

**Testimony of Dr. Richard Carnevale
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**Committee on Agriculture
Subcommittee on Livestock, Dairy and Poultry
Advances in Animal Health in the Livestock Industry**

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Mr. Chairman and members of the Subcommittee:

Thank you for holding this hearing on recent developments in animal health. I am Dr. Richard Carnevale. I am a veterinarian by training with a degree from the University of Pennsylvania and I am here today on behalf of the Animal Health Institute, a trade association that represents companies that make medicines for animals. Prior to joining AHI about 12 years ago, I served as Deputy Director for the Office of New Animal Drug Evaluation at FDA's Center for Veterinary Medicine and later as Assistant Deputy Administrator for the Office of Science at USDA's Food Safety & Inspection Service. AHI companies work to provide products to livestock and poultry producers that help keep their animals healthy. By doing this, companies contribute to public health and food safety. Research shows that the first link in the chain of producing safe meat, milk and eggs is keeping animals free from disease.

Food safety starts on the farm, and our companies spend millions of research and development dollars to find new and innovative products to keep farm animals healthy. Some animal health products are used to treat and prevent or control disease in animals. Others help increase animal productivity, allowing producers to meet the growing world food demand while minimizing the use of natural resources. More recently, products are being developed that will contribute to food safety by reducing bacteria that do not make animals sick but have the potential to make people sick.

Animal health products are subject to stringent, science-based review processes at two federal agencies: pharmaceutical products are reviewed by the Food and Drug Administration under the Federal Food, Drug and Cosmetic Act, and biologic products, or vaccines, are regulated by USDA under the Virus, Serum, Toxins and Analogous Products Act. All products are reviewed for safety and efficacy: Efficacy, which protects producers by ensuring the products deliver the benefits they promise; and safety, to ensure the products are safe for the animal being administered the drug or vaccine and to ensure the meat from the animal is safe for human consumption and safe for the environment.

One class of products important to the health of food animals is antibiotics. Antibiotics are used by livestock producers, poultry producers and the veterinarians who work with them to prevent, control and treat often fatal bacterial infections. There are many benefits to animals, producers and consumers that come from the use of antibiotics in animal agriculture:

1. Animal welfare is improved as a result of veterinarians and producers having the tools to be able to maintain the animal's health.
2. Producers are more efficient because they can produce more food from fewer animals. Without antibiotics to prevent and control diseases, more animals get sick and die with producers losing not only the animal but all the input costs, including feed, that have gone into the animal.
3. There are ecologic benefits. Without antibiotics that improve weight gains and feed conversion, more land and feed are necessary to maintain the same herd and flock sizes. Moreover, some studies have shown that certain antimicrobials used in cattle feeds reduce levels of methane emissions important as greenhouse gases.
4. Benefits to global food markets. With the concern over food costs and availability in today's economic climate, antimicrobials and other animal drugs that improve animal health and productivity are critical to American agriculture's ability to feed the world's growing population. The Food and Agriculture Organization (FAO) of the United Nations estimates that 75 million more people worldwide were below the hunger threshold in 2007 due to increasing food prices. They propose that one solution is to help producers to raise their output.
5. Consumers benefit because healthy animals are needed to produce safe food. Over the past five years, published, peer-reviewed studies have indicated that carcasses from chickens without subclinical diseases are more likely to be free of human foodborne pathogens.^{1,2,3,4} Research shows this is due in part to more standardized carcass size, reducing the potential for intestinal breakage during mechanical evisceration.

Antibiotics are approved and labeled for four specific purposes.

1. Disease treatment
2. Disease prevention
3. Disease control
4. Growth promotion, as measured by the amount of feed needed to produce a pound of animal weight or increased rate of weight gain.

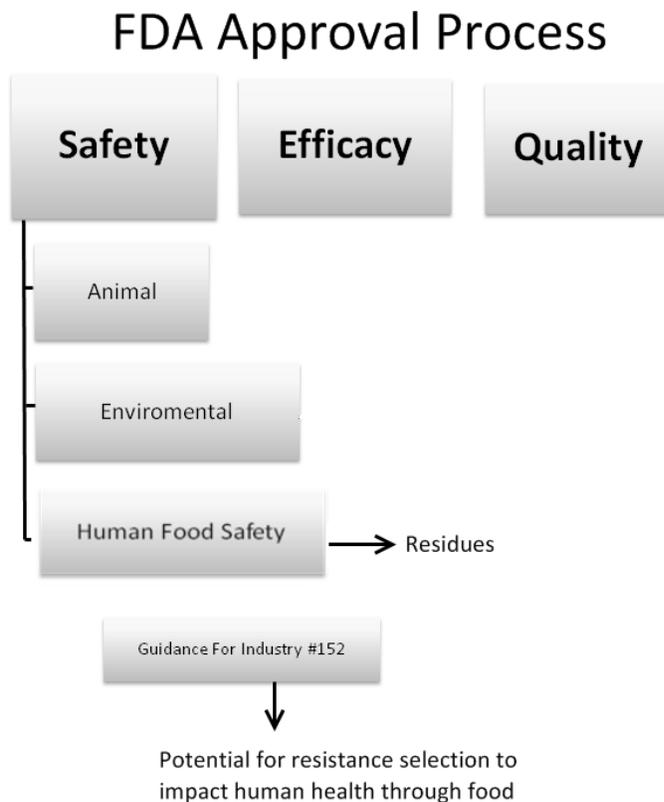
The first three uses – disease treatment, prevention and control – are considered to be therapeutic uses by FDA, the American Veterinary Medical Association (AVMA) and such international bodies as Codex Alimentarius and the OIE. While critics of antibiotic use like to use the term “nontherapeutic” to refer to disease prevention, disease control and growth promotion, this term is not used nor recognized in national or international regulation.

Many assume in-feed uses equate to growth promotion, but this confuses the use with the route of administration. In fact, any of the four uses, including therapeutic, can be administered via feed or

water, as that is under certain circumstances the only practical way to administer medication to large flocks or herds. In most cases, a veterinarian is involved in this process, recommending feed that is specifically formulated for the health management system used for the flock or herd.

How are antibiotics regulated?

Animal health companies rely on a rigorous, efficient, predictable and science-based review process at the Food and Drug Administration's Center for Veterinary Medicine (CVM) to provide these products. The standard for the approval of antibiotics used in animals is the same as that for antibiotics used in human medicine: They must be shown to be safe and effective.



The rigorous review process and monitoring systems in place are at the heart of a broad system of protections that ensure that all medicines, including antibiotics, are safe for animals and humans. Antibiotics for use in animals must meet all the same requirements as antibiotics used in humans, with two additional requirements: first, sponsors must show the meat, edible tissues, milk and or eggs from animals in which the medicine is used is safe for human consumption. Second, beginning in 2003, CVM instituted Guidance for Industry (GFI) # 152, which outlines a qualitative risk assessment process that is applied to all antibiotics approved for use in animals. This guidance process is designed to measure the risk of antibiotic resistant bacteria being transferred from animals to humans if the product is approved. Based on this risk, FDA makes decisions to either deny or approve the drug with certain restrictions to

significantly reduce risk. Restrictions can include requiring a veterinary prescription, prohibiting extra-label use in certain species or restricting the antibiotic to individual animals. In most cases antimicrobial resistance monitoring is required post approval. The methodology is very conservative – meaning it is very difficult to get an antibiotic approved. Further, the guidance is sufficiently broad so that if new, previously unidentified or undescribed, resistant organisms or genes were to become of concern, the Agency can act swiftly to take this information into account. The existing guidance allows the Agency sufficient flexibility to allocate resources appropriately to changing issues of safety related to resistance emergence.

The GFI # 152 process applies not only to new submissions, but to all existing products as well. FDA has established a priority list for the re-evaluation of all antibiotics currently approved and marketed. Most of the drugs on the list are antibiotics administered in animal feed for the prevention and control of animal diseases or to increase the weight gains and improve feed efficiency. The re-review under Guidance 152 was stimulated by new funding that FDA received and continues to receive via annual appropriated money specifically earmarked for these reviews. Bear in mind, though, the evaluation of these products did not begin with Guidance 152. In response to concerns raised some 30 years ago, the Bureau of Veterinary Medicine in FDA, in the 1970's, required sponsors of these products to conduct tests to determine the potential for resistance to be selected in the animals and to be transferred to bacteria that could cause human disease. While the standards and science may have changed over the years, the safety of these products has been an ongoing exercise at FDA. Moreover, published quantitative risk assessments performed by both the agency and individual product sponsors have generally affirmed that the risks to human health from these antibiotics in animal feed under approved conditions of use are quite low.

We fully support efforts by the agency to continue to evaluate the safety of these products using all available scientific data under a sound risk assessment approach in order to determine the true risk to public health and guide appropriate risk management interventions to protect public health.

FDA/CVM has a great deal of authority to act when data or risk assessments indicate a threat to public health. CVM can – and has -- successfully asked companies to withdraw products voluntarily or to modify their conditions of use, including restricting extra label use. The agency can also undertake a notice of proposed rulemaking against a product, setting in motion a process to rigorously review the science and determine if a product should continue to be marketed. This authority has been used to remove antibiotics from the market. Finally, if the agency determines there is an imminent hazard to public health, it can immediately remove a product from the market.

In addition to the rigorous review process and the additional public and private risk assessments that have been conducted, there are other post-approval layers of protection to ensure the safe use of antibiotics.

Monitoring programs

USDA's Food Safety and Inspection Service monitor meat samples for the presence of antibiotic residues as a check on the observance of the withdrawal times set by FDA. It is very uncommon for FSIS to find an unsafe residue, an indication that products are being used according to label directions.

The National Antibiotic Resistance Monitoring System (NARMS) is a multi-agency program coordinated by FDA to monitor antibiotic resistant bacteria and allow for implementation of management and control measures if needed. The three agencies involved are:

- The USDA Agricultural Research Service (ARS), which analyzes *Salmonella* and *Campylobacter* isolates collected from carcasses and meat samples in the USDA FSIS HACCP/Pathogen Reduction Program for antibiotic resistance;
- The FDA, which monitors for resistant bacteria in retail meats;
- The Centers for Disease Control and Prevention (CDC), which collects isolates from public health laboratories to monitor for the emergence of antibiotic resistant enteric pathogens in humans.

To date, the program has produced seven years of data representing over 19,000 *Salmonella* isolates from livestock and poultry carcasses and meats and 12,000 human *Salmonella* isolates. Most bacterial species isolated from humans and tested for resistance against drug classes potentially related to animal usage have shown stable or declining resistance to most antimicrobials. Most of the multiple-drug resistance types, such as *Salmonella typhimurium* DT104 show stable or declining prevalence in both food animals and humans since 1996, according to an expert report issued in 2006 by the Institute of Food Technologists entitled "Antibiotic Resistance: Implications for the Food System."

While AHI strongly supports continued funding of the NARMS program we would point out that there are inherent weaknesses in the sampling strategies that prevent the data from estimating a true national prevalence of resistance and yearly trends. The FDA Science Board has identified these weaknesses as well and has encouraged the agencies involved in NARMS to work to improve the data.⁵

Judicious Use Guidelines

Responsible, or judicious, use programs that are specific to different livestock species give veterinarians and producers specific guidelines to help them safely and properly use of antibiotics in their health management systems. Generally, these guidelines have been prepared collaboratively by FDA, CDC and veterinary groups. These guidelines help ensure there is no unnecessary use of antibiotics in animal agriculture. Others testifying today will provide additional detail on how these principles are used by veterinarians and producers.

There are two additional layers of scrutiny that antibiotic use receives.

First, at the international level, Codex Alimentarius is responsible for protecting the health of consumers and ensuring fair practices in food trade. Codex has established a committee on antibiotic resistance. Chaired by Korea, this committee is currently working to establish an internationally recognized process for risk analysis of antibiotics used in animals. International standards are important, because bacteria know no borders and actions taken here can be nullified if there is not concerted international action. It is also important that the international community establishes a sound scientific basis for countries to assess the risk of antibiotic use. Otherwise, government regulators are left open to outside pressure to take overly zealous precautionary measures that may be unjustified and in the long term harmful to animal health and food safety.

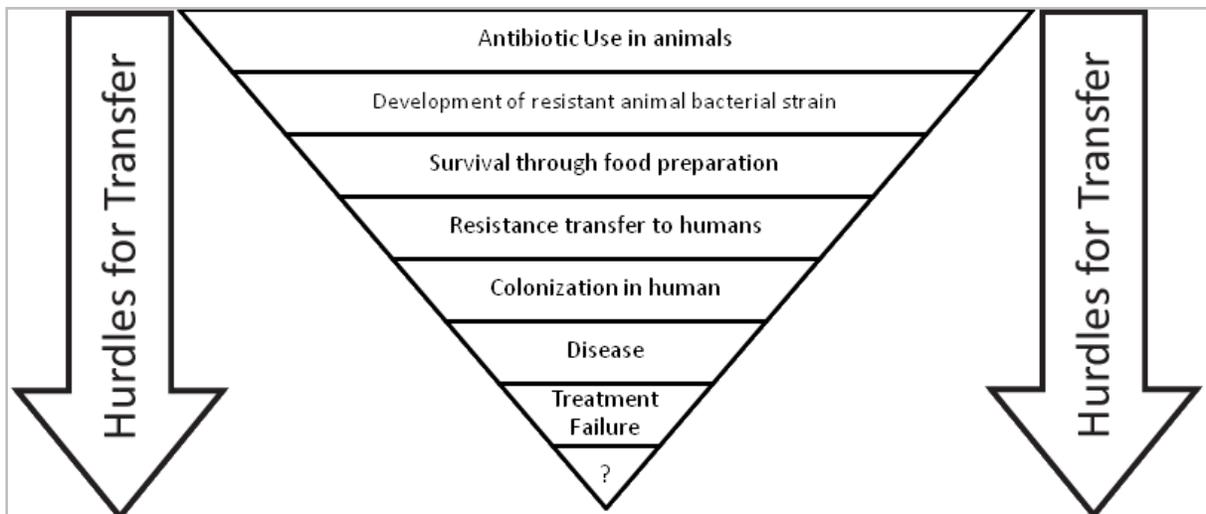
Second, several risk assessments have been conducted on antibiotic compounds, and have uniformly found extremely low levels of risk. Some of these have been conducted and published by the sponsors, some by independent authorities, and some by FDA. In particular, the FDA risk assessment on virginiamycin found there were significant differences between the resistant enterococci bacteria found in animals and those found in humans. Even after they assumed an association for purposes of conducting the risk assessment, the levels of risk they estimated were quite small.

We firmly believe that risk assessment is the proper tool for making policy decisions about the use of antibiotics in animals. Without this scientific basis for decision making, we run the very real risk of making decisions that have unintended consequences that are damaging for both human and animal health.

Does the Use of Antibiotics in Animals Contribute to Human Antibiotic Resistance?

There is no question that antibiotic resistance is a serious public health threat. But resistance is not a single problem: it is a problem comprised of several different bacteria-drug combinations. For instance, some of the most widely recognized antibiotic resistance problems in humans are in respiratory tract infections and venereal diseases like gonorrhea. In neither of these cases is there any evidence that antibiotics used in animals are associated with these problems. In fact, in a survey published in 2000 a group of medical experts estimated the animal contribution to the overall human resistance problem is less than 4 percent.⁶

That small contribution was attributed to the potential for antibiotics used in food animals to contribute to resistance in certain bacteria which can be transferred from animal food products to humans. However, there is a chain of events from the “farm to the fork” that must be traversed by bacteria that



develop resistance in animals as outlined in the accompanying chart:

In order for this to happen, the antibiotic must be used in the animal, resulting in the selection of resistant bacteria in the animal. Those bacteria then must survive the slaughtering and processing of the animal. Remember, we have successfully reduced the number of bacteria -- both resistant and not resistant -- that survive this process through the implementation of controls like HACCP. The bacteria must then survive the normal cooking process. If enough resistant bacteria survive to this point and are ingested in a large enough quantity, they can make an individual sick with a common foodborne illness. As you know, most foodborne illnesses are self-limiting -- they resolve themselves in most cases without antibiotics being necessary. In the event that an antibiotic is necessary, the illness could be treated with the antibiotic that the bacteria is resistant to, and the treatment could fail, prolonging the illness.

While we know this can happen, the question is, how often does this happen and how severe are the consequences? The answer to this much-studied question is that it does not happen enough that we can find it and measure it. So, scientifically, we cannot say it does not happen, but we can say it is rare.

Finally, there are some recurring questions in the debate about antibiotic use I would like to address.

First, what is the quantity of antibiotics used in animal agriculture? Critics have charged that we don't know how big the problem is because we don't have reliable data about the use of antibiotics in animal agriculture. However, levels of antibiotic resistance are not correlated to the amount of use. Not all antibiotics are alike. Nevertheless, each year AHI surveys its members for the amount of antibiotics sold for use in animals. Attached to my testimony are the 2006 results. Note that there are large groupings of products. This grouping is done because of the small number of companies in the market and the need to protect confidential business information. The information is not species specific, because many of the compounds sold are used in more than one species. While critics have demanded species specific information, this would only be available if it comes from producers, adding to their costs and paperwork burden. About 7 years ago CVM began work on a rule to require data collection but dropped the effort as a result of these difficulties. Congress recognized this just this summer when antimicrobial sales and distribution data reporting requirements were included in the Animal Drug User Fee Amendments of 2008. We are appreciative of the cooperation we received from Members and staff in working with the Animal Health Industry to craft appropriate legislative language for these reporting requirements.

Notably, Congress also acted on this issue in the Farm Bill that was signed into law earlier this year. That legislation contained an authorization for USDA's Agriculture Research Service to conduct additional research to study the development of antibiotic resistant bacteria in livestock on how judicious use principles can help producers use these products to protect both human and animal health.

Also, note that we ask sponsors to estimate the amount of antibiotics used for growth promotion. This estimate dropped to less than 5 percent of the total in 2006.

What happens if producers lose access to these products? This question can be answered with data from the European experiment. In the late 1990s, the European Union phased out one particular use -- the use of antibiotics for growth promotion. Data from the Danish government, which you see on the accompanying chart, shows that use of antibiotics to treat disease has doubled since the ban.

Trends in the estimated total consumption (kg active compound) of prescribed antimicrobials for production animals, Denmark

DANMAP 2007

Therapeutic group	1990	1992	1994	1996	1998	2000	2002	2004	2006	2007
Tetracyclines	9,300 b)	22,000	36,500	12,900	12,100	24,000	24,500	29,500	32,650	38,200
Penicillins, β -lactamase sensitive	5,000	6,700	9,400	7,200	14,300	15,100	17,400	20,900	22,600	23,850
Other penicillins, cephalosporins	1,200	2,500	4,400	5,800	6,700	7,300	9,900	12,900	11,550	11,500
Sulfonamides + trimethoprim c)	3,800	7,900	9,500	4,800	7,700	7,000	10,600	11,500	13,800	13,850
Sulfonamides	8,700	5,900	5,600	2,100	1,000	1,000	900	850	750	750
Macrolides, lincosamides, pleuromutilins	10,900	12,900	11,400	7,600	7,100	15,600	19,200	24,200	22,050	23,800
Aminoglycosides	7,700	8,500	8,600	7,100	7,800	10,400	11,700	11,600	10,500	8,150
Others c)	6,700	6,800	4,400	600	650	300	1,600	1,000	1,250	1,100
Total	53,400	73,200	89,900	48,000	57,300	80,700	95,900	112,500	115,150	121,100

This data, along with the discussion in the Danish report, clearly indicates the ban led to additional animal disease and death. The important question is what impact did it have on public health? There is some evidence to indicate resistance declined in animals and humans in certain bacteria. However, there is no evidence that this has resulted in reducing the public health burden of resistant bacterial infections in humans. The list of references at the end of my testimony includes published papers on the results of the ban.

In summary, Mr. Chairman, antibiotics are vitally important to the health of our nation's livestock and poultry herds and flocks. Antibiotics are highly and vigorously regulated and are used carefully by veterinarians and livestock and poultry producers. The many regulatory layers of protection that have been put in place allow us to use antibiotics to protect both human and animal health and not add to the burden of antibiotic resistant infections in humans. The FDA regulatory process and risk assessment are the proper tools for making decisions about the use of these products, and to make decisions without these tools we place unwarranted risks on both human and animal health.

NOTES

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⁴Berrang ME, et al. Subtherapeutic Tylosin Phosphate in Broiler Feed Affects *Campylobacter* on Carcasses During Processing. Poul. Sci. 2007;86:1229-1233.

⁵<http://www.fda.gov/cvm/Documents/NARMSExecSum03.pdf>.

⁶Bywater, RJ and Casewell M. An assessment of the impact of antibiotic resistance in different bacterial species and of the contribution of animal sources to resistance in human infections. J Antimicrob Chemother 2000;46:643-635.

ADDITIONAL REFERENCES

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