

Feed Additives and “Subtherapeutics” in Cattle

Mike Apley, DVM, PhD

Diplomate, American College of Veterinary Clinical Pharmacology
Kansas State University College of Veterinary Medicine

First, what is a “subtherapeutic”?

The Food and Drug Administration Center for Veterinary Medicine (FDA/CVM) has a variety of approval classifications for antimicrobials in food animals. These include...

1. Improvement in rate of gain
2. Improvement in feed efficiency
3. Control of disease
4. Prevention of disease
5. Treatment of disease

The first 2 would fall into the “subtherapeutic” category by all of the definitions I am aware of. This is regardless of whether these applications have an effect on disease or not. Control and prevention of disease are considered therapeutic uses by the FDA/CVM and the American Veterinary Medical Association. However, anti-food animal activist groups attempt to cast control and prevention uses into the “subtherapeutic” categories in an attempt to sway public opinion that these are irresponsible uses.

Actually, I don't know as I have ever heard the FDA/CVM use the term “subtherapeutic”, probably because it is a term designed more to incite public indignation than describe an activity of a drug. It is also typically used to imply that somehow these uses cause more of a problem with selection for resistant bacteria than uses for control, prevention, or treatment.

Antimicrobials don't cause mutations for resistance in bacteria. Antimicrobials select for bacteria in populations which have developed mutations, or have acquired genes for characteristics which allow them to resist the activity of antimicrobials at concentrations above that at which the general population of bacteria would be either growth-inhibited or killed.

Sometimes these resistant bacteria can be present in animals as a subpopulation which we would not normally be able to detect in the lab, even with special media designed to promote the growth of these resistant organisms. However, exposure to antimicrobials may allow these organisms to proliferate at a higher rate than the susceptible organisms, resulting in a population which may now be detected.

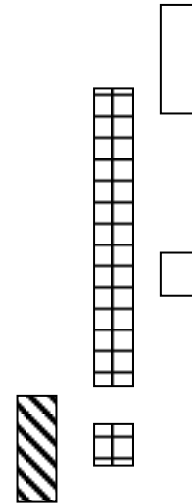
Selection for these resistant organisms is most likely dependant on the magnitude and duration of the exposure; in other words, the effect is dependent on the dose of the antimicrobial and how long it is applied. To get an idea of the variety of dose exposures possible through the




feed, the tetracyclines are a good example in cattle. Here is the range of in-feed approvals for tetracyclines in cattle, with the highest dosing regimens at the top. These are spaced to illustrate the range of doses. (CTC = chlortetracycline, OTC = oxytetracycline, TC = tetracycline)

CTC: 10 mg/lb BW for up to 5 days
 CTC: 400 g/ton to provide 10 mg/lb per day in calves up to 250 lbs
 TC: 22 mg/kg for 3-5 days in calves

OTC: 0.5 to 2.0 g/hd per day

CTC: 350 mg/hd per day in beef cattle under 700 lbs
 CTC: 0.5 mg/lb per day in beef cattle over 700 lbs
 CTC: 350 mg/hd per day in beef cattle
 CTC: 25-70 mg/hd per day in calves 250-400 lbs
 CTC: 70 mg/hd per day in growing cattle over 400 lbs
 CTC: 0.1 mg/hd per day in calves up to 250 lbs



-  Rate of gain/Feed efficiency
-  Prevention or control claims
-  Treatment claims

From this illustration, it is apparent that focusing on the rate of gain/feed efficiency claims as the “subtherapeutic” bogeymen implies that somehow there is a line where selection for resistant organisms increases or decreases based on label claims. Obviously, there is no science-based information to drive this assumption, but rather, in my opinion, it is based on selecting the most politically acceptable route for an initial removal of food animal antimicrobial uses. The challenge in allowing the rate of gain/feed efficiency antimicrobials to be removed based on the “precautionary principle” is that we then end up with this precedent in evaluating the prevention/control claims.

In reality, the probability is very low that we will somehow stumble across a scientific method to decide which feed antimicrobial uses stay and which should go based on the potential to select for resistant organisms. Value judgments and perceptions of risk are seamlessly woven into the context of the issue.

In my opinion, it is well established that the use of antimicrobials in the feed to food animals can alter the antimicrobial susceptibility profile of organisms such as *E. coli* in the gut. This is a tremendously complicated issue, the study of which has been the basis for countless PhD programs. For today, we should recognize that the actual evaluation of the effects of these changes are poorly defined and that these changes may be transient in nature. In order for

these changes in the animal to have an effect on human health, a multi-tiered cascade of events much happen.

1. Bacterial populations in the animal exposed to antimicrobial(s) on the farm
2. Selection for resistant organisms in the food animal
3. Increased incidence of resistant organisms in the animal/farm
4. Transfer through the food chain or direct transfer to a human
5. Presence of food animal derived resistant bacteria in a human
6. Contribution of food animal derived resistant bacteria to human disease
7. Treatment failure or prolonged disease course due to pathogen resistance

Events 1-3 would be termed “release” of resistant bacteria from the farm. Event 4 is the “exposure” of a human to the resistant organism. Events 5-7 are the “consequence” of the release and exposure.

In risk assessment terms, the release of the organism from the farm would be the hazard, and the chance that this hazard would result in human harm is the risk. In a nutshell, this is the issue. What is the risk that the 7 events will occur as described above from the use of each antimicrobial in food animals? However we conduct risk assessments or otherwise evaluate the risk, we can be assured that the outcome will not be zero. Here is where value judgments come into play, including individual assessments of acceptable risk and how this risk is portrayed in the media.

What antimicrobials are used in the feed or water of cattle? These are approvals. They don't indicate extent of use. A superscript of ¹ indicates classification as highly important for human medicine by the FDA. A superscript of ² indicates classification as critically important (the highest category) for human medicine by the FDA. The drugs with the superscripts are the ones most likely to be addressed through regulatory or legislative action. No group is proposing that the ionophores (monensin, lasalocid, laidlomycin) have any impact on human health. The ionophores make up approximately one third of the antimicrobials used in food animals.

For increased rate of gain and/or increased feed efficiency

- Bacitracin Zinc
- Bambermycins
- Chlortetracycline¹
- Laidlomycin
- Lasalocid
- Neomycin/oxytetracycline¹
- Oxytetracycline¹
- Sulfamethazine/Chlortetracycline¹
- Virginiamycin²

Rate of gain or feed efficiency AND a prevention/control claim

- Monensin
- Chlortetracycline¹
- Monensin
- Neomycin/oxytetracycline¹
- Oxytetracycline¹

Prevention or control of disease only

- Amprolium
- Bacitracin methylene disalicylate
- Chlortetracycline¹
- Decoquinate
- Lasalocid
- Monensin
- Tylosin²
- Virginiamycin²

Treatment of disease AND prevention or control

- Neomycin¹
- Neomycin/oxytetracycline¹
- Oxytetracycline¹
- Sulfaquinoxaline
- Tetracycline¹

Treatment of disease only

- Amprolium
- Chlortetracycline¹
- Oxytetracycline¹
- Sulfachlorpyridazine
- Sulfamethazine
- Sulfadimethoxine

Regulatory initiatives addressing the use of antimicrobials for rate of gain/feed efficiency in food animals.

Guidance 209 was put out on June 28, 2010 by the FDA/CVM to get input on two proposed directions. The input was given by the end of 2010, and the CVM is currently evaluating comments and preparing a response. There are extensive review comments related to previous evaluations, but the key components of the guidance are the two principles and the conclusion, which are reproduced here as excerpts of the document.

***“Principle:** The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.*

In light of the risk that antimicrobial resistance poses to public health, FDA believes the use of medically important antimicrobial drugs in food-producing animals for production purposes (e.g., to promote growth or improve feed efficiency) represents an injudicious use of these important drugs. Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products. In contrast, FDA considers uses that are associated with the treatment, control, or prevention of specific diseases, including administration through feed and water, to be uses that are necessary for assuring the health of food-producing animals.

Although some may have concerns that the use of medically important antimicrobial drugs in food-producing animals for disease prevention purposes is not an appropriate or judicious use, FDA believes that some prevention indications are necessary and judicious. . Veterinary involvement in the decision-making process associated with the use of medically important antimicrobial drugs is an important aspect of assuring appropriate use, including judicious preventive use. Important factors to consider when determining the appropriateness of a preventive use include whether there is: (1) evidence of effectiveness, (2) evidence that such a preventive use is consistent with accepted veterinary practice, (3) evidence that the use is linked to a specific etiologic agent, (4) evidence that the use is appropriately targeted, and (5) evidence that no reasonable alternatives for intervention exist.

***Principle:** The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.*

Most of the feed-use antimicrobial drugs are currently approved for over-the-counter use in food-producing animals for purposes that include the treatment, control, and prevention of disease as well as for production purposes (i.e., for growth promotion uses such as increased rate of weight gain). In addition to instituting measures that would limit use of medically important antimicrobial drugs in food-producing animals to uses that are considered necessary to assure the animals' health, FDA also believes it is important to phase-in the practice of including veterinary oversight or consultation in the use of these drugs. As noted above, FDA believes that this practice is an important mechanism for helping to assure appropriate use. Veterinarians can play a critical role in the diagnosis of disease and in the decision-making

process related to instituting measures to treat, control, or prevent disease. FDA recognizes that the nature of veterinary involvement can vary due to numerous factors such as geographic location and animal production setting. In fact, there are limited numbers of large animal veterinarians, which can make consultation or oversight challenging in certain situations.

For example, some animal disease events require immediate attention.. In some cases, veterinarians may be directly diagnosing and administering therapies, while in other cases they are visiting and consulting with producers periodically to establish customized disease management protocols for that producer's herd or flock. Of key importance to FDA is the fact that, in both of these cases, the veterinarian is involved in the decision-making process regarding antimicrobial drug use. FDA recognizes that increasing veterinary involvement in the use of antimicrobial drugs has significant practical implications for animal producers, veterinary practitioners, and the veterinary profession as whole. Therefore, FDA is particularly interested in receiving comments on strategies for effectively phasing-in such a change.

VIII. Conclusion

In order to minimize the development of antimicrobial resistance, FDA believes that steps need to be taken to ensure the judicious use of medically important antimicrobial drugs in animal agriculture. Such steps should include phased-in measures that would limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and that include veterinary oversight or consultation. Such limitations would reduce overall medically important antimicrobial drug use levels, thereby reducing antimicrobial resistance selection pressure, while still maintaining the availability of these drugs for appropriate use.

FDA is committed to working with animal drug sponsors, the veterinary and public health communities, the animal agriculture community, and all other interested stakeholders in developing a strategy to address antimicrobial resistance concerns in a manner that is protective of both human and animal health. In regard to comments on this draft guidance, FDA is especially interested in hearing from the public and stakeholders on how the agency can best use its regulatory authority and take non-regulatory measures to support the two principles, while minimizing adverse impacts on animal health and disruption to the animal agriculture industry.”

Critical Legislation in the U.S. House and Senate

The most critical bill related to the practice of veterinary medicine on the date these proceedings were prepared is HR 1549 - The Preservation of Antibiotics for Medical Treatment Act of 2009. The companion bill in the Senate is S 619

Thomas.gov is a government site for reading and tracking bills introduced in the U.S. Senate and House. By searching on the Bill Number you can find the available information on the text of the bill, related bills, all congressional actions and other information.

H.R. 1549 SUMMARY AS OF 3/17/2009--Introduced.

Preservation of Antibiotics for Medical Treatment Act of 2009 - Amends the Federal Food, Drug, and Cosmetic Act to require the Secretary of Health and Human Services to deny an application for a new animal drug that is a critical antimicrobial animal drug unless the applicant demonstrates that there is a reasonably certainty of no harm to human health due to the development of antimicrobial resistance attributable to the nontherapeutic use of the drug. Defines "critical antimicrobial animal drug" as a drug intended for use in food-producing animals that contains specified antibiotics or other drugs used in humans to treat or prevent disease or infection caused by microorganisms.

Requires the Secretary to withdraw approval of a nontherapeutic use of such drugs in food-producing animals two years after the date of enactment of this Act unless certain safety requirements are met. Directs specified congressional committees to hold hearings on the implementation of such a withdrawal of approval.

From the text of the bill:

Critical Antimicrobial Animal Drug- The term `critical antimicrobial animal drug' means a drug that--

`(1) is intended for use in food-producing animals; and

`(2) is composed wholly or partly of--

`(A) any kind of penicillin, tetracycline, macrolide, lincosamide, streptogramin, aminoglycoside, or sulfonamide; or

`(B) any other drug or derivative of a drug that is used in humans or intended for use in humans to treat or prevent disease or infection caused by microorganisms.

`(ss) Nontherapeutic Use- The term `nontherapeutic use', with respect to a critical antimicrobial animal drug, means any use of the drug as a feed or water additive for an animal in the absence of any clinical sign of disease in the animal for growth promotion, feed efficiency, weight gain, routine disease prevention, or other routine purpose.'

So where is this bill today (2011)? The bill sponsor (Slaughter, D-NY) is no longer chair of the House Rules Committee, which was used (against the House rules) as the venue for a hearing on the bill. The Rules Committee is intended to address issues related to House rules (hence the name) and not hearings on the content of legislation. Now the bill would have to move through legitimate channels, where fair questioning and hearing of the bill would happen.

Some version of this bill has been in circulation for quite a few years now, one of the originals with Brown when he was in the House and Kennedy and Snowe in the Senate.

The PEW Foundation has been an aggressive supporter of this bill. Their full report on industrial farm animal production and executive summary may be accessed at <http://www.ncifap.org/>. The AVMA response to the report may be accessed at <http://www.avma.org/advocacy/PEWresponse/>.

State legislative activity related to antibiotics

Most Recent – New York state, text of the bill....

STATE OF NEW YORK

80

2011-2012 Regular Sessions

IN SENATE

(Prefiled)

January 5, 2011

Introduced by Sen. SQUADRON -- read twice and ordered printed, and when printed to be committed to the Committee on Agriculture

AN ACT to amend the agriculture and markets law, in relation to non-therapeutic use of antimicrobial agents in animals

The People of the State of New York, represented in Senate and Assembly, do enact as follows:

- 1 Section 1. The agriculture and markets law is amended by adding a new
2 section 84 to read as follows:
3 Â§ 84. Non-therapeutic use of antimicrobial agents. 1. As used in this
4 section:
5 (a) "Antimicrobial agent" shall mean any drug or derivative of a drug
6 that is used in humans or intended for use in humans to treat or prevent
7 disease or infection, or any substance, whether produced synthetically
8 or naturally, used to kill or inhibit the growth of bacteria, viruses,
9 fungi, parasites, or other microorganisms.
10 (b) "Non-therapeutic use of antimicrobial agents" shall mean any use of
11 antimicrobial agents, including without limitation as a feed or water
12 additive, for an animal for growth promotion, feed efficiency, weight
13 gain, routine disease prevention, or other routine purpose, in the
14 absence of any clinical sign of disease in the animal.
15 2. (a) No person shall engage in the non-therapeutic use of antimicro-
16 bial agents in cattle, poultry, sheep, swine, or any animal raised for
17 the purpose of providing food for human consumption, including animals
18 that provide non-meat food products such as eggs and milk.
19 (b) No person shall sell, expose for sale, or transport for sale with-
20 in this state, regardless of place of origin, any food product derived
21 from an animal that has been subject to non-therapeutic use of antimi-
22 crobial agents.
23 3. Violation of this section shall constitute a class A misdemeanor.