination TBA/E2 implants required an additional 12 and 15 days on feed, respectively, to attain a similar degree of marbling compared to non-implanted animals. Cornell University researchers (Guirou et al., 2002) calculated that live empty body weight (the body weight of a live animal with an empty digestive tract) of steers implanted twice in the feedyard with combination TBA/E2 implants would be 44 kg heavier at comparable body fatness compared to steers which receive no feedyard implant, and steers would have similar quality grade. Anderson (1991) reported the difference between implanted and non-implanted feedyard cattle would be 58 kg.

Beta-Adrenergic Agonists

Beta-adrenergic agonists are classified as phenethanolamine compounds and are approved for use in food-animal production in several countries. These compounds are neither steroids nor peptide growth factors; rather, they are compounds similar to endogenous catecholamines, such as norepinephrine and epinephrine that are found in all animals, including humans.

In the US, ractopamine hydrochloride (RH) and zilpaterol hydrochloride (ZH) are both approved as growth promotants for beef cattle (Table 3). Ractopamine, marketed by Elanco Animal Health as Optaflexx, was approved (June 2003) to be fed the last 28 to 42 days before slaughter with no pre-harvest withdrawal. Zilpaterol, marketed by Merck Animal Health as Zilmax, was approved (August 2006) to be fed to cattle the last 20 to 40 days before slaughter. Zilmax was approved by FDA with a 72-hour withdrawal time before harvest.

Mode of action of Beta-adrenergic agonists

One of the most pronounced effects of feeding a BAA to ruminants is the preferential dramatic increase in skeletal muscle mass and/or cross-sectional area of individual muscles. Due to the dramatic increase in skeletal muscle hypertrophy following BAA administration to ruminants, one would expect satellite cell proliferation and subsequent fusion of the satellite cells to provide a source of DNA to support the rapid changes in muscle mass, similar to action of steroid implants. However, the majority of previous work suggests during the three to five weeks of BAA agonist-stimulated muscle hypertrophy, no change in number of nuclei occurred. A constant DNA amount (nuclei number) coupled with rapid changes in muscle mass and, consequently, protein accumulation results in decreased DNA concentration of individual muscles in BAA-fed animals compared to untreated controls. Since DNA accumulation during rapid periods of muscle hypertrophy does not occur due to feeding a BAA, many researchers have focused on the direct binding of BAA to their receptors (Beta-adrenergic receptors; BAR), affecting either rate of protein synthesis or protein degradation, or both. Skeletal muscle in cattle has been shown to have abundant numbers of BAR on the cell surface. Previous research has shown that many BAA are capable of increasing protein synthesis and decreasing protein degradation. The net effects of these changes are dramatic changes in accretion of protein within skeletal muscle tissue. It appears that BAA cause existing nuclei within the muscle fiber to become much more efficient at increasing muscle protein accumulation without the support of additional DNA from satellite cells. These compounds cause the existing muscle fibers to exhibit muscle hypertrophy very efficiently without the need for additional nuclei. This effect is brought about due to direct binding of BAA agonists to its receptor on skeletal muscle tissue. Following receptor activation, key pathways regulating protein accretion are regulated resulting in an increased protein accumulation in the muscle fiber.
**Performance response to Beta-adrenergic agonists**

Beta-adrenergic agonists are known as repartitioning agents. Ricks et al. (1984) proposed that the repartitioning activity of BAA are due to the use of free fatty acids as an alternative source to amino acids, which results in hypertrophy of skeletal muscle and decrease in protein degradation. It has been reported extensively in the literature that BAA increase ADG, hot carcass weight, and area of the *longissimus dorsi* muscle (Vasconcelos et al., 2008; Winterholler et al., 2008; Rathmann et al., 2012), improve the gain:feed efficiency measurement (Scramlin et al., 2010; Baxa et al., 2010; Parr et al., 2011), and decrease backfat thickness, yield grade, and intramuscular fat (Vasconcelos et al., 2008; Winterholler et al., 2008; Baxa et al., 2010).

Interestingly, the increase in hot carcass weight is greater than the increase in BW in most reports. Results from experiments using zilpaterol hydrochloride show greater response in hot carcass weight vs. body weight (8.2 vs. 17.2 kg, 9.4 vs. 16 kg, and 11 vs. 19 kg; Vasconcelos et al., 2008; Elam et al., 2009; Parr et al., 2011, respectively). However, results from ractopamine hydrochloride studies are not as consistent when compared to zilpaterol hydrochloride studies. Avendaño-Reyes et al. (2006) reported an increase in body weight of 10.6 kg vs. 13.6 kg increase in hot carcass weight using ractopamine hydrochloride. However, Winterholler et al. (2008) and Scramlin et al. (2010) results show that the increase in body weight was greater than the increase in hot carcass weight (12 vs. 10 kg and 7.53 vs. 5.3 kg, respectively). In a review of the use of zilpaterol hydrochloride in beef cattle, Delmore et al. (2010) hypothesized that zilpaterol hydrochloride feeding regulates the metabolism and mobilization of noncarcass components, shifting nutrients to carcass components.

Research has also shown that the use of BAA can increase toughness in beef. Scramlin et al. (2010) compared the effects of ractopamine hydrochloride and zilpaterol hydrochloride in finishing steers and found that the use of ractopamine hydrochloride and zilpaterol hydrochloride increased the values of Warner-Bratzler shear force in *longissimus dorsi* muscle steaks. However, both BAA did respond to aging in a similar manner (Figure 2).

![Figure 2](https://example.com/f2.png)

**Figure 2.** Non-linear regressions characterizing postmortem aging changes in Warner-Bratzler shear force (WBSF) for longissimus muscle steaks from steers fed no Beta-adrenergic agonist (control), 200 mg of ractopamine hydrochloride (Optaflexx, Elanco Animal Health, Greenfield, IN) for 33 days (RAC), 75 mg of zilpaterol hydrochloride (Zilmax, Merck Animal Health) for 30 days and a three-day withdraw period (ZH) (Adapted from Scramlin et al., 2010).

**Conclusions**

In closing, growth promotants have been safely used in beef cattle production for over 50 years. Growth-enhancing compounds, including steroidal implants and BAA, increase production and improve feed efficiency of beef cattle. The changes in performance result in an economic benefit to beef cattle producers and impact the relative price competitiveness of beef as compared to other dietary protein sources. Long-term use of the growth enhancing technologies has proven that the compounds are a safe, effective way to enhance lean-tissue deposition in cattle. The compounds are rapidly metabolized and excreted from the animal, assuring no risk of potential residues in the edible tissues. The safe use of growth-enhancing compounds benefits the consumer. First, consumers benefit from the reduced production cost associated with the use of this technology in beef production. Second, consumers benefit from the improved lean protein options through beef from cattle reared with growth-enhancing technologies. Finally, land necessary to produce equivalent amounts of food for consumers and the carbon footprint of the beef cattle industry is greatly decreased when growth technologies are used. Combined, growth-promoting technologies are an important tool for production of lean, healthy beef.
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