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# Regulatory and legislative actions – implications for antimicrobial use in pork production

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## Introduction

Antimicrobials used in animals are regulated by the Food and Drug Administration (FDA) – as are antimicrobials used in human medicine. An antimicrobial approved for use in animals by the FDA goes through several steps in the approval process demonstrating efficacy, safety to the animal, lack of environmental impact, safety to humans consuming products from animals that have been treated by the antimicrobial and, more recently, an assessment of the potential for that use to result in antimicrobial resistance that may be harmful to humans. FDA may also have a new animal drug application (NADA) reviewed by the Veterinary Medicine Advisory Committee prior to approval. Post approval monitoring may also be required as part of the approval process.

FDA has approved antimicrobials for the following uses: growth promotion/improvement of nutritional efficiency, prevention, control and treatment of disease. FDA and other scientific organizations have grouped prevention, control and treatment of disease as therapeutic uses of antimicrobial and consider growth promotion to be sub-therapeutic.

In the last decades, as concerns over antimicrobial resistance in human and animal health have emerged, uses of antimicrobials have come under increasing scrutiny. This scrutiny has come not only from regulatory and public health agencies, but also from advocacy groups who have engaged legislators and the media. Many of these groups have emphasized what they view as unnecessary uses, especially what they term the “non-therapeutic” use of antimicrobials in animal agriculture. Most of these groups include not only nutritional efficiency/growth promotion, but also disease prevention and control, within their definition of non-therapeutic use.

## Regulatory actions

### 1. FDA Guidance for Industry #152

FDA “*Guidance for Industry (GFI) #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern.*” was issued in October of 2003. GFI #152 describes a qualitative risk assessment

process which is conducted by the sponsor company and then evaluated by FDA. Data is provided to FDA in 3 basic areas:

- Potential for drug use to select resistant bacteria in the animal;
- Potential for these resistant bacteria to contaminate the meat resulting in possible human exposure to the resistant pathogen and potential illness ;
- Importance of the antibiotic to human medicine in treating food borne disease and other serious human infections.

A ranking is established (high to low) for each of the above components, then, an overall risk ranking is developed. Other options, such as quantitative risk assessments, which rely on more extensive scientific data, may also be accepted by CVM to replace GFI #152 risk assessments.

The overall risk ranking is used by FDA to consider if marketing or use limitations should be implemented. Examples of such limitations include Rx only, animal class restrictions, or individual animal only administration. GFI #152 also provides for Veterinary Medicine Advisory Committee input on the compound approval. The Committee has been utilized on several occasions to review the safety data provided by the company and evaluated by the agency.

### 2. Veterinary medical advisory committee recommendations on cefquinome

In 2006 FDA announced that a new animal drug application for cefquinome, a fourth generation cephalosporin was submitted for approval to CVM for treating respiratory disease/shipping fever in feedlot cattle. Because this was a new antimicrobial FDA requested the sponsor conduct an evaluation under Guidance #152 for microbial safety. The company conducted the evaluation concluding that the drug was a medium risk but should be approved since it was for short term therapy in individual animals under veterinary prescription labeling. CVM concurred with the sponsor but prior to approving the product decided

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to seek an opinion from the Veterinary Medical Advisory Committee as is suggested as an option in Guidance #152. The meeting was held in September 2006 after the release of the risk assessment and interested parties were permitted to make comments either for or against the approval. After significant deliberation the Committee recommended FDA not approve the product at that time as certain unanswered questions based on European data were still outstanding and that other products were available. Despite the clear CVM position that this product is safe and effective under the proposed label conditions of use and restrictions and that the availability of other products is not a reason for denying approval, CVM has never approved cefquinome. The product remains approved in Europe.

### 3. Veterinary Feed Directive docket

In the Spring of 2010 FDA issued Docket No. FDA-2010-N-0155 asking for comments on improving the Veterinary Feed Directive (VFD). The comment period closed in August. Some specific questions they asked included information on what conditions should be met by a veterinarian issuing a VFD, what veterinarians should do with the VFD (physical disposition of the form) and what records should be kept.

### 4. FDA Guidance for Industry #209

In June of 2010, FDA released *Draft Guidance for Industry #209 - The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*. The guidance addresses two principles:

A. *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 this principle it is stated “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.” The Guidance does indicate that uses of antimicrobials to preserve animal health, including disease prevention, are important uses of antimicrobials in veterinary medicine.

B. *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.* While there is a discussion of the importance of veterinary oversight for all uses of antimicrobials in food-producing animals no one system, such as VFD, is recommended.

The document stresses FDA’s desire to work with stakeholders to address the above principles.

## Legislative activities

Legislation to ban “non-therapeutic” uses of antimicrobials belonging to the classes of antimicrobials used in human medicine has been introduced in the US Senate and House of Representatives for many years. This legislation known as the Preservation of Antibiotics for Medical Treatment Act (PAMTA) was originally introduced in the Senate by the late Senator Ted Kennedy. The last several years it has been championed on the House side by Mrs. Louise Slaughter. Mrs. Slaughter is currently the only microbiologist in the legislature (University of Kentucky, 1951). She serves as the chair of the very powerful House Rules Committee.

The Senate Health, Energy, Labor and Pensions held a hearing in June 2008 “Examining the Public Health Impacts of Antimicrobial Resistant Bacterial Infection”. While much of the hearing focused on medical uses and surveillance of resistance, there was also a considerable emphasis on animal uses of antimicrobials.

The House Agriculture Animal Health Subcommittee on Livestock, Dairy, and Poultry held a hearing on September 25, 2008 that focused on how antimicrobials are used in animal production, judicious use of antimicrobials, quality assurance programs and other topics related to the importance of antimicrobials to animal agriculture.

In July 2009 Mrs. Slaughter conducted a hearing on PAMTA in the House Rules Committee. This was extremely unusual in that the Rules Committee does not consider bills, rather it addresses matters of procedure for the House of Representatives. It was at that hearing that the Deputy Commissioner of the FDA, Dr. Joshua Sharfstein, first publically announced FDA’s departure from previous policy and firmly stated that growth promotion was not judicious use of antimicrobials. An oft stated position by Mrs. Slaughter and others advocating for the passage of PAMTA is that antimicrobial growth promoters were banned in Denmark with no negative results to animal health and positive impacts on human health.

Subsequently, several members of the Animal Health Subcommittee of the House Agriculture Committee traveled to Denmark in September 2009 to study the impact of the AGP ban on Danish pork production. Upon returning to the United States Chairman Peterson issued a statement that they did not find definitive evidence that the ban had resulted in demonstrable benefits to public health. In an unusual move, one of the Danish government officials that presented information to the Congressional Delegation sent copies of his presentation to the entire House Agriculture Committee accompanied by a cover letter that read, in part, ‘We know that various rumours and sometimes ‘creative’ interpretations of what has taken

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place in Denmark have been circulated to members of the US Congress, and we are grateful for having been given this opportunity to correct some of these stories.’

During the Spring and Summer of 2010 the Health Subcommittee of the House Energy and Commerce Committee conducted a series of hearings on antibiotic use concluding with a hearing on July 14 on the “Misuse of Antimicrobials in Animal Agriculture”. This hearing included panel members from CDC, FDA, USDA, Infectious Disease Society of America, Pew Charitable Trusts, AVMA, Alliance for the Prudent Use of Antimicrobials, University of Minnesota, Animal Health Institute and the Danish government. At the time of this writing, these hearings have not lead to movement toward a vote in the committee on an antimicrobial use bill.

In addition to the above mentioned hearings, there have been numerous briefings sponsored by groups such as the Pew Charitable Trusts, the Union of Concerned Scientists, IDSA and others advocating for legislation to limit the availability of antimicrobials in animal agriculture. Briefings have also been held by groups involved in animal health and production to advocate for the alternate viewpoint. There have been considerable lobbying efforts on both sides around this issue, including active lobbying by members of the Danish government in support of banning antimicrobial growth promoters in the US.

In addition to PAMTA, there is one other piece of legislation known as the Strategies to Address Antimicrobial Resistance Act (STAAR) that was first introduced in 2007 and has been reintroduced each session since. STAAR seeks to codify and fund the recommendations of the

Public Health Action Plan to Combat Antimicrobial Resistance. It would set up an office of Antimicrobial Resistance in the Department of Health and Human Services to coordinate resistance activities across the government. It calls for setting up an advisory committee that could advise FDA on pending approvals of new animal drugs.

### **Implications for swine veterinarians and the pork industry**

Current regulatory and legislative actions make it likely that some currently approved antimicrobials may become unavailable, or that certain uses of these antimicrobials will no longer be allowed. The animal health manufacturers will need to conduct additional clinical trials to demonstrate therapeutic actions of many of the feed grade antimicrobials currently used in pork production. There will likely be significant changes in both dose and duration of administration.

It is uncertain how “veterinary oversight” will be operationalized under Guidance #209. However, it is likely that some formal relationship between veterinarians and producers will need to be demonstrated, as well as records of consultation on antimicrobial use. With FDA’s request for comments on the VFD process it is possible that moving all feed grade antimicrobials to VFD status is under consideration. This would result in additional manpower needs to issue VFDs for producer clients and significant record keeping for compliance with current VFD requirements.

