Testimony to the House Energy and Commerce Committee

Subcommittee on Health

"Reauthorization of Animal Drug User Fees: ADUFA and AGDUFA"

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Note: In this testimony, the common term antibiotic is used to represent both antibiotics and antimicrobials.

Summary:

Uses of antibiotics in food animals are highly regulated, starting with specific indications on the label. Currently, the indications may include treatment, prevention, or control of disease, improved feed efficiency, and improved rate of gain. The FDA/CVM has indicated through Guidance for Industry #209 that indications on labels for medically important antibiotics which include feed efficiency and rate of gain are to be removed from the labels. This guidance also indicates the intention to require veterinary authorization for all feed and water uses of antibiotics in food producing animals. The remaining label indications (treatment, prevention, and control) are therapeutic uses.

Antibiotics labeled for administration in the feed must be used only for label directions, any other use is illegal. Any extralabel use of other food animal antibiotics must meet the strict requirements of the Animal Medicinal Drug Use Clarification Act regulations, including strict oversight requirements for veterinary involvement as well as standards for rationale for this use.

Examples of antibiotic approvals for cattle and swine indicate that there is a wide variety of antibiotics approved for use with varying indications. A 2012 estimate of 2006 swine in-feed antibiotic use indicates that approximately 20% of in-feed antibiotic use of classes medically important in human therapy was attributable to growth promotion uses.

The Relationship of Veterinarians to Food Animal Producers

Veterinarians are a vital part of the drug-use decisions by food animal producers, especially for antibiotics. This relationship is described and promoted in programs such as beef quality assurance and pork quality assurance.

Label Indications for Uses of Antibiotics in Food Animals

Antibiotics may receive approval by the FDA Center for Veterinary Medicine for these indications

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

Indications 4 and 5 are production uses, also referred to as growth promotion claims. These claims are specifically referred to in FDA Guidance for Industry #209, in which the FDA/CVM refers to these indications as injudicious uses and asks for voluntary withdrawal of these label approvals by the sponsors (GFI #209, 2012). The initial time frame for withdrawal of these indications is 3 years after the mechanisms for label revision are established in the form of FDA Guidance for Industry #213 (GFI #213, 2012). Guidance for Industry #213 is intended to provide streamlined methods for removing these claims and adding veterinary oversight to all feed and water uses of antibiotics in food animals (which are also specified as an intended change in Guidance for Industry #209). The FDA/CVM has indicated that they may alter this time frame if necessary, but will take regulatory action to remove these label claims if voluntary removal does not occur.

While the FDA/CVM has not released official definitions for indications 2 and 3, as a clinical pharmacologist, my working definitions in the field are as follows.

- Prevention: Use of an antibiotic to prevent disease occurrence in a population of animals when experience suggests that this particular time in the production cycle is very likely to result in a disease outbreak in a population of animals. The need for prevention varies according to the current disease pressure in the population, therefore the need for this preventive practice may vary over time.
- Control: Use of an antibiotic to reduce the number of additional clinical cases in a population where clinical observation or recent stressors and exposure indicate that the disease process is clinically apparent or in developmental stages in some of the animals. Treatment at this time will interfere with advancement from the incubatory stage to the clinical stage of disease.

The overarching goal of veterinarians and producers is to replace the need for prevention or control uses of antibiotics through practices such as biosecurity and vaccination. Uses of antibiotics for therapy and control are considered a therapeutic use by the American Veterinary Medical Association, the FDA Center for Veterinary Medicine, the OIE (World Organization for Animal Health), and Codex Alimentarius (International Food Standards).

Cattle antibiotic labels include a wide variety of indications. Table 1 summarizes in-feed labels by type of indication. These indications are for different diseases and represent different dosing regimens intended for different ages use classes of cattle. This table is for summary purposes only. Summaries of label inclusions for FDA/CVM-approved drugs for all veterinary species may be accessed through a search engine on the FDA/CVM website (Animal Drugs @ FDA, 2013).

Table 1. Examples of in-feed approvals for antibiotics in cattle. These approvals are not ranked by frequency or amount of use. Shaded drugs indicate individual antibiotics or antibiotic combinations which contain a medically important antibiotic as defined in Food and Drug Administration Guidance for Industry #152, Appendix A (GFI #152, 2003) for which the rate of gain and/or feed efficiency label indication will be affected by FDA/CVM GFI #209.

Improvement in rate of gain or feed efficiency only
Bacitracin Zinc
Bambermycins
Chlortetracycline
Laidlomycin
Lasalocid
Neomycin / oxytetracycline
Oxytetracycline
Sulfamethazine / Chlortetracycline
Virginiamycin

Rate of gain or feed efficiency and a prevention/ control claim
Monensin
Chlortetracycline
Neomycin / oxytetracycline
Oxytetracycline

Prevention or control of disease only
Amprolium
Bacitracin methylene disalicylate
Chlortetracycline
Decoquinate
Lasalocid
Monensin
Tylosin
Virginiamycin

Table 1 (continued):

Treatment of disease and prevention or control
Neomycin
Neomycin / oxytetracycline
Oxytetracycline
Sulfaquinoxaline
Tetracycline

Treatment of disease only
Amprolium
Chlortetracycline
Oxytetracycline
Sulfachlorpyridazine
Sulfamethazine
Sulfadimethoxine

Table 2 gives examples of antibiotics labeled for cattle which may be administered by the water (individually or to a group) or which are administered individually to cattle either by injection or by administration in the mammary gland for mastitis (IMM). As for Table 1, the list does not imply extent or amount of use.

Table 2: Injectable, intramammary, and water antibiotics for cattle. The vast majority of these require a veterinary prescription.

Class	Antimicrobial	Route
Thiamine analog	Amprolium	Oral in water or as a drench
Penicillins	Amoxicillin	IMM
	Ampicillin trihydrate	Injectable
	Cloxacillin	IMM
	Hetacillin	IMM
	Penicillin G procaine	Injectable, IMM
	Penicillin G procaine / Benzathine	Injectable
Cephalosporins	Ceftiofur	Injectable and IMM
	Cephapirin	IMM
Tetracyclines	Oxytetracycline	Injectable and in water
	Chlortetracycline	Oral as bolus
Fluoroquinolones	Danofloxacin	Injectable
	Enrofloxacin	Injectable
Phenicols	Florfenicol	Injectable
Aminoglycosides	Dihydrostreptomycin	IMM
	Gentamicin	Ocular spray
	Neomycin	Oral In water/milk
Sulfas (all non-potentiated)	Sulfachlorpyridazine	Injectable
	Sulfamethazine	Oral as bolus
	Sulfamethazine	Injectable
	Sulfadimethoxine	Injectable, oral as drench, in water, or bolus
Macrolides	Gamithromycin	Injectable
	Tildipirosin	Injectable
	Tilmicosin	Injectable
	Tulathromycin	Injectable
	Tylosin	Injectable
Aminocoumarin	Novobiocin	IMM
Lincosamides	Pirlimycin	IMM

An estimate of in-feed use of antibiotics in swine was recently published, in which I served as lead author (Apley, et al., 2012). This estimate utilized the USDA National Animal Health Monitoring System's Swine 2006 Survey data in conjunction with a veterinary swine practitioner survey to estimate the amount of antibiotics use in swine feed for the year 2006. The following table is reproduced from this publication.

TABLE 5. NATIONAL ESTIMATE OF TOTAL KILOGRAMS OF SWINE IN-FEED ANTIMICROBIALS FOR ALL PRODUCTION CYCLES IN A YEAR BY ANTIMICROBIAL AND REASON

	Antimicrobial	*Growth promotion*	*Prevention*	*Therapy*	*Any reason 'yearly basis'*
Antimicrobials **not listed** in FDA/CVM Guidance 152 Appendix A	Arsanilic acid	0	10,494	0	10,494
	Bacitracin	72,760	11,032	24,914	108,707
	Bacitracin zinc	4,844	0	0	4,844
	Bambermycins	543	0	0	543
	Carbadox	3,787	7,409	12,923	24,119
	Roxarsone	461	51	4,456	4,967
	Sulfamethazine[a]				
	as Chlortetracycline/Sulfamethazine/ Penicillin G (ASP)	2,735	3,663	1,148	7,546
	as Tylosin/Sulfamethazine	7,500	149	3,460	11,109
	Sulfathiazole[a]				
	as Chlortetracycline/Sulfathiazole/ Penicillin G (CSP)	942	14,673	3,784	19,398
	Tiamulin	2,393	6,770	3,571	12,734
Antimicrobials or classes **listed as Highly Important** in Guidance 152 Appendix A	Chlortetracycline[b]				
	as Chlortetracycline alone	83,331	206,076	217,622	507,029
	as Chlortetracycline/Sulfathiazole/ Penicillin G (CSP)	942	14,673	3,784	19,398
	as Chlortetracycline/Sulfamethazine/ Penicillin G (ASP)	2,735	3,663	1,148	7,546
	Lincomycin[c]	356	4,246	20,844	25,446
	Neomycin				
	as Neomycin/Oxytetracycline	4,068	2,632	16,394	23,094
	Oxytetracycline[b]				
	as Oxytetracycline alone	2,615	31,699	97,547	131,862
	as Neomycin/Oxytetracycline	4,068	2,632	16,394	23,094
	Penicillin				
	as Chlortetracycline/Sulfathiazole/ Penicillin G (CSP)	471	7,336	1,892	9,699
	as Chlortetracycline/Sulfamethazine/ Penicillin G (ASP)	1,367	1,832	574	3,773
	Virginiamycin[d]	26,108	54,858	493	81,459
Antimicrobials or classes **listed as Critically Important** in Guidance 152	Tilmicosin[e]	1,068	46,906	22,786	70,761
	Tylosin[e]				
	as Tylosin alone	25,641	37,893	91,160	154,694
	as Tylosin/Sulfamethazine	7,500	149	3,460	11,109

[a]Only potentiated sulfonamides are listed in Guidance 152, Appendix A.
[b]The tetracycline class representative in Guidance 152, Appendix A is tetracycline.
[c]The lincosamide class representative listed in Guidance 152, Appendix A is clindamycin.
[d]The streptogramin class representative in Guidance 152, Appendix A is dalfopristin/quinupristin.
[e]The macrolide class representatives listed in Guidance 152, Appendix A are erythromycin, azithromycin, and clarithromycin.
Antimicrobials are grouped according to classification or lack of classification in Appendix A of FDA/CVM guidance 152.

From this table it is evident that of the antibiotics listed as either highly important or critically important in FDA/CVM GFI #152, Appendix A, the estimate indicates that 15% was used for growth promotion purposes. The greatest use, on a kg basis, was attributable to the tetracyclines (chlortetracycline and oxytetracycline).

As for cattle, there are other antibiotics which have an injectable or in-water route of application on the label. These include ceftiofur, ampicillin trihydrate, tulathromycin, Procaine penicillin G, oxytetracycline, chlortetracycline (water only), tetracycline (water only), and enrofloxacin.

Use Other than According to the Label

Use of antibiotics in the feed for major food animal species in any manner other than specified on the label is illegal. This would include any changes in dose, duration, or disease indication. Provisions are available to allow some extralabel use in minor food animal species (e.g., sheep and goats) (FDA, 2007).

Any other extralabel use of antibiotics in food animals must be done in compliance with the Animal Medicinal Drug Use Clarification Act regulations (AMDUCA, 1994). These regulations require that a veterinarian prescribes the use within the confines of a valid veterinarian-client-patient relationship and that an extended withdrawal time be used as specified by the veterinarian.

Extralabel use of fluoroquinolones in food animals is prohibited by the FDA/CVM, along with other drugs on a list which is a standard knowledge base for all veterinarians (CFR 530.41, 2012). This extralabel use prohibition includes cephalosporins, with the exception of cephapirin, which may be used in an extralabel manner only for disease indication, with no allowable alteration of the dosing regimen (dose and route, duration, or frequency of administration).

References

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