Bovine Growth Promoting Implants: Current Status-Future Thinking

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It is well recognized that implanting cattle for growth promotion purposes has been one of the most successful practices toward improvement of profit per head of any employed by the industry. Implanting for desired goals along with proper deworming programs, successful crossbreeding programs, good reproductive management to shorten the calving interval and have cows calve at desired times as well as advances in nutrition serve as the key management practices for profitable beef production. From the many many trial results available one can find increases of 5 to 15% in average daily gain (ADG) and up to 15% increase in feed efficiency (F/G). Most use and benefit has been realized in the feeder segment of the industry although implanting per-weaning and stocker cattle also give favorable results albeit more inconsistent. The latter may well be due to the much greater variability in environment, nutrition and management of these classes of cattle.

Considerable experience and information concerning the use of hormonal implants for growth promotion in cattle has been gained during the past three decades. Ongoing efforts at maximizing the benefits have been directed at selection of products used, implanting regimens, implantation techniques, types of cattle implanted, ages of cattle implanted and management of implanted cattle. The recent introduction of a new combination product (Revalor-S) has stimulated renewed interest in this effort. The purpose of this presentation is to give an overview of the current status of this management practice and some thinking of changes one might expect in the future.

Products Available

Following is a list of the various products available along with comments concerning content, dosage and use for the different classes of cattle:

1. Synovex S/C. This is a Syntex product. This is one of the oldest products on the market with the first clearance coming in 1958. The calf product clearance came much later (1984). The product is a combination of natural steroids containing progesterone and estradiol benzoate in a 10 to 1 ratio. The dosage for steers is 200mg progesterone and 20mg estradiol benzoate. For suckling calves and heifers over 45 days of age intended for breeding purposes the dosage is 100mg progesterone and 10 mg estradiol benzoate. These doses are administered as 8 pellets for steers and 4 for calves given subcutaneously in the middle of the ear. The product should not be used for bull calves intended for breeding purposes.

2. Synovex H. This is a Syntex product. This product also has a long history of being on the market (1956). It contains testosterone propionate and estradiol benzoate in the ratio of 10 to 1. The dosage for feedlot heifers is 200 mg testosterone propionate and 20mg estradiol benzoate (given as 8 pellets subcutaneously in the middle of the ear). This product is not intended for use in dairy or beef replacement heifers due to the testosterone content.

3 & 4. Implus S/C and Implus H. These products are identical to the Synovex products described in 1 and 2 above. They were developed and cleared by Ivy Laboratories, Inc. of Lenexa, Kansas. They were initially licensed and sold by Boehringer Ingelheim Animal Health, Inc. with the names Steer-Oid, Heifer-Oid and Calf-Oid. They are now being sold by The Upjohn Company, Animal Health Division with the name being changed to Implus. These were first cleared in 1982 and 1984.

5. Ralgro. This is a Pitman-Moore product. It was cleared in 1969. It is a nonsteroidal anabolic agent, zeranol, which has more estrogenic activity than androgenic activity. It is cleared for cattle and sheep as a growth promotant but is not to be used in heifers or bulls intended for breeding purposes. It is supplied in 12 mg pellets with three (36mg) being the dose for cattle and a single pellet being the dose for sheep.

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6. Compudose. This is an Elanco product. It was cleared in 1982. It contains estradiol 17ß impregnated in a silicone matrix and coated with silicone to control the release. It is cleared for use in suckling and pastured growing steers and for confined steers and heifers. In one formulation each implant contains 24 mg estradiol and is coated with oxytetracycline powder as a local antibacterial. This product is labelled as effective for 200 days. There is also a clearance for a 45 mg implant which has a 400 day duration of action listed. The implants are to be given subcutaneously in the middle of the ear.

7. Finaplix-H/S. This a Roussel UCLAF product distributed in the US by Hoechst-Roussel Agri-Vet Company. The product was cleared in 1987. The active ingredient is trenbolone acetate, an androgen with increased anabolic activity compared to the androgenic activity. It is cleared for growing and finishing feedlot heifers for ADG and F/G benefits and for increased F/G in growing and finishing steers. The product is presented as pellets containing 20mg trenbolone acetate. For heifers the dosage is 200 mg (10 pellets) while for steers the dosage is 140 mg (7 pellets) given subcutaneously in the middle of the ear. It is not to be used in dairy animals or animals intended for subsequent breeding.

8. Revalor-S. This is also a Roussel UCLAF product distributed in the US by Hoechst-Roussel Agri-Vet Company. It is the most recent addition to the implant field with the clearance coming in late 1991 and launch in early 1992. It is a combination of trenbolone acetate and estradiol with the clearance for increased ADG and improved F/G in feedlot steers. One implant consists of 6 pellets each containing 20 mg trenbolone acetate and 4 mg estradiol. A single dose contains 120 mg of trenbolone acetate and 24 mg estradiol.

Mechanism of Action

The goal of all of these products is to increase protein anabolism resulting in increased skeletal muscle production. The androgenic compounds accomplish this primarily by direct action of the muscle cells while the estrogenic compounds act primarily via secondary pathways. Estradiol increases growth hormone output by the pituitary which in turn induces somatomedin output by the liver resulting in increased protein production. Growth hormone also causes increased insulin production by the pancreas and an initial reduction in thyroxin output as well as a reduction in the catabolic effect of cortisol from the adrenal. Estradiol also does have a direct effect on the muscle cell. Zeranol acts similarly to estradiol except that it has little or no effect on the thyroid or adrenal cortex.

Androgens such as testosterone and trenbolone acetate act more directly on the muscle cells exerting their influence primarily in the nucleus by increasing the DNA controlled production of RNA resulting in increased ribosomal protein production.

The role of progesterone in some of these implants is not fully understood or agreed on at the present time. It is interesting to note that the increase in muscle production caused by these hormonal substances is not accompanied by an equal increase in fat production by the animal. Thus, a repartitioning effect is seen. This results in a more lean carcass. This in turn may affect the quality grade of the meat. For this reason some persons have speculated that feeding implanted cattle to heavier weights may help in maintaining a high percentage of choice grading carcasses. This effect appears to be especially true in the trenbolone/estrogen combination product. In studies concerning this issue it was found that animals would have to be fed to be up to 70+ kg heavier to attain the same percentage of choice grades at slaughter. This must be considered when planning an implant program.

Efficacy Expectations

Considerable study has been given to the specific actions expected from each of the active ingredients of the various products and how this information can be used to further enhance the benefit that might be realized. Many combinations of existing products have been tested with varying results. The entry of trenbolone into the implant scene has provided many such opportunities for combination and comparison trials. The goal of these efforts, of course, is to maximize the increase in ADG and improvement in F/G while at the same time maintaining a very high percentage of the animals grading choice at the slaughter plant. The ultimate product or combination of products to satisfy all of these goals under all management situations and in all classes and types of cattle has not yet been fully realized although considerable progress has been made. The already realized success and the opportunity for continued success certainly provides an exciting field for research and development for years to come.

In preparation for this presentation the literature search resulted in a vast number of articles for review along with a sizable volume of technical material provided by the companies producing and supporting these products. Since the purpose of this presentation is to provide some practical advice to the practicing veterinarian in the Minnesota and surrounding areas as to which products might be considered, when they might

be used and on what type of animals they are best used, the following interpretive observations of the data are presented rather than a presentation of a myriad of data charts and tables:

A. All products on the market have been shown to provide results sufficiently better than untreated controls to satisfy the FDA that they will do what the label claims they will do. This statement sounds trite but with the current atmosphere in the FDA it is no small matter in getting a product to the market. It is recognized that the efficacy of the recently introduced combination product has claims of higher ADG and F/G than products previously on the market. However, along with this higher level of efficacy comes the impact on the quality grade percentage at slaughter. In head to head comparisons using single implant results Revalor-S has shown consistently greater gains and feed efficiency improvement than Synovex-S and Ralgro. It appears that one would expect an advantage in ADG in the range of 1 to 10% and an advantage of 1 to 7% in improved F/G of Revalor over Synovex-S and Ralgro using a single implant regimen. However, it is noted that this comes at the expense of percentage grading choice wherein the reduction may range from 1 to 11% grading choice. One must use the current cost of feed along with the difference in prices paid by the packers to arrive at the final decision when using the single implant regimen. It is noted here that since the Implus-S is identical to Synovex-S the comparisons would be the same. Direct comparisons of single implanted Revalor-S vs Compudose were not easy to find at the time of this review.

B. With the exception of Compudose the products on the market do not give recommendations on the label concerning duration of effective action. This is due to the very difficult problem of determining just where an end point of effective pay-out of the hormone from the implant actually occurs. One cannot depend on blood or tissue levels for this determination since the levels are so low that they are in the marginally detectable range. Efficacy studies are subject to so many variables that end points based on efficacy in ADG or F/G are also very difficult. Thus, the FDA and the company development people have agreed that no duration of effective action will be on the label. This makes it very difficult for the consulting veterinarian or nutritionist to plan effective reimplanting regimens for their clients.

C. The issue of reimplantation is a complex one given the fact that the cattlemen are faced with the variable results from efficacy studies testing reimplantation and the increasing intensity of the regulatory climate and the FDA's interest in "off label use" in food producing animals. Since most products do not have reimplantation on the label the FDA would consider this as off label use. To date they have pretty well overlooked this issue realizing that many experts in the field feel reimplantation is necessary and profitable and therefore recommend it. With the many many studies involving reimplantation one would think that there would be sufficient data available to allow the FDA to give permission to the companies to make those recommendations on the label of their products. It would be expected that the companies would have to conduct residue studies following reimplantation as well as provide the necessary efficacy data to get the claims on the label. It will be interesting to see if the FDA continues to overlook reimplanting as an off label use.

Some key questions concerning reimplanting that need to be resolved are the following:

1. Does implanting pre-weaning and / or stocker or grower calves affect the efficacy of implantation of these animals when they go into the feedlot? There are sufficient study results in this regard to induce some to suggest that if you are to own and feed the cattle through to finish then don't implant them as suckling calves or as growing cattle. Where the calves are sold after weaning &/or growing then it is recommended to implant them as calves and stockers. If this is the recommendation to the cow/calf and stocker people what do you recommend for the feedlot operator? Some buyers for feedlots do try to obtain the implant history on animals they buy and some dock for previously implanted cattle. It is speculated that if the initial doses given during the pre-weaning or growing phase are lower than in the finish phase then the results might be satisfactory. Synovex C (and Implus C) are at half dose for the suckling animals vs the doses recommended for the finishing phase. If dosing related to body weight is important then this might solve the potential problem. If using different products during the different growth periods will prevent the problem in the finishing stage this too could be another possible solution.

2. Is reimplantation necessary in the feedlot? Many feeders automatically reimplant at ap-

proximately 70 days. Far more studies show positive results from reimplanting than those that do not. Compudose, with its long duration of action, is not regularly considered for reimplantation. Finaplix-S and Revalor-S have been shown to give quite consistent positive results used in reimplantation regimens. This is true whether the reimplantations are with the same product or with a different product. Synovex-S followed by Synovex-S does not always give the improved ADG and F/G expected. Ralgro has been used in many reimplantation schemes with generally good but variable results. The problem one encounters when trying to compare all the available results is the fact that so few of the studies are conducted under the same protocol and many variables confound the comparative picture.

With the ongoing interest in this area we will continue to see results of many studies looking at different reimplant regimens under many different conditions. It would seem practical for industry and feeder scientists to get together and design studies (using the existing knowledge) that would be acceptable by the FDA and conduct these studies under the sponsor/monitor guidelines for clinical investigations and thus obtain the right to put these recommendations on the label and in the technical information given out by industry to the cattlemen.

D. At the present time it appears that for increase in ADG and F/G combinations of trenbolone with estradiol in various reimplantation regimens has the upper hand. On the negative side is the fact that the percentage of animals grading choice is lower when trenbolone is used close to the slaughter date. When one considers the fact that trenbolone acetate-estradiol is a potent muscle growth promotant and estradiol does not reduce the grade quality, then one might logically think that the appropriate regimen would be to implant with the trenbolone acetate-estrogen product during the major growing phase of the animal and follow this with an estradiol product during the finishing phase. The problem with this approach is that the very significant ADG and F/G benefits of the trenbolone acetate-estrogen combination can be lost with time following last implantation (estimated at 110 days) while the beneficial effects of estradiol are maintained for longer periods. Therefore, reimplantation regimens tend to involve reimplantation with a trenbolone acetate containing product rather than with non-trenbolone acetate containing products (Synovex-S for example). Again, attention must be given to the duration of time of the trenbolone acetate implant in relation to the expected slaughter date if grade at slaughter is of concern.

This brings up the next issue: efficacy expectations must be related to the goals of the beef producer. If the producer is only interested in increasing ADG and F/G then a reimplantation program with trenbolone and estrogen is the route to go (with trenbolone being in both implants). If there is some concern about the % of animals grading choice than one must consider reducing the amount of trenbolone going into the animals during the feeding period.

E. Factors other than product used that can affect efficacy:

1. Implantation technique is very important. Implants that are abscessed, bunched, crushed, lost, fibrosed or implanted in the cartilage will result in reduced efficacy. Loss of implants may be due to improper placement in the ear or from abscessing at the implantation site. In surveys conducted the incidence of problem implants varied from 5% to as high as 60%. Abscess at the site of implant is by far the greatest problem encountered. Special effort must be made when cattle come for implanting with wet and dirty ears. If the ears are caked with manure or mud they should be scraped and the implantation site wiped with a suitable disinfectant. If ears are wet they should be wiped with dry paper towel and an appropriate disinfectant applied to the implantation site. This is often a difficult thing to get the implanting person to do. Most companies selling implants now have some type of quality control program they offer to the cattle producers. The quality control programs in which rewards are given for improving the technique and thereby reducing problem implants have proven quite successful and cost effective.

2. Nutrition can have a dramatic effect on the efficacy of the implant program. If nutrients are not present there is not way an anabolic implant can do the expected job. Nutrition often becomes a serious factor in reduced performance when cattle are on poor or dried up pastures. One reason it is so difficult to assess the efficacy of different products on pasture trials is the variation in nutritive value of the pastures the implanted animals are on during the trial. If animals are to be carried through win-

ter in a low plane of nutrition it is better to hold off implanting until spring and they are put on grass or go into a feedlot. Recent studies indicate that in feedlot cattle limited feeding of high energy diets results in higher efficacy levels for implants than keeping animals on the traditional silage based diet.

3. Age of the animal implanted is not as significant a factor in efficacy of the implant as the management environment of the animals at various ages. Calves on poor pasture for example are not going to show good implant results. Since implants affect the muscle growth it stands to reason that they will be more effective in the rapidly growing animals.

4. Breed and class of cattle may affect the efficacy results of different products. Heifers do not respond to trenbolone-acetate to the same degree as do steers. This is reflected in the higher dose recommended for Finaplix for heifers than for steers. It is known that trenbolone acetate-estrogen gives positive but lower results in Holstein steers than in beef breeds. Differences in response between beef breeds is more difficult to find. More work is needed to determine more fully the differences that might be expected between different classes of cattle using the different trenbolone acetate products alone and in combination, and in different reimplant regimens. Although not cleared for cull cows trenbolone acetate showed significant gains in both ADG and F/G. Whether other products give this benefit and whether estrogen combined with the trenbolone acetate would give enhanced results is not known.

F. Safety for breeding animals is a topic that must not be overlooked when planning implanting regimens for the suckling and growing groups of animals. None of the present products should be used in young bulls intended for breeding purposes. The question as to whether or not to implant heifers intended for breeding purposes has received attention both by industry and university scientists. Synovex-C (the same as Synovex-S but at half the dose) is cleared for heifers intended for breeding purposes provided the implants are put in after 45 days of age. Although sufficient data were generated to allow clearance of the product for heifers intended for replacement breeding animals there is still skepticism concerning the implanting of heifers intended for breeding purposes. Considerable variation in the design of trials and results leaves the picture cloudy. It appears that there is more danger for reduced fertility when heifers are implanted with the product at birth than at later stages.
Although some reports indicate implanting young heifers with either Synovex-C or Ralgro results in increased pelvic size at weaning much of this gain in size is lost by the time the animals calve. One study did show an advantage in reduction of dystocia as a result of implanting heifers at 2 and 6 months of age. It is apparent that we have more to learn on the subject before solid recommendations can be made.

G. Human food safety issues are often brought up with regard to implantation of cattle intended for food. Many in depth studies were conducted by several university groups in cooperation with the FDA in the late 1960's and early 1970's to address the issue of safety of the natural steroid compounds. The results were presented at the Symposium on Natural Hormones in Edible Animal Products which was held during the A.S.A.S. Annual Meeting at Texas A&M University in August of 1976. The conclusions drawn were that the levels of these hormones occurring naturally in man are many times the levels possible through food sources. Also, many plants and plant products eaten regularly contain much higher levels of these substances than would be in beef from implanted animals. For the synthetic products present in the non-natural products extensive studies have given them a clean bill of health as far as human safety is concerned. Restriction of these products in the EEC was taken in spite of their own scientific advisors presenting them with evidence for wide margins of safety for these products. In essence they are trade embargo type of restrictions. Ironically, restricting the use of these products for the legal market has resulted in a very active black market for the products in EEC Countries.

H. Thoughts on what is coming in the future: It is obvious that impressive progress has been made in understanding many of the variables that need to be addressed for successful implanting. As veterinarians, consultants, university researchers and cattlemen continue to apply this knowledge we will see continued advances in adjusting specific management practices to fit available product to realize more consistent and increased benefits. With the increasing knowledge of what is desired in terms of delivery times and amounts of specific hormones improvements in the delivery release systems will be developed. Efforts along those lines

has resulted in clearance of the product in Canada which is delivered as a one mL dose containing 20mg estradiol benzoate which is impregnated into biodegradable microspheres. The intent of the development is to present a product with more precise control of the release and one which circumvents some of the problems associated with implanting pellets into the ears. Application has been made to the FDA for clearance in the United States. Clearance is expected within the next year. Further efforts directed at more controlled release can be expected.

Summary

- Growth Promoting Implants have and will continue to be one of the most economically beneficial practices in the field of beef production.

- Of current products on the market the recently introduced combination of trenbolone acetate and estradiol (Revalor-S) appears to give the best results in ADG and F/G compared to other products when used as single implants.

- Most products are used in reimplantation regimens in which many combinations have been successfully tested, however, much variability has been seen with several of these regimens.

- Due to many variables affecting efficacy of the implants and the different modes of action of different implants the most beneficial use of the existing products requires an assessment of the goals of the beef producer and selection of regimens to best satisfy these goals.

- Implantation of heifers intended for breeding can be legally done with Synovex-C after 45 days of age. The advisability of this practice is in question due to potential impact of subsequent reproduction but appears to be safe. More work is needed.

- Implantation with growth promoting hormones will continue to be a key part of beef production and will continue to be improved through new methods and new products.

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