

THE USE OF CERTAIN ANIMAL DRUGS IN MARYLAND AGRICULTURE: CONTEXT AND CONSIDERATIONS



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The Use of Certain Animal Drugs in Maryland Agriculture: Context and Considerations

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Contributing Staff

Writer(s)

Scott D. Kennedy

Reviewer(s)

Amanda M. Mock

For further information concerning this document contact:

Library and Information Services
Office of Policy Analysis
Department of Legislative Services
90 State Circle
Annapolis, Maryland 21401

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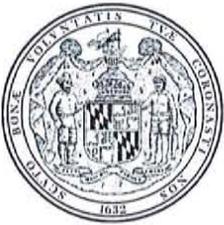
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DEPARTMENT OF LEGISLATIVE SERVICES
OFFICE OF POLICY ANALYSIS
MARYLAND GENERAL ASSEMBLY

Karl S. Aro
Executive Director

Warren G. Deschenaux
Director

October 28, 2013

The Honorable Thomas V. Mike Miller, Jr., President of the Senate
The Honorable Michael E. Busch, Speaker of the House of Delegates
Members of the Maryland General Assembly

Ladies and Gentlemen:

Legislation has been introduced in Maryland seeking to eliminate or limit the use of arsenic-containing drugs and antimicrobial drugs administered through the feed and drinking water of food-producing animals in the State. Legislation was enacted in 2012 restricting the use, sale, or distribution of most arsenic-containing drugs in poultry feed. There have been differing views expressed about the need for and impact of such State level restrictions. The U.S. Food and Drug Administration (FDA) has taken certain actions but has not imposed comprehensive, mandatory restrictions on the use of the drugs.

In an effort to compile information that may be helpful in considering future legislation, this report discusses the recent Maryland legislation, recent FDA actions, the regulation of animal drugs and animal feed in general, and certain policy considerations related to limiting the use of antimicrobial drugs in the feed or drinking water of food-producing animals in the State.

We trust that this report will be useful to the General Assembly in considering this issue. If you would like additional information regarding this report, please contact Scott D. Kennedy at (410) 946-5510.

Sincerely,

Warren G. Deschenaux
Director

WGD/SDK/kjl

cc: Mr. Karl S. Aro

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The Use of Certain Animal Drugs in Maryland Agriculture: Context and Considerations

Background

In the most recent Census of Agriculture in 2007,¹ approximately 47% of Maryland farms had sales of livestock, poultry, and/or their products, and animal agriculture accounted for two-thirds of the total value of sales by Maryland's agriculture industry (\$1.2 billion of \$1.8 billion of total agriculture sales). Legislation has been introduced in the General Assembly in recent years seeking to eliminate or limit the use of arsenic-containing drugs and antimicrobial (or antibiotic)² drugs administered through the feed and drinking water of food-producing animals in the State. Animal drugs are used both for health-related uses, such as disease treatment or prevention, and production-related uses, such as growth promotion. A prohibition on arsenic-containing drugs was enacted in 2012, but legislation first introduced in 2013 to limit the use of antimicrobial drugs was unsuccessful.

In both the case of animal drugs that contain arsenic and antimicrobial animal drugs, there have been differing views about the effects of the use of the drugs and the potential impact on agriculture of eliminating or limiting the use of the drugs. There has also been action taken at the federal level, by the U.S. Food and Drug Administration (FDA) in both cases. This report (1) provides background on arsenic-containing and antimicrobial animal drugs, the recent Maryland legislation addressing the two issues, and related FDA actions; (2) describes the federal and State regulation of animal feed and animal drugs in general; and (3) discusses considerations relevant to a proposal to limit the use of antimicrobial drugs in the State.

Animal Drugs Containing Arsenic

In 2011, an FDA study found elevated, but relatively low, levels of inorganic arsenic, which has been found to be a human carcinogen, in livers from chickens that had been treated with roxarsone, an arsenic-containing animal drug associated with both disease prevention and production uses. According to FDA, arsenic-containing animal drugs "have as their active ingredient forms of organic arsenic, which is less toxic than inorganic arsenic and not known to be carcinogenic." FDA's study was conducted following the publication of scientific reports on the potential for organic arsenic to transform into inorganic arsenic in the environment or in the

¹ The 2012 Census of Agriculture will be released in 2014.

² The terms "antimicrobial" and "antibiotic" are sometimes used interchangeably in the context of antibiotic or antimicrobial resistance but "antimicrobial" is a broader term than "antibiotic." A U.S. Centers for Disease Control and Prevention glossary of terms related to antibiotic/antimicrobial resistance defines "antibiotic" as a "type of antimicrobial agent made from a mold or a bacterium that kills, or slows the growth of other microbes, specifically bacteria." "Antimicrobial agents" are described as "drugs, chemicals, or other substances that either kill or slow the growth of microbes ... [including] antibacterial drugs (which kill bacteria), antiviral agents (which kill viruses), antifungal agents (which kill fungi), and antiparasitic drugs (which kill parasites)."

edible tissues of animals that consume it. In response to the FDA study, U.S. sales of roxarsone were voluntarily suspended in 2011. FDA indicated that the levels of arsenic detected were very low and that continuing to eat chicken, as sales of roxarsone were suspended, did not pose a health risk. In Maryland, prior to the suspension of the sale of roxarsone, the drug had been used by certain chicken companies operating on the Eastern Shore.

Legislation was introduced in Maryland in 2010 and 2011 and enacted in 2012 (Chapter 652) prohibiting the use, sale, or distribution in the State of poultry feed containing roxarsone or any other additive containing arsenic. Chapter 652 contains an exception for a drug marketed as Histostat,³ which is used primarily to prevent blackhead disease (or histomoniasis) in turkeys. In addition, under Chapter 652, if FDA *newly* approves any specific additive, the prohibition would not apply to it.

While U.S. sales of roxarsone were suspended in 2011, the drug was still approved by FDA when Chapter 652 was enacted. In a recent September 30, 2013 letter,⁴ FDA indicates that while there are four arsenic-based animal drugs approved for use in medicated feed – roxarsone, carbarsone, arsanilic acid, and nitarosone (marketed as Histostat) – the sponsors of roxarsone, carbarsone, and arsanilic acid have recently requested that FDA withdraw approvals of the drugs, which FDA is in the process of doing. Carbarsone and arsanilic acid both have not been marketed for a number of years. FDA is currently reviewing the remaining drug nitarosone, which currently is marketed, to determine, among other things, whether there may be grounds for withdrawal of its FDA approvals.

Antimicrobial Animal Drugs

A recent report by the U.S. Centers for Disease Control and Prevention (CDC) refers to antimicrobial (or antibiotic) resistance as one of our most serious health threats, and there is concern about the extent to which use of antimicrobial drugs in animal agriculture contributes to antimicrobial resistance in humans and animals. A 2012 FDA guidance document (Guidance for Industry #209), which establishes principles for judicious use of antimicrobial drugs in the feed and drinking water of food-producing animals, states that “[t]he scientific community generally agrees that antimicrobial drug use is a key driver for the emergence of antimicrobial-resistant bacteria.” In the document, FDA summarizes past reports and studies on the use of antimicrobial drugs in animal agriculture and determines that judicious use of medically important antimicrobial drugs is important to minimize resistance development and preserve their effectiveness as therapies for humans and animals. The guidance recommends that the use of the drugs be limited to uses in food-producing animals that are “necessary for assuring animal health” and “include veterinary oversight or consultation.”

³ Histostat is the trade name for an FDA-approved drug called nitarosone.

⁴ The FDA letter is in response to a 2009 citizen petition seeking the withdrawal of FDA approval for all arsenic-containing compounds used as feed additives for animals.

Legislation has been introduced in Congress and in a small number of states including Maryland, Minnesota, New York, and Pennsylvania, proposing stronger mandatory standards to reduce the use of antimicrobial drugs in animal agriculture. In Maryland, Senate Bill 520 of 2013 would have, beginning in October 2016, prohibited the use, sale, or distribution in the State of any commercial feed or drinking water that contained certain antimicrobial animal drugs and was used in the absence of a disease diagnosed by a veterinarian. SB 520 received an unfavorable report from the Senate Education, Health, and Environmental Affairs Committee and was withdrawn.⁵

The 2012 FDA guidance considers the use of animal drugs in animal feed or water for treatment, control (administration to a group of animals where a certain amount of the group have a disease), and prevention of specific diseases as uses that are necessary for assuring animal health and, therefore, appropriate uses. The guidance recommends veterinary oversight or consultation but notes that the oversight or consultation could include direct diagnosis and administration of therapies by a veterinarian or simply a veterinarian periodically visiting or consulting with a producer to establish customized disease management protocols. Unlike the FDA guidance, SB 520 would not have allowed for disease prevention uses⁶ and would have required a direct diagnosis of a disease by a veterinarian in order to administer treatment in all cases.

The group of antimicrobial drugs that the FDA guidance applies to and that SB 520 would have applied to differ. The FDA guidance refers to “medically important antimicrobial drugs,” which FDA has indicated includes drugs listed in a 2003 guidance document (Guidance for Industry #152) that have been determined to be important for treating bacterial infections in people. SB 520 targets “critical antimicrobial animal drugs,” which, in addition to specifically listed types of drugs, includes any other drug or derivative of a drug that is used or intended for use in human beings to treat or prevent disease or infection caused by microorganisms. Both the FDA guidance and SB 520 target a relatively broad group of antimicrobial drugs. SB 520, however, may impact a broader group of drugs since it applies to any drug or derivative of a drug used or intended for use in humans to treat or prevent disease or infection caused by microorganisms.

⁵ While not addressed in this report, a bill was also introduced during the 2013 session (SB 521) that required meat or poultry processed and sold in the State for human consumption, that was derived from an animal that was fed or administered antibiotics while being raised in the State, to bear a label identifying each antibiotic that was fed or administered to the animal.

⁶ The bill may have also prevented disease control uses (where a drug is administered to a group of animals to control a disease seen in a portion of the group) based on the bill’s wording of the definition of “nontherapeutic use” as “the use of a critical antimicrobial animal drug as a feed or water additive for an animal in the absence of disease that has been diagnosed by a veterinarian in the animal.”

Current Regulation and Policies

Federal Level

Both food consumed by humans and feed consumed by animals are regulated by FDA under the Federal Food, Drug, and Cosmetic Act (FDCA). “Food” is defined under the Act to include “articles used for food or drink for man or other animals.” FDA indicates that “any article that is intended to be used as an animal feed ingredient, to become part of an ingredient or feed, or added to an animal’s drinking water is considered a ‘food’ and thus, is subject to regulation” under the FDCA. Animal drugs and certain feed additives are subject to approval by FDA. The FDCA also requires all animal feed to meet standards for safety, accurate representation, and labeling.

Animal drugs, including those included in animal feed, go through an FDA approval process called the New Animal Drug Application (NADA) process. The drug sponsor, often a pharmaceutical company, is responsible for collecting information on the safety (both with respect to the target animals and humans) and effectiveness of a new animal drug, which FDA reviews. There is also a process for withdrawal of approval based on various grounds, such as later experience or scientific data showing that the drug is unsafe under the approved conditions of use. Certain modified approval procedures apply to drugs for minor species or for minor uses in major species.

Antimicrobial resistance is considered during the NADA process, and FDA has had guidance in place since 2003 (Guidance for Industry #152) establishing a risk analysis methodology “for evaluating human food safety with respect to the potential microbiological effects of antimicrobial new animal drugs on food-borne bacteria of human health concern.” FDA’s 2012 guidance regarding judicious use of antimicrobial drugs in the feed and drinking water of food-producing animals appears to be aimed at those “medically important antimicrobial drugs” approved prior to the implementation of the 2003 guidance. The 2012 guidance distinguishes between drugs approved before and after the implementation of the 2003 guidance and states that “FDA believes the approach outlined [in the 2003 guidance] for evaluating microbiological safety as part of the drug approval process has been very effective ... and is protective of public health.” Additional FDA guidance is anticipated by the end of 2013 (Guidance for Industry #213) to help drug sponsors better align product use conditions with FDA’s 2012 guidance.

There is pending federal litigation that could result in FDA taking stronger action to limit the use of antimicrobial drugs in animal agriculture. In 2012, a federal magistrate judge ordered FDA to begin an administrative process (subject to a subsequently approved multi-year timeline) that could lead to the withdrawal of approvals for nontherapeutic use of penicillin and tetracyclines in animal feed. FDA was also ordered to reevaluate two citizen petitions that sought the withdrawal of approvals for nontherapeutic use of medically important antibiotics in food-producing animals, which FDA had denied in 2011. The case has been appealed by FDA, and the appellate decision is pending as of mid-October 2013.

State Level

The Maryland Department of Agriculture's (MDA) State Chemist Section (SCS) administers the Maryland Commercial Feed Law. Under the Maryland Commercial Feed Law, SCS must sample, inspect, test, and make analyses of commercial feed distributed in the State to the extent considered necessary to ensure compliance with the law. A distributor generally must register each brand name or product name of commercial feed before distributing it in the State, unless it has been registered by another person and the product label has not been altered or changed. Although Maryland law, for the most part, does not specifically address drugs in animal feed and SCS does not have a formal agreement with FDA to regulate drugs, SCS ensures the safety of feeds containing drugs by requiring conformance with FDA law.

Considerations Relating to Restrictions on Antimicrobial Use

Impact on Maryland Agriculture

Use Limitations

It is unclear how prohibiting the use of critical antimicrobial animal drugs in feed or drinking water for disease prevention and growth promotion would impact Maryland agriculture overall. MDA has indicated that “[a]ntibiotic use in feed and water by food animal producers and veterinarians is relatively common but difficult to fully quantify or otherwise describe either nationally or in Maryland.” MDA and industry representatives indicated that SB 520 would have put Maryland producers at a competitive disadvantage to producers in other States, implying that prohibition of disease prevention and growth promotion uses of the critical antimicrobial animal drugs in feed and drinking water would have lowered Maryland producers’ production level and/or raised the producers’ costs. At least two studies in the United States regarding broiler chicken flocks indicate that elimination of growth promotion/disease prevention uses of antimicrobial drugs may have little or no negative impact on producers (see References on page 9). Another study, however, indicates the potential for producers to bear higher costs to realize a certain level of output. The studies have limitations in some cases, and it does not appear that conclusions can be drawn from the studies about the overall impact of legislation similar to SB 520 on the various types of producers and production settings making up Maryland’s animal agriculture industry.

Veterinarian Diagnosis Requirement

Requiring a veterinarian’s diagnosis as a precondition to disease treatment use of feed or drinking water containing critical antimicrobial animal drugs could negatively affect smaller producers. FDA indicates that most of the feed-use antimicrobial drugs are approved for over-the-counter use, and, based on discussions with MDA, farmers with smaller animal agriculture operations may use feed containing antibiotics without the services of a veterinarian

to treat or control diseases. Under State law governing the practice of veterinary medicine, a person may administer “to the ills and injuries of [his or her] own animals if they otherwise comply with all the laws, rules, and regulations relative to the use of medicines and biologics” without being licensed as a veterinarian. Under legislation like SB 520, smaller producers would have to seek the services of a veterinarian and bear the associated costs for disease treatment.

Impact on Public Health

CDC describes antibiotic resistance as a worldwide problem and indicates that antibiotic resistant bacteria can spread quickly and across international boundaries and between continents with ease. Because a Maryland law would only reduce antimicrobial drug use in the State, its impact on public health may be limited, to a certain extent, as a result. CDC, however, does indicate that “[s]topping even some of the inappropriate and unnecessary use of antibiotics in people and animals would help greatly in slowing down the spread of resistant bacteria.”

The extent to which antimicrobial use in animal agriculture is contributing to the antimicrobial resistance threat, with respect to human health in particular, is unclear. CDC states that there is “strong evidence that antibiotic use in food-producing animals can harm public health” and that “[b]ecause of the link between antibiotic use in food-producing animals and the occurrence of antibiotic-resistant infections in humans” antibiotic use in food-producing animals should be limited. FDA, in its 2012 guidance, similarly finds that “[u]sing medically important antimicrobial drugs as judiciously as possible is key to minimizing resistance development and preserving the effectiveness of these drugs as therapies for humans and animals.” The CDC report and FDA guidance, however, do not appear to clearly establish the magnitude of the contribution of antimicrobial use in animal agriculture toward the overall threat of antimicrobial resistance. The CDC report does suggest that antimicrobial use in animal agriculture could play a significant role by stating that (1) “the use of antibiotics is the single most important factor leading to antibiotic resistance around the world”; and (2) while “[i]t is difficult to directly compare the amount of drugs used in food animals with the amount used in humans ... there is evidence that more antibiotics are used in food production.”

Enforcement Costs

Establishing prohibitions relating to the use, sale, or distribution of feed or drinking water containing specific animal drugs may require additional resources for enforcement. The fiscal and policy note for SB 520 indicated that State general fund expenditures would increase by just over \$120,000 annually to hire an additional inspector and laboratory technician in SCS to inspect affected facilities and their records and conduct random sampling and analysis of feed to ensure compliance with the bill. Existing SCS staff, including four inspectors handling enforcement responsibilities of the section for the whole State, did not have the capacity to handle the additional work.

Federal Preemption

Some of the testimony submitted with respect to SB 520 indicated that, if enacted, the bill may have been preempted by the federal regulatory scheme under the FDCA. The concept of federal preemption is based in the Supremacy Clause of the U.S. Constitution (Art. VI). Based on communications with FDA, MDA, the Attorney General's Office, and certain private attorneys familiar with FDA law, there does not appear to be a definitive answer at this time as to whether a law similar to SB 520 could be subject to federal preemption.

Conclusion

The use of animal feed and drinking water containing arsenical-based and antimicrobial animal drugs has raised concerns related to human health. FDA has taken certain actions in response to those concerns that so far have stopped short of comprehensive, mandatory prohibitions or limits on the use of the drugs. Stronger action has been sought at the State level in Maryland. With respect to legislation proposing limitations on the use of antimicrobial drugs, there is uncertainty about how and to what extent such legislation would impact Maryland's animal agriculture industry and impact public health. It is also unclear how such legislation would interact with federal law.

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