

# Antimicrobial Resistance, Antibiotics and Implant Use in Cattle

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Farmington, NM  
May 10, 2023

# Antimicrobial Usage in Cow/ Calf Operations

- Why the discussion today? Because Judicious Use of Antimicrobials deemed important for human use is our responsibility to protect, due to AMR.
- A very complex problem with no one single cause or solution
- Should Agriculture be concerned? Absolutely YES!!!
- FDA has issued Guidelines for using Medically Important Antimicrobial Drugs (MIAD) including: GFI #152, #209, #213 and the Veterinary Feed Directive
- GFI#263- will become effective June 2023 requiring ALL antimicrobials given to livestock by ANY route come under veterinary oversight- no exceptions

# Antimicrobial Usage in Cow/ Calf Operations

A few definitions...

- Prescription drug- a drug or medication for use by, or on the order of, a licensed veterinarian. This requires veterinary oversight and a valid VCPR.
- OTC- over-the- counter- A drug or medication that does not require veterinary oversight and can be purchased and used by anyone. You must follow the label directions exactly or you are in violation of the law. OTC antimicrobials will be gone in the near future.

# Antimicrobial Usage in Cow/ Calf Operations

Antibiotic- a naturally occurring compound (drug) that fights infection caused by bacteria by either killing it (cidal drugs) or inhibiting it's growth (static drugs)- important when **endotoxin** may be present.

Antimicrobial- does the same but also includes synthetic compounds, and includes compounds that act on other microorganisms besides bacteria, such as anti-virals, anti-fungals and parasiticides.

All antibiotics are antimicrobials, but not all antimicrobials are antibiotics.

# Antimicrobial Usage in Cow/ Calf Operations

## The Veterinarian/Client/Patient Relationship

The American Veterinary Medical Assn. defines a valid Veterinarian/Client/Patient Relationship (VCPR) to exist when:



- **The veterinarian assumes responsibility for making medical judgments and the need for treatment, and the client agrees to follow instructions of the veterinarian.**
- **There is sufficient knowledge of the animals by the veterinarian to initiate at least a general or preliminary diagnosis (the veterinarian has seen and is personally acquainted with the keeping and care of the animals).**
- **The veterinarian is readily available for follow-up in case of adverse reactions or failure of therapy.**

# Antimicrobial Usage in Cow/ Calf Operations

- LDU- Labeled drug use- any purchased drug or medication must be used **EXACTLY** as stated on the label. Legally, no variation may be used from labeled directions, including any variation in species, indication, dosage, route, frequency, timing or withdrawal time unless a valid VCPR is established and the variation is prescribed by your veterinarian. This includes OTC or RX medications.

# Antimicrobial Usage in Cow/ Calf Operations

- ELDU- Extra Label Drug Use- to use a drug or medication in a way that varies from labeled directions in any form or manner. To legally use a drug extra label, it must be prescribed by a licensed veterinarian under a valid VCPR and carry additional labeling directing the use and a stated withdrawal time.

# Antimicrobial Usage in Cow/ Calf Operations

## INDICATIONS

### Beef and Non-lactating Dairy Cattle

**BRD** - DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*; and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*.

**IBK** - DRAXXIN Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*.

**Foot Rot** - DRAXXIN Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii*.

### Suckling Calves, Dairy Calves, and Veal Calves

**BRD** - DRAXXIN Injectable Solution is indicated for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis*



# Antimicrobial Usage in Cow/ Calf Operations

## DOSAGE AND ADMINISTRATION

### Cattle

Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1.1 mL/100 lb) body weight (BW). Do not inject more than 10 mL per injection site

**WARNINGS: FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE.  
KEEP OUT OF REACH OF CHILDREN. NOT FOR USE IN CHICKENS OR  
TURKEYS**

## RESIDUE WARNINGS

### Cattle

Cattle intended for human consumption must not be slaughtered within 18 days from the last treatment. This drug is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows

# Antimicrobial Usage in Cow/ Calf Operations

- FDA GFI # 209- FDA Recommended Principles:
  1. Use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health
    - Treatment is considered judicious
    - Control/prevention is judicious in certain instances
    - Feed efficiency and growth promotion is not- so those indications were removed from label
  2. Use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation

# Antimicrobial Usage in Cow/ Calf Operations

World Health Organization identified these as highest priority, **critically** important drugs

- Fluoroquinolones- All- Baytril, Advocin (formerly A180)
- Macrolides- Tylan 40, Micotil, Draxxin, Zactran, and Zuprevo
- 3<sup>rd</sup> Generation Cephalosporins- Naxcel, Excenel, Excede
- Trimethoprim/Sulfa- Sulfa- trim

# Antimicrobial Usage in Cow/ Calf Operations

World Health Organization identified these as **highly** important drugs

- Penicillins- Pen BP, Procaine Pen G, Pen VK
- Aminopenicillins- Amoxicillin, ampicillin
- Aminoglycosides- Gentocin (prohibited), Spectinomycin, Amikacin, Kanamycin, Tobramycin, Neomycin, Netilmicin
- Tetracyclines- Chlortet, oxytet
- 4<sup>th</sup> Generation Cephalosporins (Cefepime)

# Antimicrobial Usage in Cow/ Calf Operations

World Health Organization identified these as **important** drugs

- 1<sup>st</sup> and 2<sup>nd</sup> Generation Cephalosporins
- 4<sup>th</sup> Generation Cephalosporins (Cephameycins)

# Antimicrobial Usage in Cow/ Calf Operations

- Culture and sensitivity results from samples submitted to a Diagnostic Laboratory may not fully reflect the actual picture of the infection in the animal.
  - Results are based on the organisms isolated
  - Sensitivity is based on the same
  - In actuality, mixed infections are the norm, and some organisms are very difficult to isolate
  - “in vitro” results are frequently not the same as “in vivo” results

# Antimicrobial Usage in Cow/ Calf Operations

- Critically Important:
- Antimicrobial Class- Fluoroquinolones
- Examples: Baytril, Advocin (A-180)
- Labeled use- BRD caused by MH, PM, HS, MB
- **ELDU Prohibited**

# Antimicrobial Usage in Cow/ Calf Operations

- Critically Important
- Antimicrobial Class- Macrolides
- Examples- Tylan, Draxxin, Micotil, Zactran, Zuprevo
- Labeled Use- BRD- MH, PM, HS, MB; some IBK and Foot Rot
- EDLU with VCPR



# Antimicrobial Usage in Cow/ Calf Operations

- Critically Important
- Antimicrobial Class- Cephalosporins (3<sup>rd</sup> , +)
- Examples- Naxcel, Excede, Excenel
- Labeled uses- BRD- MH, PM, HS; Foot rot due to *Fusobacterium necrophorum*
- Excede- Base of ear
- **ELDU Prohibited**

# Antimicrobial Usage in Cow/ Calf Operations

- Critically Important
- Antimicrobial Class- Potentiated Sulfas
- Example- Sulfa-Trim, (Tribrissen)
- Labeled use- Horses and Dogs
- ELDU with VCPR

# Antimicrobial Usage in Cow/ Calf Operations

- Highly Important
- Antimicrobial Class- Penicillins
- Examples- Pen G, Pen BP, Pen V
- Labeled Use- PPG- Bact Pneu- Past Mult;  
Erysipelas in swine, strangles in horses  
Pen BP- Pneu- Strep, staph, Act. Pyo,  
Blackleg
- ELDU with VCPR

# Antimicrobial Usage in Cow/ Calf Operations

- Highly Important
- Antimicrobial Class- Aminopenicillins
- Examples- Amoxicillin (NL), Ampicillin (Polyflex)
- Labeled Uses- BRD- Past Mult, Klebsiella, Staph, Strep, E. coli
- ELDU with VCPR

# Antimicrobial Usage in Cow/ Calf Operations

- Highly Important
- Antimicrobial Class- Aminoglycosides
- Examples- Gentamycin (prohibited), streptomycin, kanamycin, Spectinomycin
- Labeled uses- Pneu in turkeys
- ELDU with VCPR

# Antimicrobial Usage in Cow/ Calf Operations

- Highly Important
- Antimicrobial Class- Tetracyclines
- Examples- LA-200, Bio-mycin 200, Chlortet-(VFD)
- Labeled uses- BRD- bact pneu- Past Mult, Pinkeye
- ELDU with VCPR

# Antimicrobial Usage in Cow/ Calf Operations

- VFD

**What is the “duration of use” and how does it relate to the “expiration date”?**

**The VFD expiration date defines the period of time for which the authorization to feed an animal feed containing a VFD drug is lawful. This period of time may be specified in the approved labeling of a given VFD drug or, if not specified in the labeling, the veterinarian must specify an expiration date for the VFD that does not exceed 6 months (21 CFR 558.6(b)(3)(v)). The duration of use is a separate concept from the expiration date, and determines the length of time, established as part of the approval, conditional approval, or index listing process, that the animal feed containing the VFD drug is allowed to be fed to the animals. This period of time is specified in the labeling of the VFD drug. For example, the currently approved VFD drug tilmicosin has an expiration date of 45 days and a duration of use of 21 days. This means that when the VFD is issued, the client has 45 days to obtain the VFD feed and complete the 21 day course of therapy. It is unlawful to feed the VFD feed to animals after the VFD expiration date (21 CFR 558.6(a)(2)).**

# Antimicrobial Usage in Cow/ Calf Operations

- VFD

**This would include virtually all feed drugs except dewormers, carbadox, bambarmycins, ionophores, bacitracin and a few others**

**Summary- If Ag does not show judicious and accountable use of antimicrobials now, then antimicrobials labeled for prevention and control may be targeted.**



# Antimicrobial Usage in Cow/ Calf Operations

- As cow/ calf producers, it is our responsibility to use all the preventative and herd health care options available- ie nutrition, mineral and vitamin balance
- Fine- tune your vaccination program and include MLV's
- Developing the immune system in the calves is the key to preventing BRD
- Colostral immunity is the first step in developing immuno-competent calves- take care of the cows!

# Antimicrobial Usage in Cow/ Calf Operations

- Judicious AM usage:
- Communicate with your veterinarian!!!
- Give them all the information and clinical signs possible
- Try to determine what “system” is involved- resp vs digestive...
- Which AM to use should be based on what is the best choice for the suspected agent
- Economics of the AM choice should be secondary to what is best

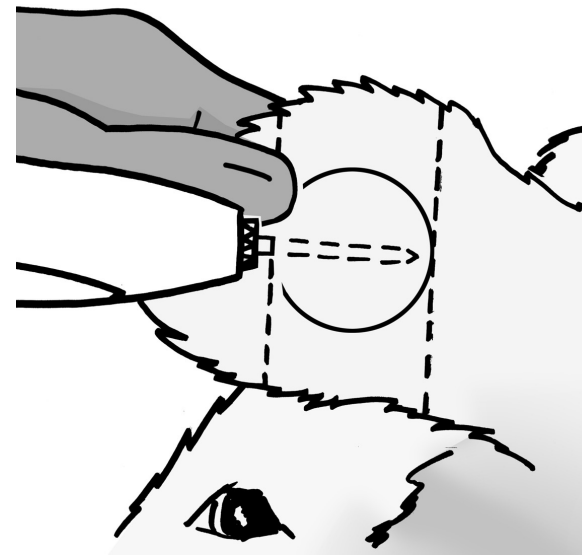
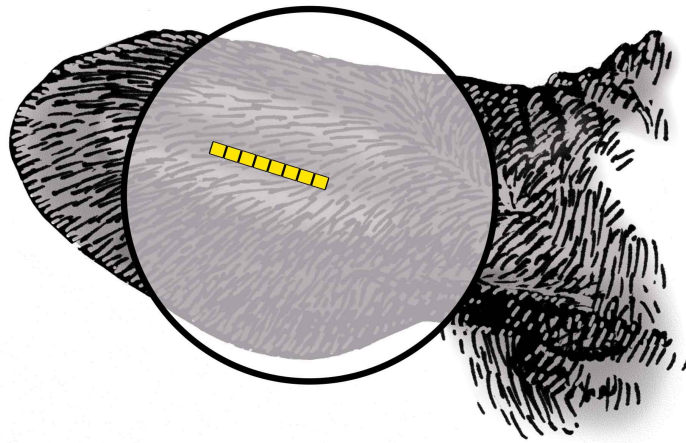
# Antimicrobial Usage in Cow/ Calf Operations

## Summary

- Resistance should be taken seriously by all involved in Industry
  - Ag groups have adopted judicious use guidelines
- Resistance is as old as bacteria
  - Most antibiotics derived from soil bacteria
- Antimicrobial use selects for resistance
  - Resistance is a growing problem
  - Preventative Health care needed to prevent antimicrobial usage
- *Selection and resistance is highly complex!*

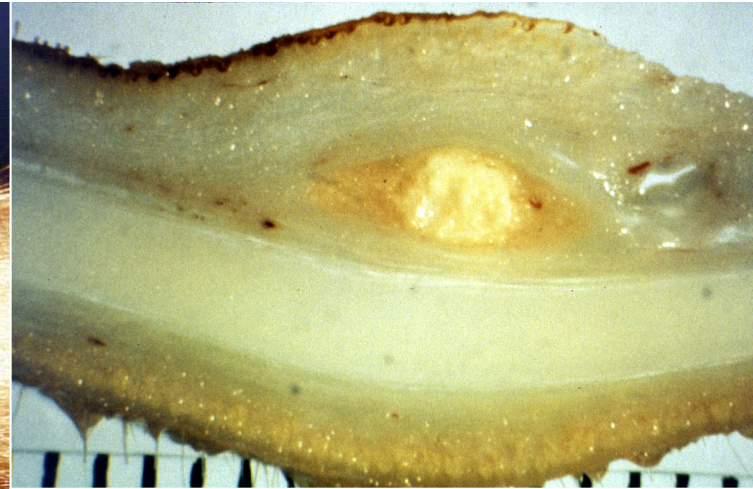
# What are Implants?

Delivered Sub-Q in Middle 1/3 of Year



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## What are Implants?

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# Why Implant Cattle?

Courtesy Dr. Gary Sides

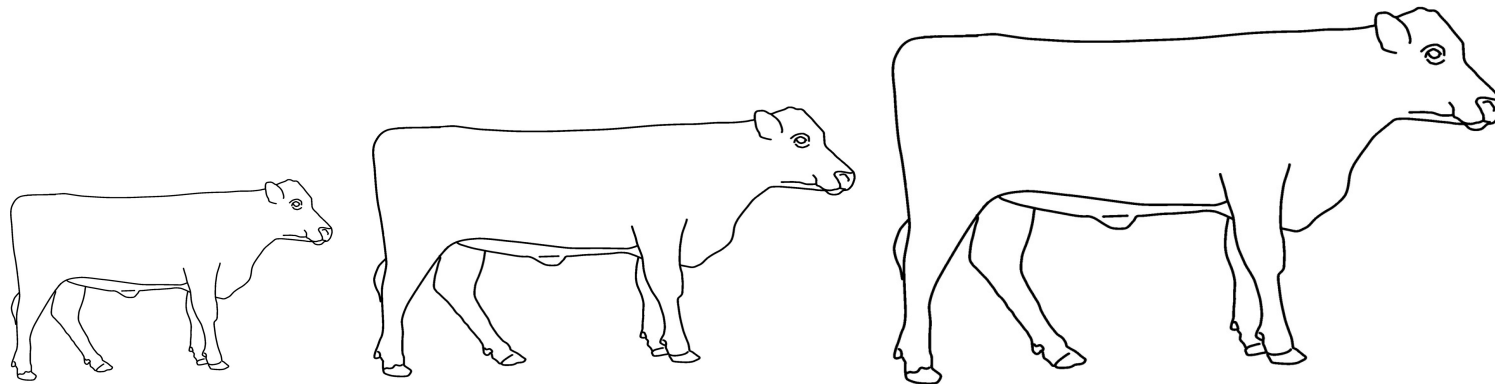
## Implants are ...

Products that help cattle  
grow faster

**Average Daily Gain  
(ADG)**

Products that help  
cattle consume less  
feed per pound of  
live animal gain

**Feed Efficiency (FE)**



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# Why is increased growth rate and feed efficiency important?

- Reduces cost of production
  - Feed costs are largest expense
  - Feed/Forage utilization per pound of gain (efficiency response)
  - Animals reach targeted end point weight faster (gain response)
  - Environmentally “friendly” (“**GREEN**”)
- Reduces production costs → improves profitability
- Dollar value to industry? > \$2.5 billion

# Protein Synthesis

## Hormones *(to excite) ...*

**A specific chemical product of an organ or certain cells of an organ transported by blood or other body fluids and having a specific regulatory effect upon cells remote from its origin.**



# Protein Synthesis

## Protein Anabolism

**Refers to synthesis of proteins - fundamental components of muscle tissue.**

**Utilizes carbon, hydrogen, oxygen and nitrogen - regulated by hormones, particularly steroid hormones**

# Implantable Steroids Used in Beef Cattle

**Estrogens**  
(Female)

**Natural - Estradiol**  
**Synthetic - Zeranol**

**Estrogen equivalency of  
zeranol:**  
**36mg zeranol = 11-12mg of  
estradiol 17B**

**Androgens**  
(Male)

**Natural - Testosterone**  
**Synthetic - Trenbolone Acetate**

**TBA 8-10 times more active  
anabolically  
than testosterone**



# Overall Animal Effect of Estrogens

- ↑ Increased feed intake
- ↑ Increased muscle protein deposition
  - ↑ Increased net protein synthesis
    - Push (increased nutrient supply to tissues) **and**
    - Pull (increased substrate demand in muscle cells)

# Overall Animal Effect of Androgens

- Altered protein metabolism  
Protein deposition increase
  - **Increase in protein synthesis (anabolism)**
  - **Decrease in protein degradation (catabolism)**
- Rates of energy expenditure are reduced in TBA treated cattle resulting in lower maintenance requirements.

# Effects of steroid hormones on cattle growth

- ↑ ADG
- ↑ Gain Efficiency
- ↑ Utilization of absorbed nitrogen by decreased urinary nitrogen loss
- ↑ Increased mature body size
- ↑ Cattle “younger longer”
- ↑ “Green” technology

# Effects of Steroid Implants on Cattle Growth

- ↑ % of muscle and with no effect on % of fat in carcass
- ↑ Hot carcass weight
- ↑ Longissimus muscle area (effect on QG?)
- ↑ Quantity of edible product in carcass
- ↓ Marbling score? No effect if fed to correct endpoint

# Effects of Steroid Implants on Cattle Growth

- Estimates that implanted cattle should weigh 25-45kg (55-99 lbs) more than non-implanted cattle to have the equivalent finished condition (NRC, 1996)
- Depends on “aggressiveness” of implant strategy

# Implanted Beef Safety

Estrogenic Levels of Several Common Foods



**35,000ng low dose birth control pill**

**2,700ng 4 ounces of cabbage**

**993ng 1 egg**

**908ng bowl of split pea soup**

**567ng 1 ounce of wheat germ**

**34ng 8 ounces of milk**

**1.9ng 3 ounces of beef (implanted steer)**

**1.2ng 3 ounces of beef (non-implanted steer)**

**Nanogram (ng) is one billionth of a gram**

Collins et al., 1989, Booth et al., 1960; Verdeal and Ryan, 1979

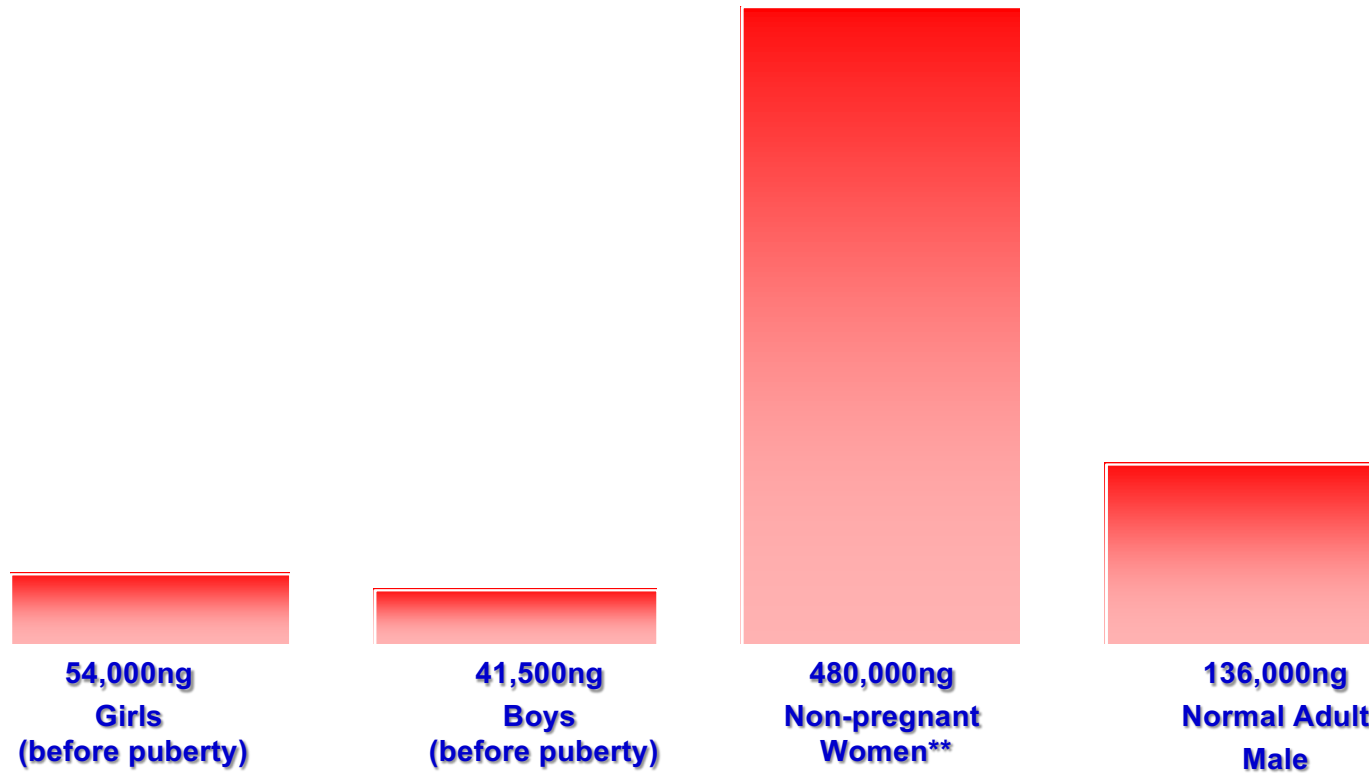
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# Implanted Beef Safety

## Daily Human Estrogen Production (Nanograms)



**Pregnancy: 90 million ng/d**

Hoffman & Evers, 1986

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# Implant Safety – no withdrawal

## Meat Withdrawals of Common Animal Health Products

Implants	Injectable Endo's	Pour-On Endo's	BRD Vaccines	AIF's
All Products	CYDECTIN Ivomec DMX	Cydectin Ivomec DMX	Pyramid Vista Bovishield	Advocin Micotil Draxxin
0 d	21-35 d	0-48 d	21 d	4-28d

# Implant Safety

- **ALL Implants have ZERO meat withdrawal times.**
- **Placed in inedible tissue (the ear) that is removed at harvest.**
- **Have been approved by the FDA since the 1950's as:**
  - **Safe for humans**
  - **Safe for cattle**
  - **“Green” Performance Enhancement**

# Changes coming for

- FDA, April, 2021: Not “legal” to reimplant within a “production phase” unless there is an approved label.
- No E/TBA implant currently has reimplant label
- **FDA: June 30, 2023 – enforcement begins**
- **Synovex Choice- labeled approval for reimplant- only one so far**

## FDA guidance document 191 – there are only three recognized production phases:

- **Suckling calves**
- **Stockers on pasture**
- **Cattle in confinement for slaughter**, which includes:
  - Backgrounding
  - Growing
  - Finishing

## History leading up to April 2021 ruling

- Revalor-XS approved 2008 – no reimplant restriction (“contraindication” is the term on a label that would denote “no reimplanting” allowed)
- Synovex Choice heifers, Synovex One Feedlot, Synovex One Grower approved in 2014 – no reimplant restriction from FDA
- **Revalor XH and XR approved 2017: Label - Reimplant contraindication (reimplanting not allowed)**
- **Synovex One Grower, 2018: Label - Reimplant contraindication (reimplanting not allowed)**

# Solutions

- Design, implement and provide data to the FDA on animal performance, human/food safety and environmental studies to get reimplant labels
- **Do nothing to jeopardize the use of this OTC steroid hormone technology - follow the labels as FDA reimplanting approvals are granted.**

# **Antimicrobial Usage in Cow/ Calf Operations**

## **QUESTIONS ???**

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