

Use of Medically Important Antibiotics in Food-Producing Animals in 2015 -- Going Up? Or Coming Down?

Stephanie Ostrowski, DVM, MPVM, DACVPM, FNAP, College of Veterinary Medicine, Auburn University, Auburn, AL and Robert Norton, PhD, College of Agriculture, Auburn University, Auburn, AL

What the FDA Reported--

On December 22, 2016, the U.S. Food and Drug Administration (FDA) published their 2015 annual report summarizing sales and distribution data for all antimicrobial drugs approved for use in food-producing animals from 2009 through 2015.¹ Some key findings --

- 20 veterinary drug sponsors had active applications on-file to market or continue marketing these antimicrobials for use in food-producing animals
- 98% of sales from 2009 – 2015 were for “over the counter” product sales. No veterinary diagnosis, prescription, or oversight of use was required based on the original product approval.
- 43 antimicrobial “active ingredients” were marketed as 149 antimicrobial products; this included the same drugs offered by different manufacturers or distributors.
 - Some products remain actively registered by the manufacturer with FDA, but are not currently being marketed for a variety of reasons.
- Many antimicrobial drugs are approved and labeled for use in multiple species. Total sales data reported therefore reflects combined data for all species (food animal species as well as non-food animal species) listed on the approved label.

Antimicrobial versus Antibiotic – What’s the Difference?

The term “antimicrobial” is a broad term includes anti-fungals, anti-virals, medications effective against parasites and protozoal infections, and anti-bacterials.

The term “antibiotic” specifically refers to anti-bacterial properties.

“Medically Important Antimicrobials” versus “Not Medically Important Antimicrobials”

As described in the 2015 report, FDA identified certain antimicrobial active ingredients as “medically important” based on their utility in treating disease in humans.¹

The basis for these designations is provided in FDA Guidance for Industry (GFI) #213, which states that all antimicrobial drugs and their associated classes listed in Appendix A for FDA GFI #152 are considered “medically important”.²

Antimicrobial active ingredients and drugs not listed in Appendix A of GFI #152 are considered by FDA to be “not currently medically important” with respect to human medical therapy.²

Ionophores: Among the most widely used of the “not medically important” drugs for veterinary applications is a class of compounds known as ionophores.

- Ionophores are used to prevent and treat common species-specific parasitic infections (coccidiosis) in poultry and in non-lactating ruminants.
- Not only do ionophores “lack utility in human medicine”, but that also they do not “pose cross resistance concern; thus, they do not have the same public health risks as medically important antimicrobials”.²

- In monogastric species (such as dogs, cats, humans, and horses), ionophores have been found to be toxic to skeletal and cardiac muscle.³

Antifungal and antiviral drugs: With the exception of formalin and hydrogen peroxide water immersion (i.e., disinfectant) products, there are currently no approved drug applications actively marketed for use in food-producing animals.

Antiprotozoal drugs without concurrent antibacterial properties (e.g., amprolium) were also not included in the FDA report.

Sales and Distribution Totals -- Going Up? Or Coming Down?

- Domestic (U.S.) sales and distribution of antimicrobials approved for use in food-producing animals increased by 24% over a 7-year period (2009 – 2015).¹
- From 2014 – 2015, sales and distribution of antimicrobials approved for use in food-producing animals leveled off (only 1% annual increase).¹
- **The Status Quo In 2015**
 - Total sales and distribution (domestic and export) was ~ 15.6 million kilograms, of which domestic use in food-producing animals was ~100% (15.58 million kilograms)¹
 - 44% Tetracyclines (domestic sales)
 - 30% ionophores (domestic sales)
 - Medically important antimicrobials accounted for 62% of all domestic sales of antimicrobials approved for use in food-producing animals.¹
 - Labeled for production or therapeutic use
 - 74% -- labelled for administration in FEED
 - 62% Tetracyclines
 - 1% sulfas
 - 10% all others
 - 21% -- labelled for administration in WATER
 - 8% tetracyclines
 - 8% penicillins
 - 2% sulfas
 - 2% aminoglycosides
 - 2% lincosamides
 - 1% all others
 - 3% -- required veterinary Rx, Rx/OTC, or VFD
 - Categories
 - Domestic (U.S.) sales/distribution of antimicrobials for use in food-producing animals increased by 24% over a 7-year period (2009 – 2015).¹
 - 71% were tetracyclines, which showed 31% increase overall from 2009 – 2015; but slowed to just 4% growth in sales from 2014 to 2015
 - 10% were penicillins which showed a 35% increase from 2009 – 2015, which was related to 77% increase in sales of products administered in water
 - 6% macrolides —12% increase (2009- 2015); during this period the number of marketed products also increased from 10 to 17.

- 4% were sulfa drugs which showed a 25% decrease (2009 – 2015). This was associated with a 42% decrease in water administered products and a 13% decrease in feed-administered products
- 4% were aminoglycosides; these had a 54% increase in water administered products
- 2% were lincosamides, from 2009-2015 this category had the highest percentage increase (96%) in domestic sales --260% increase in water administered products. Sales dropped 22% in 2014 -2015
- Amphenicols, cephalosporins and fluoroquinolones constituted less than <1% of all therapeutic products administered to animals, although actual use increased 61% from 2009- 2015).
- **Not Currently Medically Important (NCMI) antimicrobials** accounted for 38% of total domestic sales and distribution in 2015. ¹ It is important to note that:
 - **100% of NCMI antimicrobials approved for use in food-producing animals were assigned OTC dispensing status**
 - **81% were ionophores (no safe human/ monogastric use or label indications)**
 - **72% of sales labels in 2015 included both production and therapeutic indications.**
 - **2009 – 2015 saw a 22% increase in labels listing “production” indications, and**
 - **just 26% of product labels restricted use to “solely for therapeutic indications”**

Important Changes Achieved and Implemented in 2017

- **FDA policy changes ensured that – starting with the very first day of 2017 -- medically important antibiotic use in food animals can only be authorized to treat diseases, and requires a licensed veterinarian to make that decision.**
- 1. **FDA’s Guidance for Industry #213 provided a process blueprint and timeline for elimination of all non-therapeutic use of medically important antimicrobials in food-producing species by 2017.**² By working collaboratively over a several year period with national and regional agricultural associations and food industry groups, FDA provided a robust collaborative mechanism to work out the details for implementation of these major evidence-based policy changes. Although criticized by some as being too slow and by others as rapid and radical change, both the agricultural industry sector and FDA leadership used this period to educate the producers, veterinarians, feed mill operators, and FDA regulatory enforcement personnel who would be responsible for implementing these changes. “Making haste slowly” resulted in a smooth transition.
- 2. **Veterinary Feed Directive (VFD): As of January 1, 2017 all use of medically important antimicrobials requires a valid veterinary-client-patient relationship (VCPR). Administration of medically important antimicrobials to a population of animals (herds, flocks, bee hives, etc.) in their feed or water now requires issuance of a Veterinary Feed Directive (VFD) document by a licensed veterinarian which specifies the essential details. This has significantly increased**

veterinary responsibility for active oversight, determination of a definitive diagnosis, and to provide a prescription (Rx) which includes specific instructions (dose, route of administration, and duration) for individual animals treated.

3. **Elimination of Over-the-Counter (OTC) Marketing of Medically Important Antimicrobials:** In synchrony with these other actions, FDA is in the process of approving **label changes** that will **effectively prohibit** future use of antibiotics for **growth promotion or production purposes**. As of January 1st 2017, **growth promotion** and **feed efficiency** (e.g., “production”) are no longer allowable legal uses of medically important antibiotics in food animals in the U.S.; **product labels may no longer include such language**. These medically important antibiotics may continue to be used **under appropriate veterinary supervision for therapeutic and disease control purposes only**.

Will this label change eliminate the routine use of antibiotics for growth promotion and production purposes in the U.S.?

YES, it really will. This is a watershed event... Decades of **OTC access** by laymen --farmers and ranchers--stopped as of January 1st. **Feed mills are now prohibited from routinely mixing low-level antibiotics in animal rations.** It truly is a momentous change in the status quo from 20th Century U.S. agri-business practices for raising poultry and livestock.

Can consumers be confident that this will result in real change? Will these measures halt inappropriate uses of medically important antibiotics in food-producing animals?

Again YES. Recall that through 2015 medically important antimicrobials accounted for **62% of all domestic sales** of antimicrobial use in food-producing animals, and that **95% of that amount (9.66 million kilograms in 2015) was available OTC** – without a prescription from a veterinarian. NOW... a food animal veterinarian must perform an exam (of individual animals and/or herd inspection), obtain and submit appropriate diagnostic specimens, confirm a diagnosis, establish a treatment plan, then authorize and write a prescription or VFD.

Will it eliminate all use of medically important antibiotics in food animals?

No, of course not. It does assure that antibiotics will be used only when it is medically necessary and appropriate, and that a licensed veterinarian makes that decision.

Consumers can be confident that strategic, robust, evidence-based vaccination protocols are routinely used to prevent illness in livestock to the extent possible. This is good animal husbandry, proactive and humane veterinary care, and good business. **However, if and when animals become sick it is essential to be able to treat them with effective antibiotics.**

How much of a reduction in antibiotic use are we likely to see in the U.S.? Exact numbers are hard to predict, but regulatory, public health, and ag industry leaders anticipate that the change will be substantial. FDA and USDA will continue to monitor meat, milk, and eggs for antibiotic residue levels. Time will tell.

Links:

1. FDA. 2015 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. December 2016. <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM534243.pdf>
2. FDA. Guidance for Industry #213. <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf>
3. Veterinary Toxicology -- Basic and Clinical Principles. Ramesh Gupta (Ed) 2007 Elsevier Inc., p.1021 - 41
4. Handbook of Veterinary Drugs, Dana G. Allen 1993
5. Agri Pulse: Farm antibiotic sales rise slightly ahead of FDA curbs. Philip Brasher. Dec 22, 2016. <http://www.agri-pulse.com/Farm-antibiotic-sales-rise-slightly-ahead-of-FDA-curbs-12222016.asp>
6. CIDRAP News: FDA Antibiotic Use in Food Animals Continues to Rise. Chris Dall. Dec 22, 2016. <http://www.cidrap.umn.edu/news-perspective/2016/12/fda-antibiotic-use-food-animals-continues-rise>
7. Farm Journal: Antibiotic Rules Change Jan. 1. John Maday. Dec 2, 2016. <http://www.agweb.com/article/antibiotic-rules-change-jan-1-naa-farm-journal-guest-editor/>
8. Farm Journal: Minnesota Farmers Ready for New Livestock Antibiotic Rules. Dec. 27, 2016. <http://www.agweb.com/article/minnesota-farmers-ready-for-new-livestock-antibiotics-rules-naa-associated-press/>
9. NRDC. Livestock Antibiotics Surging Up, Up, Up. David Wallinga. Dec 22, 2016. <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM534243.pdf>