Growth-Promoting Implants for Cattle: Mode of Action and Available Options

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Growth-Promoting Implants, In Brief

• Natural hormones and/or analogs of natural hormones
• FDA-approved
• Placed subcutaneously in ear
• Trigger cascade of events to improve growth and efficiency
• More than 90% of feedlot cattle are implanted at least once during their lifetime (USDA NAHMS, 2013)

Growth-Promoting Implants, A Brief History

<table>
<thead>
<tr>
<th>Growth Promoting</th>
<th>Year of FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dyclonol (DCS)</td>
<td>1954</td>
</tr>
<tr>
<td>TES implant</td>
<td>1965</td>
</tr>
<tr>
<td>Estradiol benzoate / progesterone (sustained)</td>
<td>1956</td>
</tr>
<tr>
<td>Estradiol benzoate / testosterone propionate (sustained)</td>
<td>1959</td>
</tr>
<tr>
<td>Oral oxytetracycline (sustained)</td>
<td>1968</td>
</tr>
<tr>
<td>Zonalon (5 mg) implant (cattle)</td>
<td>1969</td>
</tr>
<tr>
<td>Oral OCS removed from market</td>
<td>1972</td>
</tr>
<tr>
<td>DRS implant removed from market</td>
<td>1973</td>
</tr>
<tr>
<td>Sustained cerelast implant (cattle)</td>
<td>1982</td>
</tr>
<tr>
<td>Estradiol benzoate / progesterone (sustained)</td>
<td>1984</td>
</tr>
<tr>
<td>Tetrabolin acetate (TBA) implants (cattle)</td>
<td>1987</td>
</tr>
<tr>
<td>Estradiol (15 µg) TBA implants (cows)</td>
<td>1991</td>
</tr>
<tr>
<td>Revlon somatometrin (including dairy cows)</td>
<td>1993</td>
</tr>
<tr>
<td>Estradiol (15 µg) TBA implants (cows)</td>
<td>1994</td>
</tr>
<tr>
<td>Zonalon (75 mg) implant (cattle)</td>
<td>1995</td>
</tr>
<tr>
<td>Estradiol (15 µg) TBA implants (weaner cattle)</td>
<td>1996</td>
</tr>
<tr>
<td>Racemic estrone hydrochloride (cattle)</td>
<td>2003</td>
</tr>
<tr>
<td>Estramustine hydrochloride (cattle)</td>
<td>2006</td>
</tr>
</tbody>
</table>

H. Johnson
**Growth-Promoting Implants, A brief history**

Recently, long-acting combination implants have become available (approximately 200 days activity)

Approved in 2007

Approved in 2014

**Skeletal Muscle Growth**

- **MUSCLE FIBER NUMBER IS FIXED AT BIRTH**
  - Implants do not play a role in Hyperplasia (increase in cell numbers).
  - Implants increase muscle sizes through Hypertrophy (increase in cell size) by increasing muscle protein accretion and slowing protein degradation.
  - Net effect is higher protein content and larger muscle fibers.

Image: www.musclebiology.wordpress.com
“Despite their widespread use relatively little is known about the biological mechanism by which androgenic and estrogenic steroids enhance rate and efficiency of muscle growth in cattle”

Dayton and White, 2013 American Chemical Society

Hormones Used in Implants

- Estrogenic: Zeranol, Estradiol (E2), Progesterone
- Androgenic: Testosterone Propionate, Trenbolone Acetate (TBA)

Indirect effect on skeletal muscle

Direct and indirect effects on skeletal muscle
**Growth-Promoting Implants, Mode-of-Action**

- **GHRH**
  - Hypothalamus
  - GH = Growth Hormone (Somatotropin)
- **GHRH**
  - Anterior pituitary
- **GH**
  - Liver
- **IGF-1**
  - Skeletal muscle
  - Satellite cell
- **IGF binding protein**

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**Hormones from Hypothalamus**

- **Somatotropin releasing hormone**
  - Stimulates the release of somatotropin (growth hormone) from the anterior pituitary

- **Somatostatin**
  - Inhibits the release of somatotropin from the anterior pituitary

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**Hypothalamic Influence of Steroids**

- **Estrogen increases the release of somatotropin releasing hormone**
  - Shirasu et al., 1990 and Painson et al., 1992

- **Estrogen causes a decrease in somatostatin mRNA in rats**
  - Argente et al., 1990

- **Estrogen decreases secretion of dopamine**
  - Shirasu et al., 1990 and Labrie et al., 1978
Acidophil Concentrations in the Anterior Pituitary

• Three types of acidophils present in the anterior pituitary (Frawley et al., 1985)
  — Somatotropes – growth hormone
  — Lactotropes – prolactin (protein hormone)
  — Mammosomatotropes - GH and PRL

• Gonadal status has an affect on the percentages of acidophils (Kineman et al., 1990)

• Exogenous steroids have an affect on the percentages of acidophils (Thomson et al., 1996)
Liver Hormone Receptors

- There are low and high affinity GH receptors in the liver
- E2 increases the number of low affinity GH receptors by 50%
- E2 increases the number of high affinity GH receptors by 350%

*Brier et al., 1988*
**IGF-I Production**

- After GH binds to its receptors, liver cells secrete IGF-I
- IGF-I is a second messenger for GH and results in a positive response in protein deposition in skeletal muscle
- Steroids increase IGF-I concentrations in cattle (*Johnson et al., 1996*)

**Circulating IGF-I**

![Circulating IGF-I diagram]

*Figure showing the circulating levels of IGF-I over time following implantation.* Kirkwood, 1998

**Diagram Key:**
- **Hypothalamus**
- **Anterior pituitary**
- **Liver**
- **IGF binding protein**
- **Skeletal muscle**

**Acronyms:**
- **GH** = Growth Hormone (Somatotropin)
- **GHRH** = Growth Hormone Releasing Hormone
- **IGF-I** = Insulin-like Growth Factor I
**IGF-I binding proteins**

- IGF-I binding proteins help to transport IGF-I to the target tissues and increase the half-life of the IGF-I that is bound.

- IGF-I binding protein 3 is increased in steers implanted with steroids relative to non-implanted steers (Johnson et al., 1996).

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**Localized Production of IGF-I**

- Muscle cells have the capability of producing IGF-I locally.

- Steers implanted with TBA:E2 had higher concentrations of IGF-I mRNA in the longissimus muscles than non-implanted steers (Johnson et al., 1998).
Direct/Indirect effects of steroids on skeletal muscle

• E2 and E2:TBA had no effect on protein synthesis or degradation in bovine myoblast cultures

• Sera from steers implanted with TBA:E2 increased protein synthesis in bovine myoblasts in vitro

Thomson et al., 1996

GH = Growth Hormone (Somatotropin)
GH = GH Releasing Hormone
IGF-I = Insulin-like Growth Factor I
IGF binding protein

Johnson et al., 1998
**Influence of Implants on Muscle**

- **MUSCLE FIBER NUMBER IS FIXED AT BIRTH**
  - Implants do not play a role in *Hyperplasia* (increase in cell numbers).
  - Implants increase muscle sizes through *Hypertrophy* (increase in cell size) by increasing muscle protein accretion and slowing protein degradation.
  - Net effect is higher protein content and larger muscle fibers.

**Protein Accretion**

*Image: www.musclebiology.wordpress.com*
Carcass Response to Implants

Mode of Action Summary

- Growth-Promoting Implants:
  - Increase Growth Hormone
  - Increase IGF-1
  - Increase Satellite Cell Proliferation
  - Decrease Fasting Heat Production
  - Decrease Catabolic Hormone Influence
  - Decrease Muscle Degradation
  - Increase Muscle Synthesis
  - Increase the Growth Curve at an Efficient Rate
Implants Approved for Several Phases of Production

Low-Dose Implants, Estrogenic Only

<table>
<thead>
<tr>
<th>Implant Name</th>
<th>Active Ingredient(s)</th>
<th>Days of Activity</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ralgro</td>
<td>36 mg Zeranol</td>
<td>70 (Feedlot)</td>
<td>Suckling calves, stocker steers and heifers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100-120 (Suckling Calves and Stockers)</td>
<td></td>
</tr>
<tr>
<td>Synovex-C</td>
<td>7 mg Estradiol</td>
<td>120</td>
<td>Suckling calves, Feedlot steers</td>
</tr>
<tr>
<td>Component E-C</td>
<td>7 mg Estradiol</td>
<td>120</td>
<td>Suckling calves</td>
</tr>
<tr>
<td>Compudose</td>
<td>26 mg Estradiol</td>
<td>175</td>
<td>Steers of all classes, Feedlot heifers</td>
</tr>
<tr>
<td>Encore</td>
<td>44 mg Estradiol</td>
<td>350</td>
<td>Steers of all classes</td>
</tr>
<tr>
<td>Synovex-S</td>
<td>14 mg Estradiol</td>
<td>130</td>
<td>Stocker and Feedlot steers</td>
</tr>
<tr>
<td>Component E-S</td>
<td>14 mg Estradiol</td>
<td>130</td>
<td>Stocker and Feedlot steers</td>
</tr>
</tbody>
</table>

Low-Dose Implants, Combination

<table>
<thead>
<tr>
<th>Implant Name</th>
<th>Active Ingredient(s)</th>
<th>Days of Activity</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revalor-G</td>
<td>40 mg TBA, 8 mg Estradiol</td>
<td>130</td>
<td>Stocker steers and heifers</td>
</tr>
<tr>
<td>Component TE-G</td>
<td>40 mg TBA, 8 mg Estradiol</td>
<td>130</td>
<td>Stocker steers and heifers</td>
</tr>
<tr>
<td>Synovex H</td>
<td>200 mg testosterone propionate, 14 mg estradiol</td>
<td>130</td>
<td>Stocker and feedlot heifers</td>
</tr>
<tr>
<td>Component E-H</td>
<td>200 mg testosterone propionate, 14 mg estradiol</td>
<td>130</td>
<td>Stocker and feedlot heifers</td>
</tr>
</tbody>
</table>
**Moderate-Dose Implants, Combination**

<table>
<thead>
<tr>
<th>Implant Name</th>
<th>Active Ingredient(s)</th>
<th>Days of Activity</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revalor-IH</td>
<td>80 mg TBA, 8 mg Estradiol</td>
<td>130</td>
<td>Feedlot Heifers</td>
</tr>
<tr>
<td>Component TE-IH</td>
<td>80 mg TBA, 8 mg Estradiol</td>
<td>130</td>
<td>Feedlot Heifers</td>
</tr>
<tr>
<td>Revalor-IS</td>
<td>80 mg TBA, 16 mg Estradiol</td>
<td>130</td>
<td>Feedlot Steers</td>
</tr>
<tr>
<td>Component TE-IS</td>
<td>80 mg TBA, 16 mg Estradiol</td>
<td>130</td>
<td>Feedlot Steers</td>
</tr>
<tr>
<td>Synovex Choice</td>
<td>100 mg TBA, 10 mg Estradiol</td>
<td>130</td>
<td>Feedlot Steers and Heifers</td>
</tr>
</tbody>
</table>

**Moderate-Dose Implants, TBA only**

<table>
<thead>
<tr>
<th>Implant Name</th>
<th>Active Ingredient(s)</th>
<th>Days of Activity</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finaplix-H</td>
<td>200 mg TBA</td>
<td>105</td>
<td>Feedlot Heifers</td>
</tr>
<tr>
<td>Component T-H</td>
<td>200 mg TBA</td>
<td>105</td>
<td>Feedlot Heifers</td>
</tr>
</tbody>
</table>

**Aggressive Implants, Combination**

<table>
<thead>
<tr>
<th>Implant Name</th>
<th>Active Ingredient(s)</th>
<th>Days of Activity</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revalor-S</td>
<td>120 mg TBA, 24 mg Estradiol</td>
<td>130</td>
<td>Feedlot Steers</td>
</tr>
<tr>
<td>Component TE-S</td>
<td>120 mg TBA, 24 mg Estradiol</td>
<td>130</td>
<td>Feedlot Steers</td>
</tr>
<tr>
<td>Revalor-H</td>
<td>140 mg TBA, 14 mg Estradiol</td>
<td>130</td>
<td>Feedlot Heifers</td>
</tr>
<tr>
<td>Component TE-H</td>
<td>140 mg TBA, 14 mg Estradiol</td>
<td>130</td>
<td>Feedlot Heifers</td>
</tr>
<tr>
<td>Revalor-200</td>
<td>200 mg TBA, 20 mg Estradiol</td>
<td>130</td>
<td>Feedlot Steers and Heifers</td>
</tr>
<tr>
<td>Synovex-Plus</td>
<td>200 mg TBA, 20 mg Estradiol</td>
<td>130</td>
<td>Feedlot Steers and Heifers</td>
</tr>
<tr>
<td>Component TE-200</td>
<td>200 mg TBA, 20 mg Estradiol</td>
<td>130</td>
<td>Feedlot Steers and Heifers</td>
</tr>
</tbody>
</table>
### Long-Acting Implants, Combination

<table>
<thead>
<tr>
<th>Implant Name</th>
<th>Active Ingredient(s)</th>
<th>Days of Activity</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovex One Grass</td>
<td>150 mg TBA, 15 mg Estradiol</td>
<td>200</td>
<td>Stocker steers and heifers</td>
</tr>
<tr>
<td>Synovex One Feedlot</td>
<td>200 mg TBA, 20 mg Estradiol</td>
<td>200</td>
<td>Feedlot steers and heifers</td>
</tr>
<tr>
<td>Revalor-XS</td>
<td>200 mg TBA, 40 mg Estradiol</td>
<td>200</td>
<td>Feedlot steers</td>
</tr>
</tbody>
</table>

### Payout of Implants

- **BV-53092-Finishing**
  - **Day 0-35**: 28% Improvement in ADG
  - **Day 35-70**: 23% Improvement
  - **Day 70-105**: 17% Improvement
  - **Day 105-130**: 10% Improvement

### Single Implant “Payout” Pattern

- **Revalor-S Payout**
  - **Day 0-35**: 28% Improvement in ADG
  - **Day 35-70**: 23% Improvement
  - **Day 70-105**: 17% Improvement
  - **Day 105-130**: 10% Improvement

*BV-53092-Finishing*
Revalor-S re-implant “Payout” Pattern

Why TBA + E₂ Combination?

<table>
<thead>
<tr>
<th>TBA Estradiol</th>
<th>None (0)</th>
<th>140</th>
<th>30</th>
<th>4</th>
<th>16</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADG (Rev-IS)</td>
<td>2.83</td>
<td>2.86</td>
<td>3.03</td>
<td>3.03</td>
<td>3.26</td>
<td>3.34</td>
</tr>
<tr>
<td>F/G</td>
<td>6.19</td>
<td>6.11</td>
<td>6.00</td>
<td>5.99</td>
<td>5.72</td>
<td>5.60</td>
</tr>
<tr>
<td>DP, %</td>
<td>62.0</td>
<td>61.8</td>
<td>61.8</td>
<td>62.0</td>
<td>62.0</td>
<td>62.4</td>
</tr>
<tr>
<td>HCW</td>
<td>696</td>
<td>693</td>
<td>710</td>
<td>713</td>
<td>732</td>
<td>745</td>
</tr>
<tr>
<td>% Choice</td>
<td>78</td>
<td>70</td>
<td>74</td>
<td>76</td>
<td>67</td>
<td>63</td>
</tr>
</tbody>
</table>

3 sites (CO, NE and TX), 1,296 hd, 140-160 days on feed

Revalor-IS FDA FOI Data

Responses to Implanting vs. Control

- Single Estrogen implant
  - ADG + 16.4%
  - Feed Efficiency + 6.2%
  - Carcass Weight + 3.15%
  - Marbling Score – 3.75%

- Single Combination Implant
  - ADG + 19.1%
  - Feed Efficiency + 10.4%
  - Carcass Weight + 4.75%
  - Marbling Score – 4.62%

- Combination implant followed by a re-implant with a combination implant:
  - ADG + 20.0%
  - Feed Efficiency + 13.5%
  - Carcass Weight + 7.5%
  - Marbling Score – 9.3%

Duckett and Pratt, 2014
Why Implant?

![Chart showing body weight comparison between Control, IS/S, and Rev-XS treatments.]

Revalor-XS FDA FOI Summary, 2007

+10% (125.5 lb)
+11% (85 lb)

Practical Effects on Cattle Growth

Relationship Between Body Weight and Carcass Composition

![Graph showing the relationship between hot carcass weight and marbling score, rib fat, and backfat depth.]

Bruns et al., 2005
**Relationship of Empty Body Fat to Quality Grade**

![Graph showing the relationship between empty body fat percentage and quality grade.](image)

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**Implants Shift the Growth Curve**

- Implanted cattle will be heavier than non-implanted cattle at equal days on feed.
- Implanted cattle will reach Choice quality grade at a heavier weight than non-implanted cattle.

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**Take-Home Points**

- Growth-promoting implants have been available for approximately 60 years.
  - Have consistently improved:
    - Average daily gain
    - Feed efficiency
    - Live and carcass weight
  - Estradiol and trenbolone acetate are primary compounds
  - Positive impacts due to:
    - Indirect effects on growth hormone and IGF-I production
    - Direct effects on skeletal muscle growth
**Take-Home Points**

- Implants available for nearly all phases of beef production
  - Vary from low-dose, estrogen-only to aggressive, TBA-estradiol combination implants

- Despite 60 years of use of growth-promoting implants, much is still unknown regarding mode-of-action.

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