Regulatory Challenges in Food Animal Drug Approval

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An Underlying Theme Unique to Food Animal Drugs

- **“Consumers” are demanding more labeling on products**
  - **GMO vs. non-GMO**
  - **Organic or “natural never-ever”**
  - **Antibiotic free**
  - **Housing**
  - **Gluten free**
  - **Responsible antibiotic use**
- **The challenge is how they interpret the labeling**
- **Another challenge is how these labels are used to compete for market share**

Genetically Modified Organisms

- **Draft GFI #187 lays a basic framework**
- **Tensions**
  - **Public opinion, much of it uninformed, which can skew the structure of the approval process**
  - **Addressing “what ifs” in a relatively new science**

Pain Control

- **We have our first approval for pain in food animals**
  - **Topical flunixin meglumine for pain associated with infectious pododermatitis in food animals**
- **There is a need for approved pain control for…**
  - **Castration**
  - **Dehorning**
  - **Surgical procedures**
- **The challenge in food animals has been the model**

Unregulated Competition

- **Why would I enter into a market with poor enforcement of unapproved competitors?**
  - **Compounding vs. manufacturing**
  - **Nutritional additives with under the table promotion of disease claims**
  - **Non-VFD feed additive products with implied (or sometimes stated) performance or disease claims**

Duration of….

- **Patent protection for original compound/ formulation**
- **Exclusivity periods for additional novel claims**

Antimicrobials

In the Age of Stewardship

What is “Stewardship”?

1. Responsibility for appropriate diagnostics and establishment of an accurate and functional case definition

Enter…

2. Is there a non-antibiotic alternative which will appropriately prevent, control, or treat this disease challenge?

If not…

3. Selection of an antibiotic which has been demonstrated to be safe and effective for this purpose

While…

4. Assuring use of the antibiotic as shown to be safe and effective

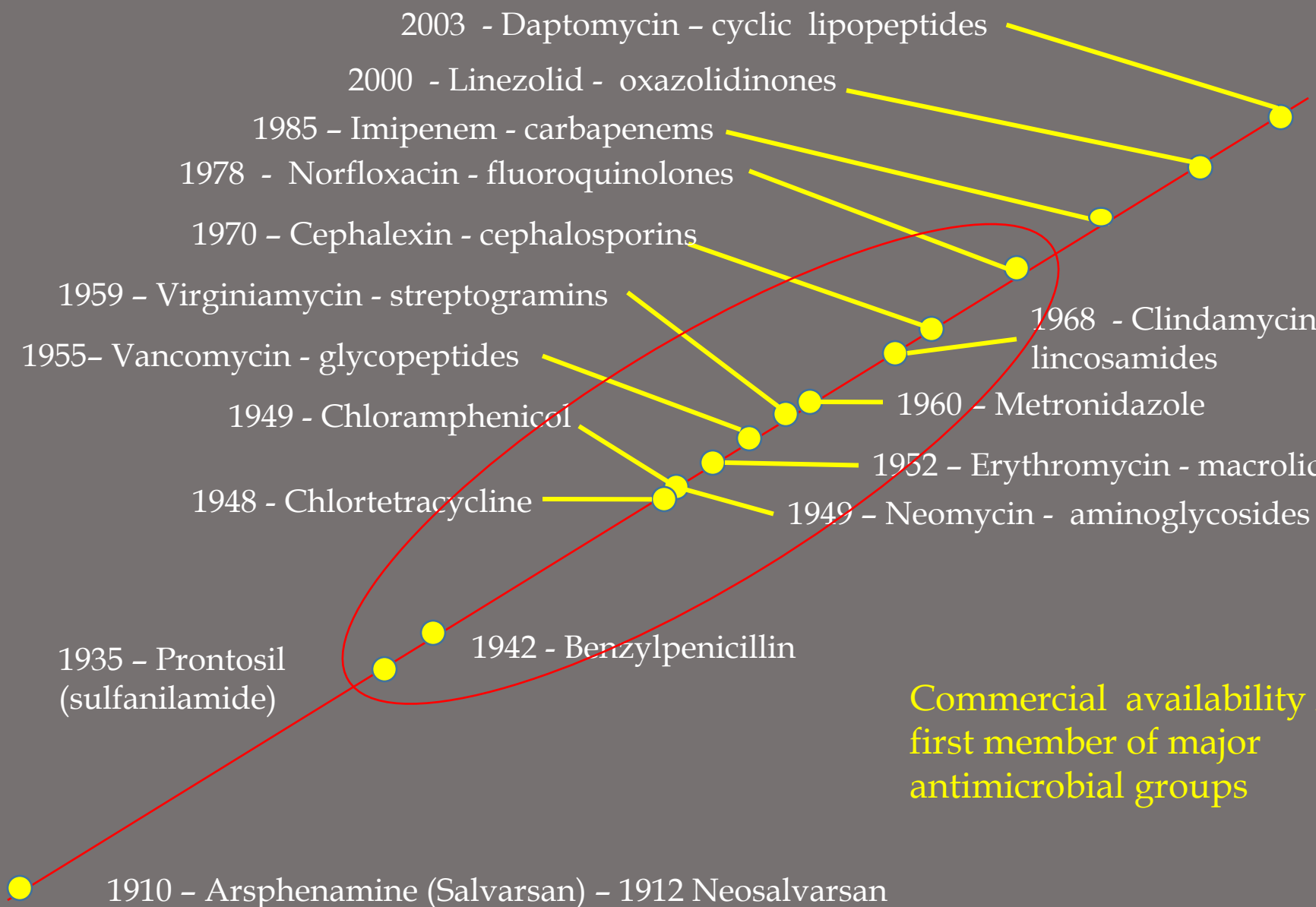
While asking…

5. Is this antibiotic intervention still necessary?

Yes…

No: Stop

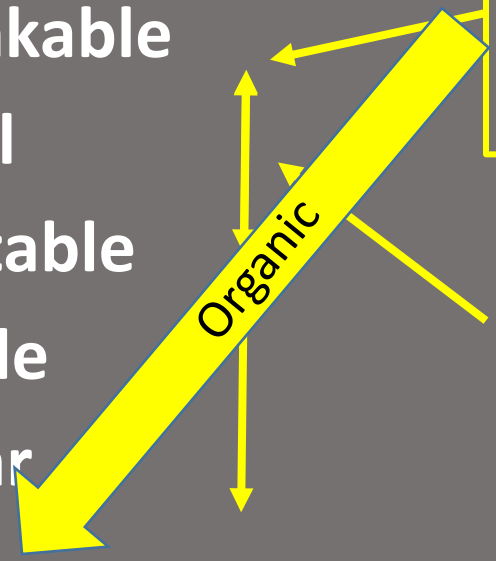
Antimicrobial Timeline



Commercial availability for first member of major antimicrobial groups

The Overton Window

- **Unthinkable**
- **Radical**
- **Acceptable**
- **Sensible**
- **Popular**
- **Policy**



Prohibition of <u>therapeutic uses</u> of medically important antimicrobials

Prohibition of <u>prevention and control uses</u> of medically important antimicrobials

Prohibition of <u>growth promotion</u> uses of medically important antimicrobials

Antimicrobial Use Monitoring

A tool for stewardship, or for mandated reductions without consideration for animal welfare?

Capturing Use Data

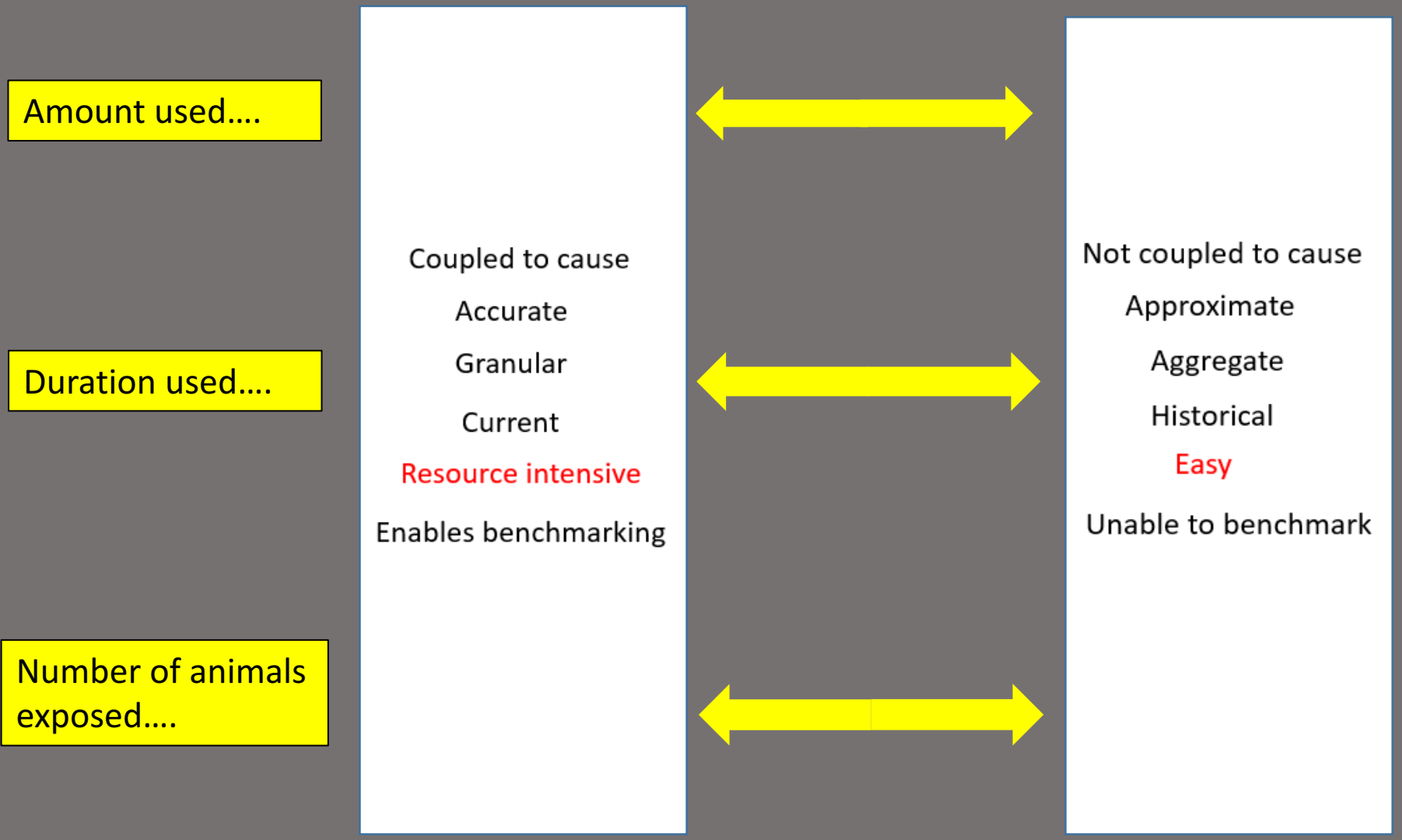
First Choice	Second Choice
Coupled to cause	Not coupled to cause
Accurate	Approximate
Granular	Aggregate
Current	Historical
Easy	Resource intensive
Enables benchmarking	Unable to benchmark

Capturing Use Data

Reality…

Coupled to cause	Not coupled to cause
Accurate	Approximate
Granular	Aggregate
Current	Historical
Easy	Resource intensive
Enables benchmarking	Unable to benchmark

What would you like to know?



FDA Center for Veterinary Medicine

FDA's Proposed Method for Adjusting Data on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, Using a Biomass Denominator

Objective

FDA is proposing a method for using a biomass denominator to adjust annual data on the amount of approved or conditionally approved antimicrobial new animal drugs sold or distributed for use in food-producing animals in the United States. A biomass denominator is defined as the population of a given livestock species in the U.S. multiplied by the average weight of that species.

The proposed method will provide estimates of annual antimicrobial drug sales adjusted for the size of the animal population (the animal biomass) potentially being treated with those drugs. The adjusted estimates will provide insight into broad shifts in the amount of antimicrobials sold for use in food-producing animals and give the agency a more nuanced view of why sales increase or decrease over time in a manner that is specific to U.S. animal production.

The agency is seeking comments from the public on the proposed methodology.

Figure 1: Example of how FDA will apply the mg/TAB formula at the antimicrobial drug class level

$$\text{mg/TAB value for Cattle} = \frac{\text{All sales of an antimicrobial drug class for use in cattle (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{cattle}}\ (\text{kg})}$$

$$\text{mg/TAB value for Swine} = \frac{\text{All sales of an antimicrobial drug class for use in swine (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{swine}}\ (\text{kg})}$$

$$\text{mg/TAB value for Chickens} = \frac{\text{All sales of an antimicrobial drug class for use in chickens (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{chickens}}\ (\text{kg})}$$

$$\text{mg/TAB value for Turkeys} = \frac{\text{All sales of an antimicrobial drug class for use in turkeys (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{turkeys}}\ (\text{kg})}$$

Drivers of Change in Food Animal Antimicrobial Use

California SB27 - 2015

PARA – S621

DART – HR2459

Legislation

Maryland SB0422 - 2017

PAMTA – HR1552

ADUFA

Oregon SB785 - 2018?

Cephalosporins

GFI 213

VFD

Regulation

AMDUCA

GFI 209

Fluoroquinolones

McDonald's

Chipotle

Tyson

Retailation

Panera

Walmart

Chic –Fil - A

Antimicrobial challenges

- **The latest efficacy requirements vs. efficacy claims which are 40 – 50 years old.**
- **GFI 152 and 159**
  - **Balancing the need for microbial safety with the need to expand label applications for existing antimicrobials**
  - **This can also serve as a barrier to continued refinement of older antimicrobial regimens**
- **Science of resistance development**
- **Risk assessment**

Antimicrobial challenges

- **Separating activist pressure from legitimate scientific concerns**
- **Utilization of NARMS data to evaluate resistance challenges**

Susceptibility testing

- **How can you develop a set of breakpoints when an antimicrobial is used in combination with other drugs in a fixed combination?**
  - **How do you get a success/failure outcome based only on the antimicrobial component?**
- **Movement from phenotypic to genotypic testing**
  - **Is there a consistent relationship?**

What the Precautionary Principle Does

- **Anything which may have a possible negative impact on human therapeutics is removed from the food animal market, or denied entry, in the name of caution**
- **This started with antibiotics**
- **It can apply to anything**

WHO GUIDELINES ON USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

World Health Organization

Recommendation I: Overall antimicrobial use

We recommend an overall reduction in use of all classes of medically important antimicrobials in food-producing animals.

Strong recommendation, low quality evidence

Recommendation 2: Growth promotion use

We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion.

Strong recommendation, low quality evidence

Recommendation 3: Prevention use (in the absence of disease)

We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed.

Strong recommendation, low quality evidence

Recommendation(s) 4: Control and treatment use (in the presence of disease)

Recommendation 4a

We suggest that antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals.

Conditional recommendation, very low quality evidence

Recommendation 4b

We suggest that antimicrobials classified as highest priority critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease.

Conditional recommendation, very low quality evidence

Best practice statement I

Any new class of antimicrobials or new antimicrobial combination developed for use in humans will be considered critically important for human medicine unless categorized otherwise by WHO.

Best practice statement 2

Medically important antimicrobials that are not currently used in food production should not be used in the future in food production including in food-producing animals or plants*.

Food Animal Challenges in One Slide

- A complex environment formed from legislative, regulatory, and market-driven influences
- A struggle of the science of new technologies vs. social media
  - Genetic technologies
- The need for continued development of model and evaluation techniques for pain control
- Unregulated competition
- Patent and exclusivity period duration
- The future of regulatory approaches to anti-infectives